Network for Risk Assessment of GMOs

Minutes of the 4th meeting

Held on 22-23 May, 2013, Parma
(Agreed on 30 September 2013)

Participants

- **Network Representatives of Member States:**

Country	Name	Country	Name
Austria	Eva Claudia Lang, Markus Woegerbauer	Italy	Massimo Delledonne Roberta Onori
Belgium	Adinda De Schrijver	Latvia	Indrikis Muiznieks
Bulgaria	Tzveta Georgieva	Lithuania	Mindaguas Morkunas, Odeta Pivoriene
Czech Republic	Miloslava Navratilova	Malta	Flavia Zammit
Denmark	Jan Pedersen	Netherlands	Boet Glandorf
Estonia	Andres Mae	Norway	Arne Mikalsen
Finland	Matti Sarvas	Poland	Zbigniew Dabrowski, Slawomir Sowa
France	Catherine Golstein, Joel Guillemain	Slovakia	Hana Drahovska
Germany	Andrea Scheepers, Beatrix Tappeser	Slovenia	Martin Batic
Greece	Dionyssia Stefanitsi	Spain	Carmen Cuadrado
Hungary	Zsuzsanna Bardocz, Barnabas Jenes	United Kingdom	Louise Ball
Ireland	Patrick O'Mahony Thomas McLoughlin		

- **Panel Members**
  - GMO: Salvatore Arpaia, Andrew Chesson, Gijs Kleter, Hanspeter Naegeli, Joe Perry.
  - ANS: Dominique Parent-Massin (for item 5.4).
  - Scientific Committee: Robert Luttik (for item 5.3.b).
- **Hearing Experts**
  - Harry Kuiper (for item 5.3.a), Fern Wickson (for item 5.3.b).

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- **European Commission:**
  - Joachim Bollmann
- **EFSA:**
  - GMO Unit: Jaime Aguilera, Hermann Broll, Anna Christodoulidou, Yann Devos, Andrea Gennaro, Yi Liu, Sylvie Mestdagh, Claudia Paoletti (Deputy HoU, co-Chair), Irina Olaru, Elisabeth Waigmann (Acting HoU, Chair).
  - Scientific Committee and Emerging Risks Unit: Andrea Germini.
  - Pesticides Unit: Maria Arena

- **Delegates from EU pre-accession countries**

Country	Name
Bosnia and Herzegovina	Armin Colakovic
Croatia	Sania Milos
Former Yugoslavian Republic of Macedonia	Suzana Popovska
Montenegro	Ervin Bucan
Serbia	Dragana Miladinovic
Kosovo	Naser Krasniqi

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Hans Christer Anderson (Sweden), Katerina Demnerova (Czech Republic), Staffan Eklöf (Sweden), Philippe Herman (Belgium) and Alenka Zupančič (Slovenia).

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 delegate(s) that have submitted an ADoI.

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

4. Agreement of the minutes of the 3rd meeting of the Network for Risk Assessment of GMOs held on 3-4 May 2012, Parma

The minutes were agreed by written procedure on 24 September 2012 and published on the EFSA website on 25 September 2012.

5. Topics for discussion

5.1 Update on recent and current EFSA's activities on GMOs

Anna Christodoulidou, scientific officer of the EFSA GMO Unit, gave an overview of the current activities of EFSA in the field of GMOs. In addition to the assessment of applications for GMO food and feed and GMO cultivation, which is a standing activity, several Guidance Documents (GD) have been released during the two last years. Moreover, a number of mandates are in progress, including safeguard clauses on GM maize and potato cultivation, and several calls for procurement and grants to outsource diverse scientific activities in the field of GM plants and animals. Some self-tasks are also foreseen, among them a GD for the comparative assessment of agronomic and phenotypic characteristics.

In an answer to a question by an Austrian delegate, EFSA recognised that it is not possible to forecast the number of adoptions of opinions on cultivation dossiers, as this depends of different factors, such as the reception of additional information requested to applicants. The delegate of Denmark asked whether deadlines are set for dossiers which are in the system for a long time. EFSA clarified that, in an effort to move forward with those dossiers, deadlines to receive additional information have been set by EFSA. With respect to its future work on agronomic and phenotypic assessment, EFSA indicated, as a reply to a question from the Dutch delegate, that the output of the self-tasking mandate will streamline the current GD, by harmonising information requirements and providing endpoints useful for the environmental risk assessment (ERA).

5.2. Statistical significance and biological relevance in the risk assessment of GMOs

Joe Perry, Chair of the EFSA GMO Panel, presented how the GMO Panel performs the comparative assessment of GM plants, and the principles underlying it, which are reflected in the EFSA GD for the risk assessment of GM plants. The methodology sets minimum data requirements and harmonised approaches, which enable a better interpretation of the results. The statistical approach is based in two tests: a test of difference, in which the null hypothesis (H_0) is that the GM plant is not different from the conventional counterpart, and a test of equivalence, in which the H_0 is that the GM plant is not equivalent to a set of reference varieties which establish a range of natural variation for each endpoint to be compared. The test of equivalence avoids the risks of subjective interpretations of differences between the GM plant and the conventional counterpart in case the test of difference results in the rejection of the H_0, by providing a range of variation based on experimental evidence. The principle for the comparison is that the reference varieties have a history of safe use. Unlike for the food/feed (FF) safety assessment, the use of reference varieties is not recommended for the ERA. Instead, the equivalence limits must be set by the applicant based in the Protection Goals (PGs) set by Member States (MSs). The translation of PGs into equivalence limits and assessment endpoints is challenging, and little progression has been made in recent years by risk managers, although efforts continue.

The interpretation of any differences found in the comparisons should take into account that the statistical tests are based on plausibility alone, and that a statistically significant difference may not reflect biological importance. To enable a better interpretation of the results of the tests, the size of a difference to be considered biologically relevant should be

defined in advance, and the tests should be designed to be able to detect such differences, in case they exist.

After the presentation, there was a general discussion. The British delegate asked how much evidence would be necessary to demonstrate safety. According to the presenter, the amount of evidence depends on the trait (for which a lot of published data is normally available and can be used), and on the event, for which specific evidence is needed.

The delegate of The Netherlands wondered whether too high standards are being implemented for GM crops, and whether this was in reaction to consumer's feelings towards GM crops rather than strictly based on scientific reasoning. In the view of Joe Perry, equivalence tests are good science, used extensively in the medical field, which in addition provide reassurance to consumers. These tests were introduced in the assessment of pharmaceutical products to avoid biased conclusions based on statistical limitations of the difference tests. As in the pharmaceutical sector, the issue of GMO safety includes discussion both within science and within society. Since, for example, EU member states set PGs, he sees it acceptable to ask for extra evidence through equivalence tests.

With respect to the limits of concern in the ERA, the Dutch delegate underlined the difficulty to define them. She stated that such limits should be defined by risk managers rather than applicants, and that, when differences are found, it is challenging to interpret them. A Hungarian delegate asked when, in this context, a given difference can be considered important, and questioned the validity of combining ranges of values from different commercial varieties because this practice can mask regional effects. For this reason, she noted that Hungary is opposed to this approach. The presenter replied that the test of equivalence is designed to put into context any difference found in the test of difference, as not all differences are biologically relevant. For FF safety, the inclusion of reference varieties provide a way to establish such a context, which assumes a history of safe use for such varieties, although this assumption can be of course disputed. Regional differences must not be dismissed, and should be assessed by looking at the differences among sites (the site x treatment interactions) carefully.

An Irish delegate asked whether this approach could be applied for the ERA of GM plants under Part B of Directive 2001/18/EC (releases for experimental purposes). Moreover, he wondered if it can also be applied for an eventual analysis of benefits. Joe Perry answered that EFSA's remit is limited to evaluations under part C of the Directive (commercial releases), and that MS have full freedom to set the criteria for part B releases which they see fit. Likewise, the analysis of benefits of GMOs is not contemplated in the legislation and therefore out of EFSA's remit.

The delegate of Denmark noted that, since the implementation of this analytical approach, the outcomes of the assessments have not varied, so it is not clear that the analyses are providing more confidence. Moreover, given that an array of commercial varieties are now introduced in the analysis, he questioned the need for a conventional counterpart. If the counterpart is to be used, he proposed to pre-define the percentage of difference per endpoint that would be considered of concern. The presenter agreed with the advantages of pre-defining differences, but highlighted the problem of how to define them.

In a reply to a question by a delegate of Austria, Joe Perry clarified that EFSA does not accept historical data for the calculation of equivalence limits.

A German delegate raised three points: One, the importance of considering possible interdependence of endpoints; two, the possibility of using data from controlled experiments in the laboratory, in combination with data from field trials, in order to better set the limits of concern in the ERA; third, the challenges in using surrogate species to establish the safety limits. Joe Perry agreed that interdependence of endpoints would not be difficult to address by introducing a multivariate analysis, and that EFSA would consider such analysis if provided by the applicant. He also stressed that EFSA supports the use of laboratory data,

although the limits of concern should reflect real environmental conditions and therefore are primarily based on field trials. With respect to the use of surrogate species, he acknowledged the difficulty to progress this issue, due to lack of data.

5.3.a. Breakout session FF: animal feeding trials. Current state of the art and practice for the risk assessment of GMOs

Overview of 90-day animal feeding studies provided in applications

Yi Liu, scientific officer of the EFSA GMO Unit, presented an overview of the various designs used in 90-day animal feeding studies conducted in the frame of GMO applications submitted under Regulation (EC) No 1829/2003, for which the EFSA GMO Panel has adopted a scientific opinion. All studies except one were conducted without a specific request from the Panel. In accordance to the EFSA GD, a 90-day feeding study is necessary if the composition of the food or feed derived from the GM plant is substantially modified, or if there are indications of potential occurrence of unintended effects based on the preceding molecular, compositional or phenotypic analysis. This happened in a single case, for which the EFSA GMO Panel asked for the study to be conducted.

In brief, a total of 21 90-day feeding studies have been provided to EFSA, 18 of which were carried out on single events and three on stacked events. Fourteen GM maize, four GM soybean lines, one GM cotton, one GM potato and one GM sugar beet were tested, most of them (18 out of the 21 studies) on the rat strain 'Sprague Dawley'. The number of GM dosage varied from a single dose up to three doses. Dosage levels ranged from 2%, in case of sugar beets, up to 90%, in case of a GM soybean study. In addition to the non-GM conventional line, some studies included also commercial varieties.

During the discussion which followed the presentation, questions regarding the formula of the commercial diet and the extent to which the GM crop under investigation was added to the diet were raised. The French delegate asked in particular if the inclusion of 90% soybean in the diet is a realistic scenario. The origin of the data summarized in the presentation was also questioned because diets reported in peer-review studies contained more than 33% maize flour (e.g. 70% or 76%). EFSA pointed out that in most cases the feed diet was formulated on the basis of an existing certified rodent diet. Diets were also analyzed in order to confirm its nutritional adequacy for rats. The data reported in the presentation correspond to those submitted in GMO applications.

EFSA protocol for 90-day animal feeding studies

Claudia Paoletti, scientific officer and Deputy Head of the EFSA GMO Unit, presented to the audience the EFSA Scientific Committee Guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole FF, published in 2011. The presenter explained that the guidance complements the existing OECD test guideline 408 and provides advice for the design of test protocols (e.g. choice of animal strain, housing conditions, diet preparation, doses, experimental units, sample size, power analysis, standardized effect size), as well as for the analysis and reporting of findings obtained from a 90-day animal feeding study carried out with whole FF. The aim of the GD is to set the frame for a proper experimental feeding study design in order to detect possible toxicological effects of the test diet compared with a control diet. The presenter emphasized that, although the fundamental principles are similar, the referred OECD test guideline 408 is intended for chemical substances, whereas the EFSA GD is intended for whole FF. This has consequences in the design of the experiment. For example, in the case of pure chemicals, dose levels much higher than those to which humans are likely to be exposed can be administered to the animals. In addition, in the case of pure chemicals it is possible to establish a dose-response relationships, whereas it is difficult, if not impossible, to do it for whole FF.

The above mentioned EFSA GD recommends the analysis of the whole FF in terms of composition, nutritional balance, anti-nutritional components, stability of the diet and feed storage conditions. It also recommends that the highest dose level of the whole FF should not cause nutritional imbalance or metabolic disturbances in the test animals, and that the lowest dose level should always be above the anticipated human/target animal intake level. It also foresees to house animals of the same sex at least in pairs. In order to estimate a sample size which enables the detection of a pre-specified biologically relevant effect size, the use of a power analysis is recommended. The concept and use of Standardized Effect Size (SES), which is the difference between treatment groups/standard deviation among all experimental units (i.e. basically a signal-to-noise ratio), was introduced.

Finally, It was pointed out that the performance of 90-day feeding studies will become mandatory for GMOs containing single events, according to the new Implementing Regulation (EU) No 503/2013.

During the discussion, EFSA clarified that the guidance is not a test protocol, but rather a document providing guiding principles for the design of 90-day feeding studies.

The application of SES was discussed in detail. A hearing expert, member of the EFSA GMO Panel Working Group on FF risk assessment, was in favour of the use SES and proposed to check the literature to investigate how specific SES levels were set in different studies. He also asked if a SES whose value is below one is of biological relevance, as in the case when the variability among treatment groups falls within the natural variation observed in the experimental units. According to an EFSA GMO Panel member, in this case it might be possible to see only some slight changes towards certain limits.

The Danish delegate was in favour of sticking to the OECD test guideline 408, as it is widely accepted and applied, without the need to go further. An EFSA GMO Panel member explained the differences between the OECD test guideline 408 and the EFSA guidance, focusing particularly on the scope (pure chemicals *versus* whole FF). He noted that the application of a dose/response relation is very difficult for FF.

The delegates from Hungary and Italy were in favour of providing a more detailed description of a study protocol that could be used to perform 90-day feeding studies, on the basis of the principles described in the EFSA GD. The Hungarian delegate also suggested a power of 95%, a value which is widely used in statistical analyses of biological experiments.

At the end of the session, EFSA asked for further feedback from all delegates. While acknowledging the difficulties, there was a general agreement on the importance of harmonizing the 90-day animal feeding studies in terms of study design and analytical endpoints, in order to make such studies comparable, therefore useful for risk assessment. At the same time, some delegates cautioned that the motivation of conducting such study should remain case-by-case, and over-standardization of the experimental findings may lead to weak results.

5.3.b.Breakout session ENV: Protection Goals

Development of PG options for ERA of pesticides

The session started with a presentation by Maria Arena, scientific officer in the Pesticides Unit of EFSA, on how PGs are developed for the ERA of pesticides. Regulation (EC) No 1107/2009 on pesticides defines PGs vaguely, leaving room for interpretation. For a robust ERA**,** it is important to specify what we want to protect, where, and over which time period, given that it is not possible to protect everything and always. Hence, EFSA has developed a conceptual framework to define specific PGs. This framework consists of the following steps: 1) listing the ecosystem services (ESs) according to the Millennium Ecosystem Assessment report of 2005 ; 2) identifying ESs that are potentially affected by the use of pesticides, both in the in-crop and off-crop areas; 3) identifying key drivers for each of the ESs (major

taxonomic or functional groups that support the ES); 4) develop specific PGs by the identification of 6 dimensions for each ES/key driver combination: ecological entity, attribute, magnitude, temporal scale, spatial scale and degree of certainty; 5) identifying vulnerable species; and 6) developing protective risk assessment schemes. This framework provides a transparent and systematic way for the definition of PGs and helps risk managers in their decisions. Some examples on how this framework has been applied to bees were presented.

Following the presentation, a member of the EFSA GMO Unit asked how to manage discrepancies among risk managers from different MS and how to reach agreements among stakeholders. Maria Arena answered that, under the current procedure, EFSA develops the PGs and presents its proposal to the SCFCAH, giving the opportunity to risk managers to agree on the proposed specific PGs. Moreover, a member of the EFSA Scientific Committee noted that stakeholders are invited to comment on draft opinions through a public consultation process. In the case of honeybees, a workshop was also organised for consultation purposes. A member of the EFSA GMO Panel asked if there were agreements on PGs for other species, such as those for biological control, citing ladybirds as an example. The presenter clarified that the Pesticides Unit is now working on an Opinion on non target arthropods. A German delegate asked how to set PGs for endangered species, and if there is any legal requirement for this. She was also wondering why temporal scale is only considered in the in-crop area. The member of the EFSA Scientific Committee acknowledged that currently is not possible to know whether endangered species are covered in the assessment in the EU. In most cases, tests are provided on a species of conservational concern in the US but not in the EU. This is a topic deserving further research. Maria Arena added that the temporal magnitude is considered negligible in the off-crop area, in contrast to the in-crop area, where the approach is more strict.

Upon request from the Dutch delegate, the member of the EFSA Scientific Committee clarified that trigger values need to be well selected in order to enable an accurate risk assessment. This is not always achieved.

Environmental PGs. Philosophy, Policy & Publics

Fern Wickson, from the Genøk-Center for Biosafety of Tromsø (Norway), delivered a presentation commenting on ethical aspects of the definition of PGs. She argued that an ERA is unavoidably linked to ethical aspects, however, the question is what to protect. There is a need to develop a standardised and consistent reasoning to define what must be valued in nature and justify why it should be protected. In her teaching experience, the presenter has found that there is a diversity in criteria on what is perceived as a harm to the environment. This perception depends on factors such as abundance of the species, extent of the damage in the population, familiarity, and a sense of friendship with the species. Moral positions on environmental aspects vary from purely anthropocentric positions to what can be called *ecocentrism*, which is the opposite; but, in general, there is a feeling that ecosystems have an intrinsic value. In her view, the EFSA GMO and Pesticides Units address PGs differently. The GMO approach is more instrumental, without providing a rationale for this position. Both Units make use of the concept of ES. There are a number of criticisms to this approach: it assumes a full understanding of the ecology, gives a pure instrumental value to Nature, does not recognise ES to non humans, and has a too polarised view towards engineering and economics, leaving aside values such as humility or reverence. The environment not only has ecological but also cultural values. However, the GMO approach does not consider cultural services, unlike the Pesticides Unit. 'Sustainability' could be chosen as a PG, as referred to in the Norwegian Gene Technology Act. However, EFSA understands sustainability in the sense of an ES without considering its cultural and human dimensions. This might be due to the absence of legislation on social and economic issues of sustainability in the EU.

After the presentation, there was an interchange of views between the presenter and several members of the audience. A member of the EFSA GMO Panel reminded that the GMO ERA GD includes consideration of species of conservation concern. Also that agro-ecosystems are not natural, and it is misleading not to have this present in ethical considerations. The GMO ERA GD provides a clear rationale on the value of the species for the ecosystem.

A member of the EFSA GMO Unit asked what can be learnt from the Social Sciences to improve the risk assessment in eliciting value judgements and differences. In the opinion of the Dutch delegate, is not possible to conduct a risk assessment by taking together scientific and socio-economical aspects, because they are incompatible. On the other hand, the view of a German delegate was that it is not possible to make a decision purely on scientific grounds, because it is always needed to establish what is acceptable, and this is normative. She stressed the need to be more explicit when taking normative decisions. Fern Wickson agreed with the German delegate. She said that it was important to incorporate ethical aspects in the definition of PGs. It was agreed that there is a need of closer collaboration between experts in ethics and risk assessors at EU level. The presenter also stressed that the EFSA GD on non-target organisms (NTO), although mentioning cultural services, does not clearly consider them as ES. While she agreed that different species have different values, she proposed that a logical and consistent argument should be elaborated explaining these differences.

A delegate of France noted that the definition of PG is not the role of risk assessors but of risk managers. She considered that the arguments raised in the presentation should be better addressed to risk managers, so they can consider them in their decisions. The presenter agreed that assessors should not be permitted to define PGs, and suggested that assessors should clearly inform managers about this.

An Austrian delegate stated that Austria has collected an amount of data on biodiversity linked to agricultural ecosystems, and that it would be positive that both risk assessors and managers take into account this data. Meanwhile, the Latvian delegate reflected on the emerging technologies which can influence in the ecosystems towards the maintenance of the human population, and agreed that ethical aspects should be covered by legislators.

A delegate of Poland raised the question of who decides on ethical questions. In his country, only 2% of the scientists were able to influence decision making on issues affecting all the population. This question was recognised as crucial by Fern Wickson, although she recognised not to have an answer.

The Chair of the EFSA GMO Panel stated that the Panel does not disagree with the need to protect biodiversity in agricultural systems. The GMO ERA GD tries to emphasize this through the integrated management approach, in line with the recent EU Directive. However, it is difficult to take social values in definitions of species of concern linked to agriculture. The whole Guidance on NTO should be considered for a comprehensive overview of PGs. The Panel, when developing the document, tried to incorporate the best components of what are often termed the *ecotoxicological* and the *ecological* schools. The species to be protected should be selected according to a list of criteria, including cultural value as a final criterion. When a negative effect is identified in the ERA, its value should be estimated. He agreed the need to involve all stakeholders to define limits of concern, and that PGs should be harmonised throughout different Panels. The EFSA GMO Panel will take the input from the presenter seriously in its future work on PGs.

The presenter encouraged the EFSA GMO panel to develop the integrative pest management baseline for the definition of PGs. In relation to this, a member of the Panel reminded that the output of the EU-funded project AMIGA (Assessing and Monitoring the Impacts of Genetically modified plants on Agro-ecosystems) is relevant – this is under revision after consultation with the MSs, which have expressed very divergent views on this issue.

5.4. Long-term animal feeding trials as a tool for the RA of GMOs

General thoughts about extended duration feeding studies in rodents

The session was opened by Dominique Parent-Massin, a member of the EFSA ANS Panel, who reviewed the principles of repeated dose testing in general toxicology, with special emphasis on tests of extended (more than 90 days) duration for the toxicological assessment of GM food or feed. In general, repeated dose toxicity testing applied to FF presents several methodological challenges. Food is a very complicated mixture, in which the compound(s) which might exert toxicological damage are usually below the limit of detection of the test. Control diets are not always compositionally equal to GM diets. Maintenance of the nutritional balance is sometimes difficult, and sufficient number of control groups must be foreseen. The selection of the animal species is also tricky. In case of rats (the most common species for repeated dose testing), they spontaneously develop tumours and other disorders when aging (especially some strains), which can mask the results.

It is difficult to justify in which cases extended duration tests for toxicological evaluation are recommended. When previous toxicological tests (such as *in vivo* genotoxic assays or 90-day repeated dose tests), reveal concerns e.g. doubtful genotoxic profile, pre-neoplastic lesions or pathologies, then a risk is identified and the assessment can be finalised, making the long-term study unnecessary. The same happens when the compositional analysis reveals an increased concentration of any compound known as toxic or carcinogen. Some specialists in the field asked by the presenter were of the opinion that, in case an extended duration assay is appropriate, they would first choose a 6-month rather than a 2-year study, as those studies always detect pre-neoplastic lesions or variations in parameters. Moreover, literature reviews have been recently published on long-term, as well as multigenerational studies, with GM plants for which 90-days study were also available. Notwithstanding some limitations, they showed that long-term studies did not find significant differences among GM and control groups, nor did they add new information to the outcome of the previously made 90-day tests.

In conclusion, extended duration tests for the toxicological risk assessment of GM FF is considered to have no added value in the absence of a strong scientific evidence. Conducting such tests should be decided on a case-by-case basis, such as reasonable doubt remaining after a 90-day study.

Answering to questions from delegates of Latvia and Ireland, the presenter noted that in vitro toxicological assays are at the moment not very useful to substitute animal tests, and that the publication by the group of Séralini on a 2-year study with GM maize (published in 2012, just after the literature review mentioned in the presentation) would not fit in the review because the protocol used by the authors was not according to the OECD guideline.

EFSA's draft Scientific Report on applicability of OECD guideline for 2-year animal feeding studies

The second presentation of the session was delivered by Andrea Germini, Scientific Officer of the EFSA Scientific Committee and Emerging Risks Unit. He introduced a mandate recently received by EFSA from the European Commission (EC) to comment on the OECD Test Guideline 453 (2-year carcinogenicity and chronic toxicity feeding study in rodents) with specific considerations related to whole FF. The background of this mandate is a plan by the EC to launch a call for a research project to perform a 2-year carcinogenicity feeding study in rodents with GM feed. The intention is that the comments from EFSA will help with the definition of guiding principles on the protocol to be used for the study.

To accomplish the mandate, EFSA has set an internal Task Force spanning different Units, which will produce a Scientific Report based on OECD TG 453, providing specific comments

on its applicability to whole FF testing, and considering general elements of the previous EFSA opinion on 90-day feeding studies with whole FF. Comments will be provided on the selection of animal species, aspects of housing and feeding, dosage, number of animals, endpoints to be measured, statistical analysis, and data reporting. Once finalised, EFSA will submit the draft Scientific Report to the Network in order to receive input from the different MSs. In anticipation to this, the presenter invited Network experts to express their views about the statistical requirements that should be taken into account during EFSA's definition of the experimental setup, dose groups selection and dosage, or any other consideration on whole food and feed testing.

After the presentation, The Head of the EFSA GMO Unit initiated the discussion by encouraging Network members to provide input to the draft Scientific Report. It was clarified, upon request from the delegate of Belgium, that the mandate is intended neither to complement any EFSA guidance, nor to develop a *de novo* protocol. The EC delegate clarified that, after the publication by the group of Séralini of the 2-year study with the herbicide-tolerant GM maize NK603, whose experimental design was criticised by many, the EC sees the need to redo the study in a proper way, avoiding methodological flaws and obtaining reliable results. From discussions with EFSA, it was clear that a protocol focusing on just one GM crop would be not appropriate, so the mandate focus is on a general protocol. The intention of the EC is that the outcome of the mandate will be useful for a potential contractor to develop the study, and encouraged Network members to provide their contributions.

A delegate of France reported the views from ANSES and the High Council for Biotechnology (HCB), both organisms officially in charge of risk assessment of GMOs in France. She first reminded that while ANSES and the Scientific Committee of HCB agreed that the Séralini study was not conclusive, ANSES called for more research on the potential health effects associated with the long-term consumption of GMOs, and the HCB's Economic Ethical and Social Committee (EESC) recommended that a long-term study on the safety of maize NK603 be conducted under the aegis of public authorities. In a recent letter to EFSA relative to such a long-term study, ANSES and HCB's EESC members asked for appropriate methods to be used in order to gain public trust and guarantee the credibility of the study. In particular, they asked for the involvement of a broad range of stakeholders in the design and monitoring of the study, and for the inclusion of Round-Up (glyphosate) in the trial.

A Hungarian delegate proposed that, in the study, a glyphosate-treated resistant GM crop should be used as tests substance. EFSA stressed that the mandate it received from the EC was to comment on a protocol considering whole FF testing, not restricted to GMOs, and therefore glyphosate is not specifically addressed, as the protocol should be applicable not only to herbicide-resistant GM crops.

The Dutch delegate expressed her worries about the fact that this long-term study is only meant to satisfy the public and has no real scientific basis. By discussing the protocol of such a study, the Network is shifting from strictly discussing scientific issues. Meanwhile, an Austrian delegate stressed the relevance of long-term effects to Austria, also from a legal perspective, and noted that no conclusions can be drawn on this issue without previous research. A German delegate asked whether there would be a follow-up to the mandate, specifically focused on GM food.

The EC delegate explained that glyphosate was not specifically included in the mandate as an evaluation of this herbicide is taking place independently in the frame of Regulation (EC) No 1107/2009 on pesticides. Addressing a question from a French delegate concerning the degree of freedom of the contractors relative to the protocol established by EFSA, the EC delegate specified that contractors would enjoy freedom as the objectives of the call would be broad. Every proposal will be welcomed as far as it meets the general objectives. It is expected that the selected proponent will fine-tune the project with the EC. He also noted

that many details of the call are yet to be decided. The presenter added that the Scientific Report by EFSA coming out from the mandate is not intended to be prescriptive, and the principles reflected in it would be also applicable to other GMOs. On the other hand, the EC delegate clarified that the date of the launch of the call is not decided yet; tentative dates could be during or after summer.

A delegate of Ireland questioned the advisability to perform the study with rats, which tend to develop tumours spontaneously, instead of pigs, which are known good models for human studies. The presenter noted that rats are widely used in toxicological studies because their known safe use and the existence of extensive historical data. With respect to tumour development, EFSA is performing simulations to study the influence of spontaneous tumours before designing the analysis. The member of the EFSA ANS Panel also noted that historical data on pigs are available from some laboratories.

5.5. ERA of GM animals

The recently adopted EFSA GD for the environmental risk assessment of genetically modified animals was presented to the audience by Sylvie Mestdagh, scientific officer of the EFSA GMO Unit. The draft GD was submitted for public consultation. Most of the over 700 comments received were from public institutions, National Authorities and non-governmental organisations. There were many opportune and useful comments which contributed to improve the document significantly. The GD on the ERA of GM animals follows the same structure of the corresponding document on GM plants, and considers three classes of possible applications: fish, insects, and mammals and birds. After the introductory chapter, Chapter 2 of the document sets the strategies and principles for the ERA, which are common to all GMOs. Chapter 3 deals with cross-cutting considerations, which are 1) selection of receiving environments, 2) choice of comparator(s), 3) use of non-GM surrogates, 4) statistical principles and modelling, 5) assessment of potential long-term effects, 6) identification and assessment of uncertainties, and 7) assessment of health and welfare of GM animals. In Chapter 4, specific areas of risks, according to Annex II of Directive 2001/18/EC, are described for GM fish, GM insects, and GM mammals and birds. Of particular importance are the risk areas on pathogens, infections and diseases (for GM fish), interactions with target organisms (for GM insects), and persistence, invasiveness and vertical gene transfer (for GM mammals and birds). Post-Market Environmental Monitoring (PMEM) is addressed in Chapter 5. A more detailed PMEM of GM animals might be the topic for a future GD.

There were some questions on the GD after the presentation. A delegate of Austria asked whether applications are expected within the next five years. Although there is currently no indication, EFSA cannot exclude the possibility that some GM animals under assessment in the USA are also submitted to assessment in the EU (such as salmon and pig). In addition, there have been some releases of GM mosquitoes, which might be target of commercialisation in EU overseas territories.

A delegate of Germany expressed some concerns on the applicability of the document. She considered that it reflected a narrow approach to the ERA, leaving aside systemic aspects such as interactions among populations or migrations. She would have welcomed a second round of comments under the public consultation exercise. She also asked how to find differences between GM and non-GM animals from desk studies. EFSA answered that, although the document gives value to literature reviews as potentially informative, the comparative approach is still the key element of the assessment. It was also clarified that issues such as transport of animals, accidental leakage and processing are also covered in the document. Nevertheless, given that no dossier has arrived to the EU yet, the first assessments of GM animals will be challenging exercises, from which much will be learned to streamline the ERA.

6. Any Other Business

6.1. Renewal of the Network

EFSA reminded that the current mandate of the Network expires in November 2013 and both Member Institutions and appointed experts will need to be renewed. EFSA will start this exercise in due time, through the Advisory Forum.

6.2. Expert database open for MS experts to work with the EFSA GMO Panel

EFSA reminded to the Network the existence of the database and encouraged members to join and/or disseminate it through contacts.

6.3. Calls for ERA on cultivation files to be performed by volunteer MSs

EFSA encouraged MSs to volunteer for conducting the initial ERA of possible future applications for GM plants including cultivation in the scope.

6.4. Call for participation in open procurements and grants

EFSA reminded and encouraged the Network to answer the request from the EFSA SAS Unit to provide information on Environmental Surveillance Networks in the frame of the project "'Review of statistical methods and data requirements to support post market environmental monitoring of agro ecosystems". Deadline is 4 June.

EFSA reminded the Network the possibility to apply for the currently ongoing calls on bioinformatics, and on the update of the fauna database, and encouraged Network members to disseminate the information through contacts.

7. Next meeting(s)

Next meeting will be the 1st meeting under the 2nd mandate of the Network. Dates to be confirmed. EFSA encouraged Network members to get involved in the development of the agenda. Network members willing to develop next agenda together with EFSA are welcome to contact EFSA in advance. The planning of the agenda usually starts by February.