European Food Safety Authority

GMO UNIT

Minutes of the 1st Meeting of the EFSA Scientific Network for Risk Assessment of GMOs[1]

held in Parma, on 22 & 23 November 2010

European Food Safety Authority[2] (EFSA), Parma, Italy

This report reflects the discussion and comments made at this meeting. This report has been agreed by EFSA and the Member States attending the meeting. This report is not, and cannot be regarded as, representing the position, the views or the policy of the European Food Safety Authority or of any national or EU Institution, agency or body.

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[1] Question No EFSA-Q-2010-01188
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PARTICIPANTS

EFSA received from 24 EU Member States and Norway through its Advisory Forum nominations of Member Organisations for the GMO Network in the area of food/feed safety and/or environmental risk assessment. In addition, other European countries and Candidate Countries were invited to nominate Member Organisations (see http://www.efsa.europa.eu/en/gmo/gmonetworks.htm). The GMO Network Member Organisations appointed 57 experts as representatives (and alternates) to attend the meeting. A list with the 41 participating Member State experts and observers is published as Appendix 1 to these minutes. The meeting was chaired by Per Bergman, Head of the EFSA GMO Unit.

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1. WELCOME BY RIITTA MAIJALA

Riitta Maijala, Director of the EFSA Risk Assessment Directorate, opened the meeting by welcoming the participants to this new EFSA Scientific Network for risk assessment of GMOs (hereafter referred to as "GMO Network"). Networks are established for all sectors of EFSA to provide a forum for MS experts to meet once a year, to discuss and harmonise risk assessment practices and methodologies and to exchange information. She thanked the Member State experts for their support in building the scientific agenda.

This GMO Network is complementary to the already established EFSA GMO Extranet, which is the network for working on GMO applications with all EU Member States experts as foreseen in the EU legislation. Other ongoing EFSA activities involving Member States are the public consultations as well as dedicated Member States consultation meetings on Guidance Documents, regular meetings with lead Member States in charge of the initial evaluation of environmental risk assessment (ERA) of GM plant applications for cultivation, technical meetings with Member States in case of diverging views, and GMO Advisory Forum meetings.

Upon introducing the establishment of EFSA as laid down in the general food law, EFSA's mandate for risk assessment and the role of its respective Scientific Panels, she welcomed the Chair of the EFSA GMO Panel, Harry Kuiper, four other GMO panel members and one *ad hoc* expert of the ERA Working Group who were invited as hearing experts in order to link the discussions in the GMO Network with the work of the EFSA GMO Panel. The European Commission (EC) DG SANCO was welcomed as observer to this meeting, underlining the importance of the link between risk assessment and risk management.

She thanked all participants for joining the meeting and wished for a constructive science-based discussion.

2. TOUR DE TABLE AND APOLOGIES FOR ABSENCE

All participants presented themselves, their background and affiliation during a tour de table. Apologies for absence are recorded in Appendix 1.

3. ADOPTION OF THE AGENDA

The draft agenda was built after reception and grouping of discussion topics proposed by the Member States experts, and published before the meeting. The draft agenda was adopted without modification. See http://www.efsa.europa.eu/en/events/event/gmo101122.htm.

4. DECLARATIONS OF INTEREST

Representatives of the organisational members of the GMO Network and their alternates were asked to fill in an Annual Declaration of interest (ADoI) to declare any interest that might be considered prejudicial to their independence. In accordance with EFSA's Policy on Declarations of Interests, EFSA screened the received ADoIs. Since representatives of the GMO Network are nominated by Member States, no conflicts of interests are expected for the nature of the activities of the GMO Network.

In accordance with the EFSA management board decision on the rules and procedures of EFSA Networks, the representatives of the organisational members of the GMO Network, their alternates, observers, staff of the European Commission were requested orally to declare any interests that might be prejudicial to their independence in relation to the items on the agenda. With regard to this meeting no other interests than those already declared in the ADoIs and screened by EFSA in accordance with its Policy on Declarations of Interests and implementing documents thereof, were declared by the experts.

5. MINUTES OF THE MEETING

Technical views expressed at the meeting are recorded in these minutes and have been subjected to a review by the intervening participant. The minutes of the meeting will be published on the following EFSA website: http://www.efsa.europa.eu/en/events/event/gmo101122.htm.

6. BACKGROUND AND SCIENTIFIC SCOPE OF THE GMO NETWORK

Risk assessors from EU Member States are offered this forum to discuss technical and science-based topics with each other. The rules for all EFSA Networks are laid down in the EFSA Management board decision http://www.efsa.europa.eu/en/scdocs/doc/panelnetworksrop.pdf. Enhanced cooperation between scientists is envisaged to discuss and harmonise the risk assessment practices and methodologies. The nominated National Member Organisations have a three-year mandate.

7. DISCUSSION & FEEDBACK FROM MS ON THE ESTABLISHMENT OF THE GMO NETWORK

The Dutch delegate asked for clarifications on the role of EFSA in the discussions among Member States in the GMO Network meetings and in the follow-up to this type of meetings. The Chair acknowledged that discussion should indeed take place among Member States and clarified that EFSA and the invited experts from its GMO Panel and ERA Working Group participate to the meeting for further assistance to express the views of the GMO Panel if so required by the Member States. EFSA will give a complete report of the meeting to the GMO Panel. The presence of GMO Panel experts is another way to secure feedback to the whole EFSA GMO Panel.

Regarding the discussion format in GMO Network meetings, the Finnish delegate was of the opinion that work in smaller groups is likely to achieve better results. On the other hand, the German delegate questioned the separation in two ERA and FF break-out sessions (see below), since some discussion topics (e.g. Novel techniques) are relevant to both groups and should be considered in a common plenary session. She also made the remark that in risk assessment the Molecular Characterisation, Food/Feed safety and Environmental safety are not separated but linked to each other.

The Chair reminded that each break-out group will report in a plenary session and took note of these remarks for the organisation of future meetings of the GMO Network. He also mentioned the available electronic tools for discussions: e.g. the secured Sciencenet to reach the whole Network or the option to use contact details for continued interactions as deemed appropriate.

8. BREAK-OUT SESSIONS

The Chair introduced the break-out sessions organised on the basis of topics proposed by the Member States: one on ERA with the appointed national experts for ERA and one on Molecular Characterisation (MC) and Food/Feed safety (FF) topics with the appointed experts for MC/FF. Each respective group addressed four topics. Per Bergman, Head of the EFSA GMO Unit, chaired the MC/FF break-out sessions. Elisabeth Waigmann, Deputy Head of the EFSA GMO Unit, chaired the ENV break-out session.

The Chair explained that those Member States who proposed the topic will introduce the discussion and all participants are expected to present their views. For each topic one or two Member States accepted to act as rapporteur and to present the summary of the discussion to the full forum of the GMO Network during the plenary session.

The Chair of the EFSA GMO Panel, recalled that the Panel produced a number of Guidance Documents (GD) (e.g. on Environmental Risk Assessment and Food/Feed safety) and that Member States were given the opportunity to comment on those documents during the drafting process. In the context of the present meeting, the EFSA GMO Panel is very keen to listen to the risk assessment experience from the national experts and to hear their views as regards new developments, challenges and upcoming issues in the framework of the GMOs risk assessment.

8.1. MC/FF Break-out session A - Risk assessment of stacked events

- *What is the appropriate approach to assess stacked events?*

The Hungarian delegate, MS rapporteur of this discussion, opened the session by stating that risk assessment of stacked events can not be made on the basis of the single events alone. The Danish delegate commented that so far no application for stacked events has been assessed solely on the basis of using such additive approach of the single events although it can be scientific justified to do this, and underlined that the genetic background into which the GM event can be introduced after approval, may also influence gene expression levels and this is (or should be) part of the risk assessment. The Dutch delegate agreed on this potential influence and confirmed that in practice the same GM event is crossed into different conventional varieties, which have a history of safe use.

Two EFSA GMO Panel experts explained that the 2007 EFSA Guidance Document for the "risk assessment of genetically modified plants containing stacked transformation events" (http://www.efsa.europa.eu/en/scdocs/doc/512.pdf) laid out a weight-of-evidence strategy to assess stacked events that are combined by conventional breeding for FF uses, import and processing. First of all, the risk assessment of the single events is the pre-requisite for that of the stacked events. Secondly, the risk assessment of stacked events focuses on 1) intactness and stability of the inserted events, 2) protein expression level in the stack versus that in its single events to identify potential interaction between newly expressed proteins, 3) targeted compositional analysis and agronomic and phenotypic characterisation as first step to identify potential interactions between the single events. Thirdly, if the outcome of the molecular characterisation and comparative analysis give rise to indications for potential interactions, the applicants are requested to evaluate the safety impacts on human and animal health.

The Hungarian delegate expressed the view that unintended effects cannot be identified without gaining actual experimental data for every event.

The Polish delegate, expressed that the case-by-case approach is valid for stacked events and that the safety assessment of the single events is important before assessing the safety of the stacked event. The complexity of risk assessment of stacked events may increase with the number of single events assembled into the stack.

- *Are toxicology tests always needed to assess stacked events?*

The Hungarian delegate remarked that toxicology tests presented in applications are usually performed with bacterial recombinant proteins and is of the opinion that these do not represent fully the properties of the proteins produced by the plant. She specified that microbially produced Bt toxins are inactive pro-toxins, which degrade in the pest gut, but transgenic Bt toxins produced by the plant are active toxins which degrade in a test tube faster than in the soil. Secondly, the delegate claimed that toxicology tests are not always performed on the stacked events to support the safety conclusion. Thirdly, the delegate suggested that in case of Bt proteins, more examination of the mammalian gut tissues must be performed to exclude potential binding of Bt proteins. In this respect, the delegate was of the opinion that *in vitro* degradation tests do not fully represent *in vivo* situations. As explained by the Panel representatives the weight-of-evidence approach would require further toxicity studies (among them animal feeding studies) only if there is any indication from the MC and comparative analysis. So far, data provided by applicants and also described in the scientific literature did not indicate potential binding of Bt proteins to mammalian intestine, and the Panel therefore does not see the usefulness of

such tests. If the genetic modification alters the metabolic pathway of a plant, the Panel would certainly consider animal feeding studies.

The issue of whether animal feeding studies with whole GM food are always needed to assess stacked events is also linked to the question how to address uncertainty. Uncertainty analysis, including identification and quantification of uncertainties, is an essential part of the RA. Quantification of uncertainties can be challenging. At EFSA, work is in progress to harmonize the expression of uncertainties.

A GMO Panel expert gave an example of a stacked event where the Panel requested a 28-day toxicity study with two proteins derived from separate single events administrated together, because the proteins expressed in this maize act in concert. The French delegate was of the opinion that in case of suspected interaction, a 28-day study with two pure proteins ingested together is not informative enough and can not reflect an adverse *in vivo* interaction between the two proteins. A 90-day study with whole food seems to be more appropriate. Upon the question whether the EFSA GMO Panel considers the actual dose of proteins that are expressed in stacked events, it was explained that the applicants provide RA using exposure estimated under worst case scenario and that intake levels are derived from the FAO database. In addition, the results of the digestibility test in simulated gastric and/or intestinal fluid are taken into account, as well as safety margins of exposure. So far in none of the applications the margin of safety has been exceeded.

- *Risk assessment endpoints for stacked events*

The French delegate underlined the importance of assessing potential DNA interaction of different events, the stability of inserted sequences, and chromosomal location of individual inserted sequences since inserts located on different chromosomes have less probability for interaction. The delegate questioned how to assess the synergistic effects in the case of stacked events expressing eight newly expressed proteins. The Czech Republic delegate, added that the copy number of the inserted gene is another important MC RA criterion. An EFSA GMO Panel expert agreed that copy numbers are considered; at the same time pointing out that a single event containing more than one copy of a transgene is rare amongst the applications received. If a GM plant would contain for example five copies of the same transgene, the EFSA GMO Panel would check whether all copies are intact and verify the segregation pattern of these five copies.

- *Summary*

In summary, all Member States experts agreed that the assessment of possible interactions between stacked events shall be the focus. Some risk assessment endpoints for stacked events were proposed. Divergent views were expressed during the discussion concerning the amount of data needed for assessment, in particular, with respect to animal feeding studies. Most of the MS experts found the case-by-case approach to be valid, meaning that it depends on the nature of the single events. One MS delegate felt that more data, in particular animal feeding studies with whole food, should always be required.

8.2. MC/FF Break-out session B – New techniques

The Finnish delegate, the MS rapporteur for this discussion, introduced some of the new techniques developed to make small but permanent changes in the genome (e.g. using Zinc finger nuclease 1 and 2, oligonucleotide-directed mutagenesis) or epigenetic changes (DNA-methylation by RNAi). These mutation-like changes do not involve permanent introduction or insertion of foreign DNA elements into the genome and are similar to spontaneous mutations frequently (on a global scale) occurring in nature or induced in conventional agricultural/breeding environments. The question if some of these techniques should be covered by GMO legislation or be excluded from Directive 2001/18/EC is being discussed in an EC-MS Working Group. While this work is still ongoing, the question can be raised if the EFSA guidance would need adjustment to be able to assess plants produced using such techniques.

The Italian delegate introduced the topic of cisgenesis mentioning that plants obtained using cisgenesis seem to have more consumer acceptance than transgenic plants. Also for this technique the question arose if it should fall under GMO legislation; if that were the case, data requirements for risk assessment would include the position of the insert in the genome and the expression level of the cisgene.

The French delegate pointed out two distinguishable categories, one where a transgene intermediate is used but is not present in the final plant and one where mutations are created without transgene intermediate. In the first case, the risk assessment should take into account the transient modification of the genome.

The delegate from the Netherlands referred to two reports on cisgenesis (one from COGEM[3] and one from RIKILT[4]. It has proven difficult to define clearly cisgenesis and the conclusions of the authors were that the endpoints/end product should be considered. Another key point to consider is if the gene comes from a plant already present in the food chain or not. It might be possible to create cisgenic plants almost identical to plants obtained via conventional breeding but without the lineage drag. The question remains whether these plants should be treated differently from conventionally bred plants.

Different Member States delegates indicated that the current EFSA guidance document on GM plants might be applicable to cisgenic plants as the case-by-case approach takes into account the origin of the introduced gene. As this discussion led to reflections on plants obtained via conventional breeding and their safety aspects, it triggered the question if legislation should be product or process based.

The EC representative reminded that before 2003 the novel food legislation which is a product based legislation was applicable for GMOs. The approach changed in 2003 when the Regulation (EC) No 1829/2003 came into force. For the EC it is important that RA is always proportionate to scientific concern regarding the product in question.

8.3. MC/FF Break-out session C – Animal tests for GMO risk assessment

- *Data quality of 90-day animal feeding studies in the dossiers*

In April 2009 the French Agence nationale de sécurité sanitaire (ANSES) started a self-task with the objective to adapt the OECD protocol 408 to become more useful for the potential toxicity assessment of GMOs. The French delegate, MS rapporteur of this discussion, informed that after comparing the 28-day, the 90-day and 6-month feeding studies, the 90-day rodent feeding study was selected as the "sentinel study" for assessment of potential unintended adverse effects of the whole food. ANSES also concluded that the 6-month feeding study doesn't bring additional pertinent information compared to the 90-day feeding study. Furthermore, from November 2009 till the end of 2010, ANSES worked in the frame of another self-task on the advantages and limitations of several statistical models for an application to the data of a 90-day rodent feeding studies. Many interesting details of both ANSES activities (including selection of test animals, endpoints and diets, etc.) were presented. Publication of the ANSES reports is envisaged for the near future. The Hungarian delegate supported this work of ANSES and made further suggestions for more endpoints, one more control diet, the young age at the start of the experiment and less difference in the initial weight of the test animals, the necropsy should be supplemented by histological studies on key organs, and the normalization of data by dry weight of an organ. The Austrian delegate remarked that both genders should be used in an animal study. The Finnish delegate asked whether the ANSES adaptations of the OECD protocol 408 would distinguish

[3] "Signalering 'Vereenvoudiging van regelgeving bij cisgenese, een reële optie?'" COGEM report CGM/060428-05 (2006) http://www.cogem.net/ContentFiles/CGM%20060428-"05%20Signalering%20cisgenese%20vereenvoudiging%20regelgeving.pdf

[4] "Food and feed safety aspects of cisgenic crop plant varieties" by T.W. Prins and E.J. Kok, RIKILT report 2010.01, RIKILT-Institute of Food Safety, Wageningen University and Research Centre, Wageningen, The Netherlands, http://www.rikilt.wur.nl/NR/rdonlyres/BDEEDD31-F58C-47EB-A0AA-23CB9956CE18/121352/R2010001.pdf

novel food RA from GMO food RA and the French delegate clarified that the revised protocol will be applicable to both types of food in theory but the Working Group concentrated their work on 90 days feeding studies used for safety GMO assessment.

The use of commercial varieties to set the equivalence limit was questioned by the Hungarian delegate in light of the so called "dilution effect". The EFSA GMO Panel explained that the commercial varieties are grown under the same environmental conditions as the GM plant in order to provide reference for the natural variability. Regarding the testing of even higher numbers of commercial varieties in animals (e.g. 7-8), an EFSA GMO Panel expert said the intention is to stimulate applicants to use background historical data that can save unnecessary killing of animals. The Working Group experts of ANSES are still undecided whether to include commercial varieties into the 90 day animal feeding study: six commercial varieties would use more animals and it may be better to allocate these animals to the GMO and control groups.

To address the question of the Belgian delegate as to why poorly designed toxicology tests are often accepted in the applications, the Chair of the break-out session explained that applicants submit data which they believe are necessary for the risk assessment. Poor quality data may be readily identified (e.g. "cut and paste" lanes in a southern blot) and the application would be stopped during the completeness check. Other cases of insufficient quality may be hard to spot during the completeness check or complex (e.g. inadequate design of a toxicology test), and the EFSA GMO Panel would ask the applicants to improve or reanalyze such data during the course of risk assessment. The Finnish delegate agreed that there is room for better study design and statistical analysis of a 90-day study in order to reduce uncertainty. Tests designed for cancer research are not necessarily applicable to GMO food. The French delegate reminded that the importance of better experimental design led to the set up of two ANSES self-tasks. Also the European Commission delegate informed that at international level (under the Codex *alimentarius*), some MS are of the opinion that testing whole GMOs is difficult and better guidance is needed, while other MS are not in favour of performing such type of experiments. This led the EC to give a mandate to EFSA to design a proper 90-day test protocol and possibly harmonize current practises. The EC delegate urged for good collaboration between ANSES and EFSA to co-ordinate the timing of the publications and to ensure no confusing message are given to the scientific communities. This was agreed by both the French delegate and an EFSA GMO Panel expert, who confirmed that the Chair of the ANSES Working Group is part of the EFSA Working Group. This ensures proper information exchange. Further meetings between the ANSES and EFSA experts are envisaged. The EFSA GMO Panel expert informed the Network on the progress of the EFSA WG on the 90-day protocol, focused on harmonizing diet preparation, number of animals etc. He expressed some reservation as to the possible expectations for improving the test's sensitivity by using different statistical methods.

- *Is the 90-day study necessary for risk assessment?*

The Irish delegate recalled that the same discussion on the necessity of a 90-day study a few years ago[5] resulted in requesting a 90-day study only when necessary. This is reflected in the EFSA Guidance Document, confirmed the Chair of the session. The Irish delegate asked where the MS stand today and how they perceive the usefulness of such analysis.

The Danish delegate pointed out the many steps in risk assessment prior to the animal tests and while in reality a 90-day study was never needed or asked for, such a study is often provided by the applicants. The French delegate responded that often a 90-day study in applications gives reassurance and gave an example of a particular case where differences in chemical composition were found during the

[5] See the "Special meeting of the EFSA Advisory Forum on GMO risk assessment in Europe" - 13 November 2007 , Brussels http://www.efsa.europa.eu/en/events/event/af071113.htm

compositional analysis. The Dutch delegate said the outcome of the comparative analysis leads the EFSA GMO Panel to decide whether an animal feeding study with whole GM food is needed. She requested EFSA to indicate in the scientific opinions which data are used for core evaluation and which are not necessary. An EFSA GMO Panel expert confirmed that it is mentioned in the scientific opinion when a study was considered not necessary.

The French delegate informed that discussions within France had led to the following view: The French scientists would ask for a 90-day study for any new GM single event, because this is the only toxicity study using whole food. It would reduce uncertainty (unintended adverse effect). It may not be necessary for stacked events if its single events are assessed by 90-day animal feeding studies.

The German delegate supported the case-by-case approach since data generated from MC and compositional analyses often suffice to conclude on the safety of a GMO. In these cases animal tests have so far provided little additional information. Only if there is a strong indication, studies on hormonal activity and carcinogenesis should be performed.

The Hungarian delegate commented that a plant is comprised of millions of compounds, and therefore it would be easier to set up a test diet using the whole plant. Overall, a 90-day test is more adequate to test whole food.

- *Animal models for other purposes*

The Hungarian delegate remained of the opinion that 90-day study should be mandatory both for single and all stacked events although alternative testing models exist. Furthermore the delegate mentioned that other type of animal tests (toxicology, nutrition, reproduction, cancer, allergy, hormonal effects) may also be considered for GMO risk assessment. The Czech Republic delegate mentioned a guinea pig intratracheal test used to set occupational operating guidelines for new enzymes used in the detergent industry.

Two EFSA GMO Panel experts mentioned animal testing models for allergenicity were taken into account in the 2010 allergenicity report of the Panel, although these tests are not yet validated for risk assessment purposes. One needs to bear in mind that none of these test *per se* gives absolute proof and that only all the evidence taken together allows reaching a conclusion.

- *Summary*

In summary, this breakout session addressed the necessity of a 90-day animal feeding study and the data quality of 90-day animal feeding studies in the dossier. Several MS brought forward that a 90-day animal feeding study may be required on a case-by-case basis only if the MC and/or comparative analysis on composition and agronomic and phenotypic traits indicate differences that require a further safety assessment answer trough animal testing. One MS further specified that in practice a 90-day animal feeding study shall be mandatory in case of a new single event. Another MS considered that the 90 day animal feeding study should be mandatory in all cases. Regarding data quality, the common view was that good experimental design is necessary and should be communicated to the applicants. Work on this aspect is ongoing in ANSES and EFSA and the Chair confirmed that collaboration between the two organizations is ongoing and will be further promoted. Animal models for other purposes were also discussed.

8.4. MC/FF Break-out session D – Exposure and novel traits assessment

The Belgian delegate, MS rapporteur for this discussion, raised the specific issues of the level of details in fibre analyses and if both soluble and insoluble fibres should be analysed. These issues, originally identified by the Belgian national experts, are now discussed internationally at the OECD. The Belgian delegate enquired if the EFSA GMO Panel would already act at this moment to ask the applicant for

more fibre analyses. An EFSA GMO Panel expert informed that the EFSA GMO Panel did not plan to include these details in its upcoming 2011 guidance document, but follows the developments in OECD closely.

Regarding novel traits (e.g. nutritionally enhanced plants), the Hungarian delegate raised the issue of specific animal feeding studies, stating that there is a need to develop specific tests to assess novel traits, and said the requirement for nutritional studies should be carefully considered. She also considered that when agronomic traits have been changed, the chemicals applied on plants should be assessed in the food as well. Participants held different views regarding the necessity of animal feeding studies: some were of the opinion that animal feeding studies with whole GM food for toxicity and nutrition should be required in all cases, while other MS preferred the weight of evidence and case-by-case approach.

The Italian delegate introduced the concept of post-marketing monitoring (PMM), in order to complement the studies in the pre-market risk assessments, with analysis of long term effects (e.g. immunological impact considering the diversity of animals fed with GM feed). In the EU, the consumption of GM food processed products is quite rare or absent at all and in addition, an Italian study has not shown that there would be transfer of genetically modified DNA from the GM plants into the animal milk. Therefore it can be concluded that PMM studies for consumers are not needed at this moment.

The Hungarian representative added that reproductive studies are useful. In mammals the egg cells are already formed during the development of the mother in the womb of the grandmother. That is why Hungary advocates analysis of possible effects in animal models with a short life cycle.

The EC representative stated that PMM is only performed on a case-by-case basis and it is not compulsory. Only if a hazard has been identified PMM might be required. For feed it would be useful but challenging to assess the impact of GM feed.

An EFSA GMO Panel expert stated that uncertainties related to toxic effects should be primarily addressed pre-market and not post-market. Animal models should be used when there is uncertainty. For allergenicity PMM can be useful because also for conventional food (such as kiwi) allergenic reactions in the population have been identified soon after introduction. Furthermore, he indicated that various data sets on different animal species fed with GMOs are available.

8.5. ENV Break-out session A - Risk assessment of stacked events

- *Interactions and sub-combinations*

The topic of assessing potential interactions (e.g. synergistic effects of the newly expressed proteins) was shortly introduced by the Polish delegate, MS rapporteur for this discussion. The Danish delegate remarked that the recently published updated EFSA Guidance on the environmental risk assessment of genetically modified plants (GD) as well as recent publications cover this aspect. The topic of sub-combinations was tabled by the German delegate who asked about the rationale behind opinions that include the highest stack as well as sub-combinations with a lower number of events, while data on the protein expressions in such sub-combinations are not always provided or recommended in the applications. The German delegate referred to a draft guidance document on stacked events produced by the *Ad Hoc* Technical Expert Group AHTEG group established in 2008 with decision BS-IV/11 of the Meeting of the Parties to the Cartagena Protocol[6] in Bonn (http://www.cbd.int/doc/meetings/bs/bsrarm-02/official/bsrarm-02-05-en.pdf, see Annex Part II). This Working Group proposed (1) "Assessment of sequence characteristics at the insertion sites and genotypic stability", and (2) "Assessment of potential interactions between combined events (e.g. proteins expression levels influenced by the combination) and the resulting phenotypic effects" and (3) "Assessment of combinatorial and cumulative effects of stacked event LMOs on the sustainable use of biological diversity in the likely receiving environment

[6] The Cartagena Protocol on Biosafety is a Protocol to the Convention on Biological Diversity. It has 162 parties (as of Nov. 2010)

taking also into account potential adverse effects to human health" as supplementary steps of the assessment of stacked events effects.

Upon the question of the Czech Republic delegate about the link between today's discussion and the updated EFSA ERA GD, the EFSA GMO Panel experts welcomed feedback from the Member States on the stacked events section in the 2010 updated ERA Guidance Document. An important element of the described approach is that the RA of single events is a pre-requisite for the RA of stacked events. The current GD furthermore gives details on how to approach the interactions between traits and the potential effects on non-target organisms (NTOs).

The German delegate acknowledged that the updated EFSA ERA GD covers the important aspect of *in planta* data on the stack in addition to data on the single events and emphasized that provision of such data should be mandatory. The Dutch delegate acknowledged that the available molecular characterisation data form the basis to assess potential interactions at a molecular level, but asked about the tools available to assess unexpected interactions between proteins. The French delegate explained that the omics technologies could help to predict possible interactions. An EFSA GMO Panel expert reported that the potential added value of omics to the risk assessment depends on the crop/trait combination.

The British delegate said a case-by-case approach is important with regard to the usefulness of field trial data and no generalisations should be made. She exemplified that there are no volunteers for maize plants. In addition to field trials, RA should also look at scale-up effects.

The Austrian delegate acknowledged that the data requirements in the updated ERA GD have been increased and asked when applicants will be requested to meet these new requirements. The Chair clarified that the updated EFSA guidance documents describe in detail several of the data requirements that the EFSA GMO panel is now currently requesting during the assessment of applications. Examples from the updated ERA GD are some of the requirements for NTO studies, information on farming practices etc.. From the moment in which the ERA GD and FF GD will be transformed in regulatory guidelines, all requirements will be required from applicants on a legal basis.

The Czech delegate expressed a concern in relation to changes in cultivation practices for stacked events compared to the single events and would like to see this issues addressed in a study.

- *Unintended stacks*

An unintended stack is a cross (through pollinating) with other GM cultivars in the field (cultivation of different GMOs in the same area) that may cause unintended effects. The Austrian and Dutch delegates are of the opinion that this is rather a risk management than a risk assessment issue. In addition, the Austrian delegate specified that co-existence rules to be implemented by all EU Member States, should cover this hypothetical scenario. The German delegate however considers potential unintended stacks as part of the ERA and exemplified that the stacking of Bt or HT proteins in conventional cultivars or other crossable relatives might have effects on the environment and should be assessed accordingly. The Dutch delegate asked what risk managers could do in case risk assessors would identify a hazard in relation to an unintended stack. The British delegate reminded that the scale at which such unintended stacks would occur is likely rather low. An EFSA GMO Panel expert reported that the updated ERA GD addresses the issue by requesting from applicants to also take into account GM events that are already or likely to be present in the receiving environment.

8.6. ENV Break-out session B - Impacts on biodiversity, including non-target organisms

- *General on ERA and PMEM*

The Danish delegate raised comments on the assessment of effects of Bt proteins on flora and fauna (e.g. pollinators, butterflies) within and in the surroundings of GM fields. He was of the opinion that impacts of changes in agricultural practices are not properly considered during the ERA (e.g. effects on NTOs) and that this aspect could be covered under PMEM, more particularly under General Surveillance (GS) to detect unanticipated effects. However, in his view, one problem under General Surveillance is the lack of detailed tests for comparing non-GM and GM crops. Furthermore the Danish delegate mentioned tools to reduce possible adverse effects such as non-Bt refuges to delay resistance development in the populations of target pests.

- *Baseline for comparison*

The Polish delegate commented that the comparative analysis for HT or Bt crops use conventional agriculture as a baseline, including treatments with herbicides or insecticides. The Latvian, Italian and Dutch delegates concurred that current 'normal' agricultural practices followed by conventional farmers should be considered as adequate baseline for a proper comparative analysis. The German delegate together with the Hungarian delegate MS rapporteur for this session emphasized the difficulty to define what are "common" agricultural practices considering the specificity of production systems varying from region to region and even from field to field. The Hungarian delegate referred to different agricultural practices (e.g. conventional and organic). The Czech delegate added to the discussion on the definition of the relevant baseline, by saying that farmers use the Bt crop only in environments where the target pest is present. The Spanish delegate reminded about the importance of the case-by-case approach also in this context. In addition, it was highlighted that, for the ERA of soil NTOs, the selection for proper NTOs to be further tested is paramount.

The EFSA GMO Panel experts asked the delegates from Member States how they propose to implement the compulsory Integrated Pest Management plans (as requested latest by 2014 under Directive 2009/128/EEC) as this is relevant to define baselines in the future. The EFSA ERA GD includes information on the choice of relevant baselines and applicants are requested to suggest the appropriate baseline depending on the receiving environments. The use of baselines is also reflected in the upcoming EFSA Guidance Document on the choice of comparators.

- *Data generation under General surveillance*

The Spanish delegate mentioned the difficulty to monitor changes in biodiversity throughout General Surveillance (GS). The Dutch and British delegates considered that GS is the only practical approach available to detect unintended effects on biodiversity in general and acknowledged that this can be a relevant way to obtain data, although mathematical modelling could be an alternative way. The Austrian delegate reminded the difficulty to address long-term effects due to lack of appropriate (i.e. scientific, obtained by standardarized methods) data and linked this to PMEM as the only chance to generate those data. Even if a modelling approach is taken, some data still need to be generated via Case Specific Monitoring (CSM) and/or GS. The Dutch delegate raised the point that, for CSM, NTO species/functional groups to be tested have to be predefined. GS on the other hand aims at monitoring unintended effects, and not at collecting specific data: therefore, GS data will generally lack detail and specificity.

With regard to PMEM the following issues were considered important: the issue of funding; the generation of "independent" PMEM data that cannot be afterwards challenged on the basis of who has produced the data (meaning, produced e.g. by stakeholders with opposite views); cost-effectiveness and causality, linking the effect to the GMO, were considered important. The Austrian delegate called for an

in-depth discussion on the usefulness of data from GS for ERA and the British delegate provided as an example the farmer questionnaires that prove to be useful by looking at plant health and therefore give indications as to the GM plant behaviour and other key functions such as those in the soil. The EFSA GMO Panel experts mentioned that with respect to long-term data it is indeed possible to get fairly simple indicators and that such data are available for other ecosystems. For example, a comprehensive set of data on water ecosystems is available. This information could be found useful and applicable also for agricultural ecosystems.

8.7. ENV Break-out session C - Procedure related to cultivation applications

Due to lack of time, the ENV break-out group decided to not discuss this topic but to focus on the next topic instead: assessment of long-term effects.

8.8. ENV Break-out session D - Assessment of long-term effects

The Danish delegate, MS rapporteur for this discussion together with Austria, introduced the topics for discussion and noted the importance of assessing long-term effects on biodiversity, the duration of field trials (mentioning the minimum of 10 years) to be able to conclude regarding long-term effects. The Hungarian delegate asked for an agreement on what is the meaning and common understanding of "long-term investigations" and noted that the meaning might differ depending on the crop and the cultivation practice. For example, the definition of "long-term" should be different for soybean grown in crop rotation than for maize grown as monoculture year after year. The German delegate recalled considerations for long-term effects usually depend on extrapolation from short-term data. She further stated that modelling of long-term effects could also be an approach but that a standardisation of monitoring data would be needed. The German delegate further recommended for maize the collection of data on the same plot for three consecutive years, and called for further guidance on field data collection (e.g. experimental design of the plots) for other situations.

The Czech delegate mentioned that a clear separation is to be made between what can be done under ERA as regards long-term effects and what can be monitored under PMEM activities. The Danish delegate mentioned that a book of the Danish council on monitoring/general surveillance/long-term effects is available.

The Dutch delegate made a distinction between long-term effects that are likely to occur in the future but difficult to assess and effects that cannot be predicted. The first type of effects would be monitored under CSM while the other type would fall under GS. The Austrian delegate mentioned effects that risk assessors cannot foresee during their ERA and that can only be observed in a long term period. He referred to the annual PMEM reports for GM crops grown in EU as the only source of data, but did not find enough scientific quality in such reports. The German delegate recalled national programmes for biodiversity surveys such as in Switzerland where relevant scientific data are available. The Spanish delegate disagreed about the alleged lack of data from PMEM activities and clarified that in his opinion the key-point is how to connect and harmonise available data. The Austrian delegate acknowledged that some studies exist but these studies cover only partially the need; he called for a more scientific basis in the PMEM reports (e.g. the connection between locations and collection of data) and called for a concerted, science based data collection in the growing areas.

The Dutch and German delegates acknowledged that risk assessors should look at science-based aspects and agreed with the approach of some Member States to use existing networks to collect data in the frame of GS. The German delegate highlighted the need for adaptation in the data collection practices of such networks in order to collect data relevant in the context of GMO cultivation.

EFSA informed that the EC has mandated EFSA to adopt an opinion for cultivated GM crops on the yearly post market environmental monitoring reports.

The EFSA GMO Panel experts explained that unanticipated long-term effects as such are not defined and that a concrete example would help to focus the discussion. The chapter on long-term effects of the

recently published updated ERA GD was less prescriptive than the rest of the document, mostly due to this difficulty, the complexity and specificity of the topic. The updated ERA GD recommends risk assessors to look at the overall natural dynamics of the agro-ecosystems in terms of life cycles and biodiversity. It is found that the baselines are changing substantially in a 5-20 years period due to changes in pesticide use, fertilisers, etc. The difficulty is to predict what the introduction of a GM crop into such a changing receiving environment will trigger some years later, considering the interactions and complex dynamics of the agro-ecosystems. Therefore the updated ERA GD recommends the applicants to look at what drives the dynamics, to look at how the GMO could/would be able to impact on such drivers and to carry out a desk study. The aim of the desk study is to pin-point areas with potential long-term effects and to thus inform the monitoring. One example is to investigate if the genetic modification can change the nitrogen metabolism in the plant. One could then monitor the nitrogen cycle during cultivation of the plant and analyse the data. Data would be needed from 5 to 10 years of experience. Data from the actual cultivation of GMOs within Europe would be informative, but at present the risk managers have to rely on the above described strategy of desk-studies, in most cases.

The Finnish delegate acknowledged the EFSA GMO Panel for showing the way forward and demonstrating that the assessment of long-term effects is possible. Further references to particular study designs would be welcomed.

The Spanish delegate made clear that endpoints for PMEM (GS) could be determined from relevant protection goals. The Dutch delegate remarked that monitoring everything could give a safe feeling, but without clear scientific hypotheses, such monitoring could become useless.

9. PLENARY SESSION: PRESENTATION AND DISCUSSION ON SUMMARIES OF THE BREAK-OUT SESSIONS

All discussions were summarized and presented to all GMO Network participants by the rapporteurs.

Regarding the discussion on new techniques, the Hungarian delegate stressed that also organelle-based transformation techniques should be considered and the Dutch delegate asked if the EFSA GMO Panel plans to update its GD in light of the new techniques. The EC stated that EFSA would be consulted at an appropriate stage, after EC Working Group on new techniques at the JRC has finished its report (estimated beginning of 2011).

Regarding the discussion on animal feeding studies, the German delegate remarked that the control diets could contain GM feed. It was reported that this point has not been raised during the discussion. Regarding the input from the French delegate on the 90-day animal feeding study, it was requested to clarify in which cases the study should be considered mandatory and in which not. The French delegate reported that the 90-day animal feeding study is not always compulsory and that it is possible to conclude a RA without such a study. For example, in case of applications for renewal of authorisation and for stacked events (with a 90-day animal feeding study available for the single events), a 90-day animal feeding study would not be required. However, in the case of new events such a study is considered mandatory from the French point of view.

The Chair of the GMO Panel noticed the numerous different and sometimes opposing views from MS experts and he recalled that this is a long-standing reality which is reflected in different working circles. He underlined the importance for a continuous collaboration between MS, EFSA and the EC. There is clearly a need for more time to further discuss some topics of interest amongst EU risk assessors. He asked how EFSA plans the follow-up to the present meeting. The Chair of the meeting explained that a follow up meeting is already planned and will be shaped according to the feedback from MS experts after this first meeting.

10. GMO RISK COMMUNICATION AT EFSA

Anne-Laure Gassin, Director of the EFSA Communications Directorate, presented the mandate and activities of EFSA on risk communication. Promoting coherence of risk communications is an important goal and priority in EFSA's communication work since the Authority's establishment. EFSA works closely with the national food safety agencies through the Advisory Forum Working Group on Communications, in order to foster broader outreach and consistency of messages disseminated in Member States on risk communications related to EFSA's work.

The results of the latest Eurobarometer report 2010 on food-related risks were presented including: the different risk perceptions in different EU countries; the ranking of top food concerns in each country; the position of GMO as a middle-ranked concern in most countries (except in Austria where it is the top concern along with pesticides); trust in information sources on food safety issues; and perception of the role of public authorities in protecting consumers from food-related risks.

EFSA will continue proactive dialogue and communications on its work and on GMOs. In this area, ongoing efforts are needed to continue to build understanding for EFSA's role in the authorisation process and risk assessment advice. Openness, transparency and dialogue contribute to building trust and understanding of how EFSA ensures the independence of its scientific advice. Working closely with Member States and in dialogue with stakeholders, EFSA will pursue efforts to increase outreach of EFSA's advice to the scientific community, informed lay audiences and all interested parties.

11. AOB

The nominated experts to the GMO Network and their alternates have been granted access to the Information Exchange Platform to facilitate information exchange among Member States (e.g. opinions, guidance documents, technical reports, risk assessments).

Public consultations are ongoing on draft guidance documents prepared by EFSA. Member States are invited to actively provide feedback through the online consultation on the guidance on selection of comparators and the guidance on the risk assessment of GM microorganisms (http://www.efsa.europa.eu/en/calls/consultations.htm).

EFSA called for lead Member States volunteering to carry out the initial Environmental Risk Assessment of GM crops for cultivation as required by Regulation (EC) No 1829/2003. A collaboration between MS would be accepted.

12. CLOSING OF THE MEETING

The Chair of the meeting summarised that some discussions reveal the current contrasting views, for example on the framing of GS and on animal feeding studies. At this inaugural meeting MS were involved in building the agenda, and EFSA was asked to coordinate future discussion on ongoing topics with MS. The whole EFSA GMO Panel will be made aware of the discussions at the GMO Network meeting.

He thanked all participants for the constructive discussion and closed the meeting.

APPENDIX 1 - LIST OF PARTICIPANTS

	Appointed experts of EU Member States, other EU countries and Candidate Countries			
1	Adinda de Schrijver	BE	ERA	Apologies
2	Akar Taner	TR		Apologies
3	Alenka Zupancic	SI	FF	Present
4	Andreas Heissenberger	AT	ERA	Present
5	Anke Meisner	DE	FF	Present
6	Arne Mikalsen	NO	FF	Present
7	Barnabas Jenes	HU	FF	Present
8	Beatrix Tappeser	DE	ERA	Present
9	Boet Glandorf	NL	ERA	Present
10	Carlo Brera	IT	FF	Present
11	Carmen Cuadrado	ES	FF	Present
12	Chantal Arar	FR	FF	Present
13	Dimitar Djilianov	BG	ERA	Present
14	Esther Kok	NL	FF	Present
15	Felix Ortego	ES	ERA	Present
16	Frank van der Wilk	NL	FF	Apologies
17	Gosta Kjellsson	DK	ERA	Present
18	Indrikis Muiznieks	LV	ERA	Present
19	Ingrid Busuttil	MT	FF	Present
20	Jan Pedersen	DK	FF	Present
21	Joseph Abela Medici	MT	ERA	Present
22	Jozef Timko	SK	FF	Present
23	Kimmo Peltonen	FI	FF	Present
24	Liina Eek	EE	ERA	Present
25	Louise Ball	UK	ERA	Present
26	Maili Vodi	EE	FF	Present
27	Margarita Karavangeli	EL	FF	Present
28	Markus Woegerbauer	AT	FF	Present
29	Martin Batic	SI	ERA	Present
30	Massimo Delledonne	IT	ERA	Present
31	Matti Sarvas	FI	FF-ERA	Present
32	Merethe Aasmo Finne	NO	ERA	Apologies
33	Patrick O'Mahony	IE	FF	Present
34	Patrick Saindrenan	FR	ERA	Present
35	Petr Hanák	CZ	FF	Present
36	Philippe Herman	BE	FF	Present
37	Odeta Pivoriene	LT	ERA	Present
38	Sandy Lawrie	UK	FF	Apologies
39	Sanja Milos	HR	FF	Present
40	Slawomir Sowa	PL	FF	Present
41	Sonja Kushevska	MKD	FF	Present
42	Staffan Eklöf	SE	ERA	Apologies
43	Tom Mcloughlin	IE	ERA	Apologies
44	Tzveta Georgieva	BG	FF	Present
45	Vaclovas Jurgelevicius	LT	FF	Present
46	Zbigniew Dąbrowski	PL	ERA	Present
47	Zsuzsanna Bardocz	HU	FF	Present
48	Zuzana Doubkova	CZ	ERA	Present

Observers		
1	Sabine Pellser DGSANCO	Present
2	Sebastien Goux DGSANCO	Present
EFSA GMO Panel Members		Presence
1	Gijs Kleter	Present
2	Geoff Squire (*ad hoc* expert)	Present
3	Harry Kuiper	Present
4	Huw Jones	Present
5	Joe Perry	Present
6	Jozsef Kiss	Present 22 Nov
EFSA GMO Unit		
1	Elisabeth Waigmann	Present
2	Karine Lheureux	Present
3	Nancy Podevin	Present
4	Per Bergman	Present
5	Reinhilde Schoonjans	Present
6	Riitta Maijala	Present
7	Sylvie Mestdagh	Present
8	Yi Liu	Present

LIST OF ABBREVIATIONS USED

Bt : *Bacillus thuringiensis*
CSM : Case-Specific Monitoring
EC : European Commission
EFSA : European Food Safety Authority
ENV : Environment
ERA : Environmental Risk Assessment
ERA GD : Environmental Risk Assessment Guidance Document on GM plants for Applicants
EU : European Union
FF : Food and Feed safety
GD : Guidance Document for applicants
GM : Genetically Modified
GMO : Genetically Modified Organism
GS : General Surveillance
HT : Herbicide-Tolerant
NTO : Non-Target Organism
MC : Molecular characterisation
MS : Member States
OECD : Organisation for Economic Co-operation and Development
PMEM : Post-Market Environmental Monitoring
RA : Risk Assessment
RM : Risk management
WG : Working Group