Scientific Network on Risk Assessment of GMOs

Minutes of the 5th meeting

Held on 13-14 May 2014, Parma

(Agreed on 21 November 2014)

Participants

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

Country	Name	Country	Name
Austria	Markus Woegerbauer	Italy	Roberta Onori
	Eva-Claudia Lang		Luigi Cattivelli
Belgium	Katia Pauwels	Latvia	Indrikis Muiznieks
	Adinda De Schrijver	Lithuania	Mindaugas Morkunas
Bulgaria	Tzveta Georgieva		Odeta Pivoriene
	Dimitar Djilianov	Malta	Flavia Zammit
Croatia	Hrvoje Fulgosi	Netherlands	Esther Kok
	Sanja Milos		Boet Glandorf
Czech Republic	Vladimir Ostry	Norway	Merethe Aasmo Finne
	Miroslava Navratilová		Arne Mikalsen
Denmark	Jan Pedersen	Poland	Slawomir Sowa
	Morten Strandberg		Zbigniew Dąbrowski
Estonia	Andres Mäe	Slovakia	Petra Gerekova
Finland	Kirsi Törmäkangas	Slovenia	Ruth Rupreht
France	Catherine Golstein		Martin Batic
Germany	Wolfram Reichenbecher	Spain	Carmen Cuadrado
	Andrea Scheepers		Félix Ortego Alonso
Greece	Argyrios Boulis	Sweden	Christer Andersson
Hungary	Barnabás Jenes	Switzerland	Martin Schrott
	Zsuzsanna Bardócz	United Kingdom	Louise Ball
Ireland	Patrick O'Mahony		
	Bernadette Murray		

- **Panel Members**

GMO Panel: Salvatore Arpaia, Jürgen Gropp (for item 5.3.a.3.), Gijs Kleter, Joe Perry and Christoph Tebbe.

- **Hearing Experts**

None.

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- **European Commission:**

Sarah Brown and Maria Mirazchiyska (DG SANCO).

- **EFSA:**

Advisory Forum and Scientific Cooperation (AFSCO) Unit: Jeffrey Moon for item 6.2.

Assessment and Methodological Support (AMU) Unit: Elisa Aiassa for item 5.7.

GMO Unit: Herman Broll, Yann Devos, Zoltán Divéki, Antonio Fernández Dumont, Andrea Gennaro, Ana Gomes, Anna Lanzoni, Sylvie Mestdagh, Irina Olaru, Claudia Paoletti, Matthew Ramon and Elisabeth Waigmann (Chair).

Scientific Committee and Emerging Risks (SCER) Unit: Reinhilde Schoonjans for item 5.3.b.1.

- **Others:** Ali Osman Sari (Turkey).

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Emmanuelle Pic (France).

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes regarding Declarations of Interests (DoIs)[1] and the Decision of the Executive Director implementing this Policy[2], members of networks, peer review meetings, networking meetings and their alternates shall be invited to complete and submit an Annual Declaration of interest (ADoI).

EFSA screened the ADoI filled in by the experts invited for the present meeting. No conflicts of interests related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of interest (ODoI) at the beginning of this meeting.

The Chair thanked the GMO Network representatives that had submitted the ADoI.

4. Agreement of the minutes of the 4th meeting of the Scientific Network on Risk Assessment of GMOs held on 22-23 May 2013, Parma

The minutes were agreed by written procedure on 30 September 2013 and published on the EFSA website 2 October 2013.

5. Topics for discussion

5.1. Update in recent and current EFSA activities on GMOs – mandates, guidance documents, procurement and grants

Elisabeth Waigmann, the Head of the GMO Unit, gave an overview of the current EFSA activities in the field of GMOs. She reported on the status of GM plant applications submitted in the frame of Regulation (EC) No 1829/2003, notifications received under Directive

[1] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[2] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

2001/18/EC, EFSA GMO Panel guidance documents that are currently under development[3], and external mandates pertaining to the assessment of post-market environmental monitoring reports and safeguard clause/emergency measures invoked by EU MS. Specific risk assessment activities that are outsourced to external contractors were also mentioned.

5.2. Data gaps in the risk assessment of GMOs

Joe Perry, the Chair of the EFSA GMO Panel, explained how the GMO Panel assesses GM plant applications, in line with the scientific principles and data requirements outlined in the GMO Panel guidance documents. He indicated that when complete datasets are provided consistent with the scientific requirements, the assessment can be completed, allowing the GMO Panel to draw conclusions on the safety of the GM plant under assessment. However, if the data are insufficient to conclude on the assessment and GMO Panel questions are answered unsatisfactorily by the applicant, the risk assessment can be inconclusive on one or more aspects, depending on the nature of the missing information. In recent years, the GMO Panel has issued five scientific opinions that were partially or fully inconclusive. In all cases, the GMO Panel asked for the data needed to conclude on the safety of the respective GMO, but the applicants did not provide the requested data. In two of the five cases, the European Commission (EC) requested EFSA to complement the scientific opinion, based on additional scientific information submitted by the applicant, and in both cases the GMO Panel was able to conclude on the safety of the respective GMO. Joe Perry indicated that the recent editions of the GMO Panel guidance documents provide more detailed explanations on how the risk assessment should be performed, thus supporting the applicants in obtaining complete data sets which allow reaching a conclusion on safety. He added that applicants have a legal obligation to follow the requirements of the Commission Implementing Regulation (EU) No 503/2013 (hereafter referred to as “IR 503/2013”), which came into force on December 8, 2013, and defines the scientific information to be provided in applications for GM food and feed submitted under Regulation (EC) No 1829/2003.

After Joe Perry’s presentation, a general discussion followed.

An Austrian delegate wondered whether inconclusive opinions can inform the decision-making process, and under what circumstances it is acceptable to reach a conclusion when experimental data are missing. Joe Perry indicated that the lack of specific data does not prevent the GMO Panel to conclude on those aspects of the risk assessment for which the dataset supplied was sufficient. Thus, scientific opinions may still include statements on safety for certain areas of concern, depending on the data provided. To improve clarity of inconclusive opinions and to help risk managers in the decision-making process, he proposed to be explicit about the degree of uncertainty associated with the missing information. EFSA added that when information was missing from an application, the GMO Panel asked the applicant to provide the information, but the questions were either not answered or the information provided was not satisfactory. Furthermore, EFSA has informed applicants about its policy of not reiterating questions.

A delegate of the Netherlands noted that EFSA has made the risk assessment process more prescriptive, but that this is in contradiction with the case-by-case principle, which is a legal requirement. Joe Perry referred to the GMO Panel guidance documents, which mention that risk assessment should be case-specific. EFSA added that applicants welcome clear and detailed guidance from the GMO Panel, including clear indications on how to conduct experimental studies, as this ensures that the data obtained will be relevant for the risk assessment.

Another delegate of the Netherlands indicated that resource availability to generate and compile the necessary data to prepare GM plant applications differs substantially between

[3] Guidance Document for the agronomic and phenotypic characterisation of genetically modified plants (EFSA-Q-2013-00606) and Guidance Document for the risk assessment of the renewal of GM plant products authorised under Regulation (EC) No 1829/2003 (EFSA-Q-2013-00684)

applicants. Therefore, not all applicants are in a position to meet all data requirements outlined by EFSA and EC. Increased data requirements may, therefore, benefit the larger companies and disadvantage the smaller plant breeders.

A Hungarian delegate noted that, while in the past, the safety assessment involved the comparison between the GM plant and the conventional counterpart, the current approach is to compare the GM plant with commercial lines, and asked how an observed difference between the GM plant and the conventional counterpart is assessed in the context of this comparison with commercial varieties. Joe Perry replied that including commercial varieties in the comparative assessment allows to place any difference observed in the context of natural variability. This is important, since an observed difference does not automatically indicate a safety concern.

A Danish delegate commented that guidance documents are a set of minimum requirements, and if additional information is needed, it could be asked for without referring to a guidance document. He added that data should be asked when needed, not because it is mentioned in a guidance document, to which Joe Perry replied that the GMO Panel asks for additional data on a case-by-case basis, when that particular information is needed. A delegate from the United Kingdom (UK) also supported the point that explaining the scientific rationale for a question is more useful than mentioning the guidance document that requires the respective data.

An Austrian delegate asked how other EFSA scientific panels deal with data gaps in risk assessment. EFSA indicated that other scientific panels issue inconclusive opinions routinely, due to data gaps that remain unsolved by the applicants. Joe Perry added that the Scientific Committee (SC) aims at harmonising scientific practices of EFSA panels, and that a new SC working group (WG) is currently developing guidance on how to address uncertainty in risk assessment. In addition, training courses on uncertainty have been organised by EFSA for panel members and staff.

A Danish delegate noted that risk assessment, in its nature, involves uncertainty, and that even when the information indicated by guidance documents is provided, it is possible for uncertainty to remain. The EC wished to clarify this point, commenting that there are two different situations, one when scientific information should have been provided by the applicant, and the other when, although the full set of information has been provided, uncertainty cannot be excluded. The Danish delegate then added that it would be useful for risk managers to have a characterisation of the remaining uncertainty in the scientific opinion, on which to base their decision.

A Belgian delegate expressed the view that scientific opinions should focus on clearly indicating if there is any risk associated with the respective GMO, and not on data gaps identified during the risk assessment, as these gaps could be addressed by the uncertainty analysis. Regarding EFSA's policy not to reiterate questions, she added that a dialogue with the applicants can ensure that questions are understood properly and relevant information is provided. To the second comment, EFSA replied that while applicants can contact staff by telephone in order to obtain clarifications regarding certain applications, other forms of interaction with applicants are limited. However, EFSA is striving for a customer-oriented approach.

A French delegate wished to clarify the point raised by the EC on uncertainty due to lack of data versus uncertainty remaining after analysis of a full data package by asking how applications with data missing were declared valid, to which EFSA replied that the completeness check has evolved over time, together with the guidance documents, and previous requirements were not as explicit as they are in the present time.

An Austrian delegate indicated that although applicants delay the assessment process by not submitting the requested information, they claim the Member States and EC are responsible for the lengthy authorisation process. She acknowledged the effort made by

EFSA to assess old applications containing insufficient data, but stressed the point that inconclusive opinions are not helpful for risk managers and that the concept of uncertainty should not be used for applications missing essential information, which, in her view, should be rejected by EFSA.

EFSA replied that the rejection of applications is not foreseen by the legislation and added that the increased thoroughness of the completeness check should reduce the time from validity to adoption of a scientific opinion. EFSA also mentioned the EFSA scientific report on timelines for additional information[4], a document that indicates the timeline for submitting additional information, depending on the nature of the respective information.

5.3.a. Break-out session MC/FF: EFSA Guidance document and EC Implementing Regulation (EU) No 503/2013

5.3.a.1. Differences between the EFSA RA GD 2011 and IR 503/2013

Zoltán Divéki, scientific officer of the EFSA GMO Unit, presented the Implementing Regulation (EU) No 503/2013, indicating the main data requirements for applications for single or stacked GM events, and the differences in comparison with the EFSA GMO Panel Guidance for the risk assessment of GM plants, where applicable. The main requirements of the IR 503/2013 not present in the EFSA Guidance are: mandatory 90-day feeding study for single events; toxicological studies to comply with GLP standards (if performed in the EU) or OECD principles (if performed outside the EU); studies other than toxicological to follow ISO or GLP standards; scope of stacks to cover all sub-combinations; systematic literature reviews covering 10 years prior to the submission of an application; applicants to submit additional information which might influence the risk assessment, in particular regarding any prohibition or restriction imposed by a competent authority of a third country. He also mentioned the update of the EFSA Submission guidance[5], which was done in line with the data requirements of the IR 503/2013.

After the presentation, a delegate of the Netherlands asked about the relevance of a perceived new requirement to provide information on the expression of the insert during the life cycle of the GM plant. EFSA replied that already in the GMO Panel Guidance document for the risk assessment of food and feed from GM plants (hereafter referred to as “EFSA RA GD 2011”)[6] it was mentioned that developmental data can be relevant to the risk assessment in certain cases.

An Austrian delegate asked whether EFSA has revised any of its guidance documents following the entry into force of IR 503/2013, to which EFSA replied that the Submission Guidance was the only document that was updated.

5.3.a.2. Allergenicity assessment of GM plants

Antonio Fernández Dumont, scientific officer in the GMO Unit, gave a presentation on two upcoming activities related to allergenicity assessment of GM plants: i) endogenous allergenicity to be discussed at the OECD Task Force meeting, and ii) a future self-task activity of EFSA on allergenicity of GM plants. With regard to the first activity, it was explained that potential unintended effects, due to the genetic modification and impacting the endogenous allergenicity of a GM plant, are assessed using a comparative approach. This

[4] European Food Safety Authority, 2014. Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products. EFSA Journal 2014;12(1):3553, 37 pp. doi:10.2903/j.efsa.2014.3553

[5] European Food Safety Authority, 2013. EFSA guidance on the submission of applications for authorisation of genetically modified plants under Regulation (EC) No 1829/2003. EFSA Journal 2013;11(12):3491, 133 pp., doi:10.2903/j.efsa.2013.3491

[6] EFSA Panel on Genetically Modified Organisms (GMO), 2011. Scientific Opinion on Guidance for risk assessment of food and feed from genetically modified plants. EFSA Journal 2011; 9(5): 2150. [37 pp.] doi:10.2903/j.efsa.2011.2150.

approach has been recommended by EFSA RA GD 2011, Codex Alimentarius (2009)[7] and the IR 503/2013. EFSA and the Austrian and Norwegian Competent Authorities have been invited to the next OECD Task Force meeting of 2015 to present the new developments on this matter. The document to be presented to the OECD Task Force will be distributed to the Member States for comments. In relation to the second topic, EFSA explained that a new WG of the GMO Panel will be created, with the task to develop supplementary guidelines for the allergenicity assessment of GM plants. These guidelines will provide clarifications on the following topics: non-IgE-mediated immune adverse reactions, *in vitro* digestibility testing and endogenous allergenicity.

The presentation was followed by a general discussion.

The first comment came from a Swedish delegate, indicating that there is a need to know more about allergen levels in plants. It is possible that the levels of a specific allergen in the conventional counterpart fall outside the interval described by the reference varieties included in a trial. EFSA indicated that comprehensive allergen databases providing information on natural variability are not available yet. However, data on allergen levels are becoming available and the reference varieties included in a trial, as described by EFSA RA GD 2011, offer information on natural variability.

A Danish delegate questioned why GMOs should receive more attention than conventional crops with regards to allergenicity assessment. A Hungarian delegate asked if the purpose of allergen assessment is only to measure known allergens or also to identify new ones, to which EFSA replied that only measuring known allergens listed by the OECD Consensus Documents is foreseen. An Irish delegate commented that food allergens are an important safety issue and that this work might affect food labelling.

EFSA replied that endogenous allergenicity of GM plants is an important aspect of the safety assessment. According to IR 503/2013, applicants are requested to quantify individual endogenous allergens, as listed in OECD Consensus Documents. In the case of soybean, fifteen allergens are listed by OECD[8]. EFSA highlighted that technical difficulties might prevent the analysis of some of these allergens. If a potential allergen included in the OECD list is not assessed, a scientific rationale must be provided.

A Danish delegate noted that for some crops it will be difficult to include non-GM commercial plants in the field trials, as proposed by EFSA RA GD 2011, due to the fact that most of the future commercial varieties might be GM. He also expressed his view that an agreement on the list of allergens to be measured is an important aspect to be considered.

A delegate from the Netherlands commented that levels outside the range established by reference varieties will be part of the compositional analysis, as other anti-nutrients, and questioned how meaningful it is to use the data on the levels of endogenous allergens for the safety assessment, in relation to allergenicity, as it has not been scientifically established that these data have added value in this respect.

EFSA agreed with the comments and indicated that, although there are no threshold levels for allergens that can be used for regulatory purposes, the endogenous allergenicity should be assessed, as increased levels of allergens might be of safety concern mainly to the allergic individuals.

A Slovenian delegate asked if major differences between GM and non-GM crops regarding allergens had been observed in the applications assessed by EFSA, to which EFSA replied that experimental data on endogenous allergenicity is requested only for crops known to be

[7] Codex Alimentarius, 2009. Foods derived from modern biotechnology. Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme. Rome, Italy. 85 pp.

[8] OECD, 2012. Revised consensus document on compositional considerations for new varieties of soybean [Glycine max (L.) Merr.]: Key food and feed nutrients, anti-nutrients, toxicants and allergens. Series on the Safety of Novel Foods and Feeds No. 25.

allergenic (e.g. soybean) and that no major differences in the overall allergenicity of the GM crops assessed by EFSA had been noticed.

5.3.a.3. 90-day animal feeding studies

Anna Lanzoni, scientific officer in the GMO Unit, gave a talk on 90-day studies in rodents on whole food/feed, explaining when they are requested according to the current GM regulatory framework and how EFSA is developing an "Explanatory statement for the applicability of the Guidance of the EFSA Scientific Committee for 90-day study on whole genetically modified food/feed in rodents to GMO risk assessment". This document is meant to provide detailed technical instructions on how to apply the general principles described in the EFSA Scientific Committee guidance document[9] and to promote a consistent approach to 90-day studies provided in the context of GM plant applications.

The presentation was followed by a general discussion. A Hungarian delegate indicated that nutritional guidelines should also be taken into consideration when developing the protocol, with special attention to the total protein content of the diet, as this could introduce effects possibly interfering with the toxicological assessment. A GMO Panel member indicated that the test material (and the control material) should be fully analysed, in order to allow the formulation of nutritionally-balanced diets for the test species.

EFSA added that considering the limited incorporation rate (dose) of the test material in a balanced diet, this type of study has considerable limitations from a toxicological point of view, as it does not allow to explore high dose levels.

A German delegate asked how to use the information from a 90-day study when the design is not optimal. A Panel member replied that studies performed by applicants should be in line with EFSA's guidelines and the IR 503/2013, and will be assessed accordingly.

The Panel member also indicated that the EFSA statement will provide clarifications on relevant topics, which will allow conducting sound studies. One of these relevant topics will be the choice of the test material. The focus will be on whole food/feed, and examples of combinations of plant-derived products adequately representing the wholeness of the food/feed will be provided.

5.3.b. Break-out session ERA: Scientific Committee Overarching ERA WG

5.3.b.1. Protection goals and endangered species

Reinhilde Schoonjans, scientific officer of the SCER Unit, presented the on-going activities on environmental risk assessment led by EFSA's Scientific Committee (SC). The following points were addressed in her presentation: the SC role in harmonising approaches across EFSA scientific panels; EFSA's Scientific Colloquium XIX "Biodiversity as Protection Goal in Environmental Risk Assessment for EU Agro-systems" (purpose, scientific programme, outline, outcomes and participation composition); the ecosystem service approach to make protection goals operational for use in environmental risk assessments; and on-going activities pertaining to endangered species and recovery.

The presentation was followed by a general discussion. An UK delegate asked whether NGOs participated to the colloquium, to which EFSA replied that despite the broad advertisement of the colloquium, the participation of NGOs to the workshop was very limited. This may be attributed to budgetary constraints, as EFSA does not cover travel and accommodation expenses of NGO representatives for this type of event.

The UK delegate continued with a question on the definition of harm, wondering why different levels of harm are found acceptable for different stressors. Harmonisation of what is considered environmental harm is currently attempted by EFSA for specific cases. However,

[9] EFSA (European Food Safety Authority) Scientific Committee, 2011. EFSA guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed. EFSA Journal 2011;9(12):2438 [21 pp.]

harmonising the concept of environmental harm is difficult, as protection goals differ between EU MS. A Polish delegate agreed that harmonisation is challenging and therefore questioned how EFSA would take into account these differences. EFSA clarified that the methodology and terminology will be harmonised instead of the protection goals themselves.

The UK delegate indicated that ACRE has been committed to identifying how environmental harm could be more effectively defined in environmental risk assessment of GM plants as part of its 2013 work programme, and that a sub-group was appointed to address this issue. The outcome of the ACRE deliberations has been published and could form an informative basis for EFSA's work on this matter.

A delegate from the Netherlands asked whether farm management practices applied in conventional agriculture serve as a representative baseline in the GM plant risk assessment.

A Finnish delegate mentioned that some herbicide-tolerant crucifers were obtained through conventional breeding, and thus are not subject to regulatory oversight, although they may pose similar environmental risks as a GM herbicide-tolerant plant. EFSA indicated that non-regulated products are excluded from its mandate. Nonetheless, EFSA acknowledged the necessity to take specific actions to facilitate the transition towards an integrated environmental risk assessment of multiple stressors. Joe Perry asked the EC delegate whether MS can set their own protection goals. It was indicated that EU legislation sets the protection goals at EU level and that specific goals can be set for endangered species under the Habitat Directive. Each MS can define which habitats should be protected in order to preserve certain species.

A German delegate asked how recurrent exposure is considered in the context of recovery, as repeated exposure is likely in regions where GM plants are grown. GM plants can either be grown continuously or be rotated with other GM plants expressing a similar or the same trait. Moreover, the stacking of traits may also increase environmental exposure (if grown in the EU). EFSA confirmed that these aspects are being discussed by the SC WG on recovery and that recommendations may be given in terms of modelling and research needs.

5.3.b.2. Taking a weight of evidence-based approach to dealing with potential unintended effects associated with a GM event

Louise Ball and Adinda De Schrijver, delegates from the UK and Belgium respectively, presented their views on the consideration of unintended effects in the risk assessment of GM plants, in particular in the context of non-target organisms (NTOs) testing. They indicated that Directive 2001/18/EC does not explicitly mention unintended effects arising from the genetic modification process. Because of the unpredictable nature of some unintended effects, the GMO Panel follows a weight-of-evidence approach that relies on *in planta* [event-specific] data for the assessment of their potential adverse effects on NTOs. This approach relies on data from the molecular, compositional and agronomic/phenotypic analyses of the GM plant itself, as well as data on interactions of the GM plant and its comparator with NTOs. These 'four pillars' of *in planta* data are used by the GMO Panel to assess whether unintended effects in the GM plant occur, and if so, whether they have adverse effects on NTOs.

Louise Ball and Adinda De Schrijver questioned the added value of *in planta* laboratory tests with NTOs as additional source of information. In their view, *in planta* laboratory tests with NTOs (the fourth pillar) will not add to the weight of evidence. They considered that event-specific data at molecular, compositional and phenotypic/agronomic level provide sufficient indication that the genetic modification process *per se* (e.g. through an insertional or positional effect) has not unexpectedly altered the phenotype of the GM plant in a way that is outside the normal variation expected for that plant species. Furthermore, it was questioned whether the current *in planta* tests set-up required by EFSA can answer the question on the occurrence of unintended effects. They concluded that undue emphasis is put on the

assessment of unintended effects, and that such effects should be considered in the frame of post-market environmental monitoring.

Louise Ball also indicated that the discussion on unintended effects is timely, as the EC is currently updating the annexes of Directive 2001/18/EC, using the recommendations outlined in the GMO Panel guidelines for the environmental risk assessment of GM plants.

During the discussion, Louise Ball agreed that unintended effects should be considered in the food/feed and environmental risk assessment, but that the added value of *in planta* laboratory tests with NTOs is debatable.

A delegate from the Netherlands asked whether it is consistent with the case-by-case approach to ask *in planta* laboratory tests with NTOs for all GM plant applications for cultivation on a mandatory basis. Since unintended effects are predominantly event-specific, Joe Perry indicated that data from other transformation events or from similar traits in other plant species will carry little weight in supporting their assessment. A Panel member argued that *in planta* laboratory tests with NTOs are suitable to capture potential unintended changes, and therefore will add to the weight of evidence.

EFSA added that the robustness of *in planta* laboratory tests could be improved by using suitable test materials: a near-isogenic line and reference varieties grown in the same field trial as the GM line. A remaining challenge, however, is whether the standard set of measured endpoints used under laboratory conditions is adequate to capture specific changes in interactions between the GM plant and NTO. Measured endpoints are typically selected on the basis of a proper problem formulation, but this process can be hampered by the unpredictable nature of some unintended effects.

A delegate from the Netherlands commented that unintended effects may arise from conventional breeding as well, not only from genetic modification. Therefore, it is not proportionate to analyse these effects only when assessing GMOs.

5.4. Evaluation of stacked GM events

Esther Kok, a delegate of the Netherlands, gave a talk on the food/feed safety assessment of stacked GM events. GM stacks are obtained by conventional breeding from two or more GM single events. The risk assessment of stacks relies on the finalised risk assessment of the single events, and focuses on the stability of the inserts, expression of the introduced genes and their products, and potential interactions. These aspects were addressed individually. The following points were raised: there is no evidence that genetic stability would be different in the case of GM stacks compared to a cross of a single event with a conventional line; there is no scientific basis to assume that changes in expression levels in a GM stack are different to those in any other type of cross; interactions between GM plant components can take place at two levels - at the level of GM components (i.e. altered components present in the GM plant) and at the level of living cells. Regarding interactions of GM components, it was noted that they are possible also in cases of food and feed containing mixtures of plant components from different single GM events or different conventional lines (interactions between components may also occur in any food or feed mixture). As for interactions at cellular level, it was explained that these are possible also when crossing conventional lines and not limited to GM stacks. The presenter concluded that in the default situation no further food-feed safety assessment of GM stacks should be done. On a case-by-case basis, where there is a scientific reason, further information on the respective stack could be required.

Boet Glandorf, a delegate of the Netherlands, gave a talk on environmental risk assessment of stacked GM events. She indicated that there is a considerable increase in the number of stacked GM events dossiers, and questioned why the risk assessment of the single events should be finalised before the assessment of the stack can start. It was argued that there was no scientific rationale for this approach, and that stacked events can be risk-assessed as long as all necessary information on the single events is included in the dossier. Starting

the assessment of the stack only after the EFSA GMO Panel issues opinions on the single events generates significant delays in the authorization process. Also, the scientific rationale to assess all stacked events was questioned, and it was noted that the assessment of GM stacks should only be done when potential interactions between the traits could be predicted. An example was given for potential synergism between two Bt proteins, in which case additional tests on NTOs could provide useful information.

The presentations were followed by a general discussion. The first comment was made by Joe Perry, who wished to point out that the risk assessment of a GM stack should cover all sub-combinations, as indicated by the EC. For higher stacks, the number of sub-combinations is considerable, so the complexity of the risk assessment increases. One solution for these cases would be toxicological modelling. When assessing interactions, other factors such as crop management should also be taken into account (applicable in the case of a GM stack with insect resistance and herbicide tolerance traits).

To this comment, Esther Kok replied that the GMO Network is a platform for scientists to discuss the scientific basis for the risk assessment. To look only at the very specific interaction between the newly expressed products in the individual GM lines is very arbitrary, in the light of possibly thousands of new interaction in any cross, including a stacked GM event. A stack with both insect resistance and herbicide tolerance will also be sprayed with chemicals other than the intended herbicide, which might lead to other interactions that are not taken into account by the risk assessment, and the discrimination between these interactions specifically, with some receiving more attention than others, is not scientifically justified.

Boet Glandorf added that assessing the impact of crop management measures is not part of the risk assessment, to which Joe Perry replied that the impact of crop management techniques is a part of the environmental risk assessment as stipulated in Directive 2001/18, as it allows the environmental risk assessment to be realistic, taking into account agricultural ecosystems.

A Swedish delegate gave a hypothetical example of a multiple-event stack with only a part of sub-combinations having herbicide-tolerance traits and asked what would be a suitable and realistic crop management for the respective multiple-event stack.

A German delegate commented that the single GM events contain regulatory elements that could interact in the stack, so it is not correct to compare stacking with crossing conventional plants. Esther Kok replied that interactions between all plant products will occur, not only in GM stacks. The German delegate clarified that the promoters present in GM plants are not present in conventional plants, therefore a comparison is not possible, to which the reply was that although interactions between regulatory elements cannot be excluded in either conventional or GM crosses, so far there is no experimental data supporting the existence of any interactions that may affect the food or feed safety.

A Croatian delegate noted that, considering the size of plant genomes and the number and type of possible interactions, it is not feasible to cover all possible scenarios, and the assessment should be realistic.

A Polish delegate pointed to the fact that unintended stacks, obtained from accidental crossings in the field, and sub-combinations of the authorised stacks could be present on the market. To this comment, EFSA replied that the assessment of accidental crosses is not in EFSA's remit, and that the assessment of GM stacks needs to cover sub-combinations because the detection methods currently available do not discriminate between a mixture of single events and a stack containing those events. An EC delegate added to the answer that, in the case of segregating crops, the regulation foresees the assessment of all sub-combinations and that when a GM stack is grown, the harvest will contain all sub-combinations. EFSA clarified that the segregating population was already covered by the

risk assessment, but the current approach is to assess all sub-combinations independently of their origin.

Boet Glandorf asked whether covering the sub-combinations is linked only to the legal provisions, to which EFSA replied that the sub-combinations should be risk-assessed in order to ensure their safety, in case independent breeding lines for sub-combinations would be place on the market. Since the current detection methods cannot discriminate whether a sub-combination is part of a segregating progeny from a higher stack or has been bred independently, the EC wants to ensure that authorisations cover all possible scenarios.

An Italian delegate commented that breeding of conventional lines is linked with even more unknowns than GM stacks. A scenario with a GM event encoding transcription factors or having two regulatory elements affecting the same gene should also be considered.

Esther Kok indicated that there is a lot of variability in interactions and that, in the case of events with altered fatty acid profile, foreseen interactions are assessed, but these are limited. Regarding the detection issue, she indicated that the European Network of GMO Laboratories has established a working group dealing with detection, but developing a method that discriminates between stacks and mixtures of singles is difficult. She replied also to the Italian delegate, clarifying that the transcription factors would be assessed in the context of the single event and that any foreseen interaction between transcription factors will be included in the risk assessment of the respective GM stack, while noting that also in traditional crosses there could be many new combinations of transcription factors.

Joe Perry pointed to the main message of the discussion, that the EC should engage more in scientific discussion with MS experts before initiating regulations. To this, a Belgian delegate added that risk management decision should be based on scientific rationale and pointed to the decision to analyse single GM events before stacks, indicating that it would save time to assess the singles, the stacks and the sub-combinations together.

The EC delegates replied to the Belgian delegate that the regulation IR 503/2013 was discussed with MS, and that the assessment of singles before stacks was decided together with EFSA. They also mentioned that a regulation for environmental risk assessment is under development, and although MS are consulted and all comments are taken into account, it is possible that the outcome would not be in line with each MS opinion.

5.6. Horizontal gene transfer

Andrea Gennaro, scientific officer of the GMO Unit, offered a presentation on horizontal gene transfer (HGT) and the use of bioinformatic tools to determine the sequence homology between the sequences inserted in the GM plant, including flanking regions, and microbial genomes.

A delegate from the Netherlands asked whether it is consistent with the case-by-case approach to ask bioinformatic analyses for HGT for all GM plant applications on a mandatory basis, as HGT should be considered only in case the inserted genes pose an environmental risk. A Finnish delegate also questioned the necessity of bioinformatic data to inform the HGT assessment of GM plants. A delegate from the Netherlands indicated that the focus should not be on homology, as the off-chance of illegitimate recombination should also be taken into account, considering the large numbers of microorganisms in the gastro-intestinal tract. From a risk assessment point-of-view, it should be assumed that recombination is possible, and the possible consequences should be investigated.

EFSA replied that the GMO Panel considers this information necessary to inform the problem formulation phase of the environmental risk assessment. Bioinformatic analyses will enable to accurately identify sequence similarities between the insert and potential receiving microorganisms, and therefore increase the quality of the problem formulation. Based on this information, applicants will be in a better position to formulate precise risk hypotheses and assess the plausibility of HGT scenarios in their environmental risk assessment. DNA

similarity searches will also help to identify the potential microbial recipients and the environment in which they occur. Therefore, bioinformatic analyses searching for sequence homologies between the insert sequence and microbial genomes will be requested systematically in the future, irrespective of the nature of the insert sequences, the plant species or the scope of the GM plant application. A Danish delegate was of the opinion that it would be sufficient to consider the origin of the (trans)gene in a narrative way. In his view, only the genes from bacterial origin may have sufficient sequence identity to be transferred successfully. Since genes from bacterial origin are already present in bacterial populations, he wondered which genes could trigger potential adverse effects. EFSA replied that not only replacement of a gene should be considered, but also deletions and rearrangements in the recipient microorganism. EFSA reiterated that the use of bioinformatic data may be considered more accurate and reliable than the narrative description typically supplied by applicants, which mostly assumes that sequence similarity to microbial genomes will only occur in microbial-derived parts of the insert. However, also for sequences of plant origin one cannot exclude similarity with microbial genome sequences. On the other hand, there is also the possibility that an insert sequence of microbial origin may have been codon-optimised for expression in plants in a way that similarity with a microbial genome sequence does not arise anymore.

A Croatian delegate considered it helpful to identify realistic microbial recipients, but argued that those may be very difficult to transform. He indicated it is difficult to predict whether bacteria are naturally transformable. Moreover, bacteria take up DNA from the environment and only maintain it if it provides a selective advantage. To this comment, a Panel member replied that all plausible HGT scenarios and their consequences should be fully addressed in the environmental risk assessment. It is considered important that all bioinformatic analyses are conducted using up-to-date databases, as the information contained in sequence databases, including the microbial genome databases, is expanding and evolving continuously. Therefore, the GMO Panel advocates the regular update of the similarity search analyses, as is currently expected for any other bioinformatic analysis. An Austrian delegate indicated that transfer of gene fragments is also possible, and that depending on their origin, they may induce a high level variability in the microbial recipients. A Panel member commented that gene transfer from conventional plants to bacteria is also possible, with similar consequences.

5.7. Systematic literature reviews

Elisa Aiassa, scientific officer of the AMU Unit, presented EFSA's activities on systematic review and evidence-based assessments. The presentation addressed the following topics: systematic review (SR) – definition, advantages, steps; use of SR in EFSA generic assessments and evaluation of applications submitted for authorisation of products; EFSA projects on SR, including a project (in preparation), which aims at defining a standardised approach for gathering, validating, analysing and integrating evidence in EFSA assessments.

The presentation was followed by a general discussion. In reply to a question from EFSA on the possibility to perform a rapid SR instead of the full one, it was indicated that performing a full SR is time- and resource-consuming, so prioritisation of questions may be needed at the beginning of an assessment process. EFSA is currently exploring the feasibility of a rapid SR by identifying SR steps that could be simplified. Joe Perry asked how applicants should perform the SR, to which EFSA replied that the Guidance for SR[10] describes how to perform the full process, while an external report published by EFSA in 2012[11] illustrates the advantages and disadvantages of both types of reviews.

[10] European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010; 8(6):1637. [90 pp.]. doi:10.2903/j.efsa.2010.1637.
[11] O'Connor AM, Lovei GL, Eales J, Frampton GK, Glanville J, Pullin AS, Sargeant J; Implementation of

A delegate from the Netherlands wondered whether a SR can be performed for a GM event for which little or no information is available in the scientific literature. EFSA replied that scientific panels could provide advice for such specific cases and that the use of reviewing tools other than SR may be advisable under these conditions.

An Irish delegate commented that a system for assessing the quality of peer-reviewed literature would also be useful. EFSA agreed with the comment and indicated that critical appraisal tools to assess scientific studies are under development.

6. Any Other Business

6.1. EFSA's RNAi workshop

Matthew Ramon, scientific officer of the GMO Unit, presented the scientific programme and objectives of the forthcoming workshop, entitled "Risk assessment considerations for RNAi-based GM plants" (4-5 June 2014; Brussels, Belgium). The objective of the workshop is to solicit scientific expertise for the problem formulation phase of the risk assessment of RNAi-based GM plants. The workshop is composed of three plenary sessions, in which the molecular biology of RNAi, RNAi-based GM plant applications and general risk assessment aspects will be considered, and three break-out sessions, during which selected issues of the risk assessment of RNAi-based GM plants will be discussed. Each of the break-out groups will focus on one of the three main areas of GM plant risk assessment: molecular characterisation; food/feed risk assessment; and environmental risk assessment.

6.2. Guest Scientist and Staff Exchange scheme

Jeffrey Moon, scientific officer of the AFSCO Unit, presented EFSA's Guest Scientist and Staff Exchange programme. This programme aims to facilitate the scientific cooperation and knowledge sharing with MS organisations[12].

6.3. GMO Panel renewal

Elisabeth Waigmann informed the GMO Network that EFSA has launched a call for experts interested in joining the GMO Panel.

6.4. Expert database

The GMO Network members were informed that the EFSA Expert database is used as a tool to select experts to contribute to EFSA's risk assessment activities.

6.5. Open procurement and grants

The GMO Network members were informed about the upcoming framework contracts on statistics and toxicological assessment.

7. Next meeting(s)

EFSA proposed to have the next GMO Network meeting in May 2015. The date will be communicated to the GMO Network members in the beginning of 2015.

systematic reviews in EFSA scientific outputs workflow. Supporting Publications 2012:EN-367 [36 pp.].

[12] http://www.efsa.europa.eu/en/supporting/pub/567e.htm