REPORT OF THE SPECIAL ADVISORY FORUM MEETING ON EU GMO RISK ASSESSMENT

13 November 2007

Introduction

Over 60 EU GMO risk assessment experts, nominated by the Advisory Forum members and representing the EU Member States, Norway, Switzerland and the European Commission, convened in a special Advisory Forum[1] meeting. The list of participants can be found in Annex 1. The experts met to share details of their national GMO risk assessment approaches, identify commonalities or possibly diverging procedures or methodologies among Member States or between Member States and EFSA. Dr Herman Koëter emphasised that science evolves, and since science drives risk assessment procedures, it is important to continuously review the scientific basis of risk assessments in order to remain at the forefront of risk assessment developments. The agenda was based on issues raised by the Member States in response to a questionnaire.

An open atmosphere and many constructive interventions from the national scientific experts ensured an appropriate technical level for discussing the elements of a robust scientific approach in GMO risk assessment.

Member States' organisation and experience with GMO risk assessment

The questionnaire revealed that differences exist from one Member State to another with respect to the practical organisation of GMO risk assessment. Differences also exist within Member States between risk assessment under Regulation (EC) No 1829/2003 and Directive 2001/18/EC. The expert from Spain emphasised the approach followed for a GMO to be authorised for feed should be different as far as the risk is different. The number of applications assessed by the Member States ranged from 0 to 394. With respect to national risk assessment guidance, all Member States refer to the EFSA guidance documents and there were no indications that national risk assessment guidance documents differ from internationally accepted guidance. A summary table of the replies from Member States to the questionnaire can be found in Annex 2 and a compilation of all the completed questionnaires in Annex 3.

Risk assessment approaches

In a brief introduction, Dr Harry Kuiper, chair of the EFSA GMO Panel, emphasised that risk assessment is done comprehensively based on all the available evidence, since there is no single test that can give a full risk analysis. Risk assessment is conducted by comparing the GM crop with its closest non-GM relatives and comparators for which safe use has been established.

He clarified that the purpose of the EFSA risk assessment guidance document for GMOs is to explain how a risk assessment should be performed and to point towards potential aspects of uncertainty and to describe how much detail should be presented by the applicants to address those uncertainties. It was of paramount importance that guidance documents should be science based.

A great majority of the Member State experts were supportive of this general approach and the level of detail in the EFSA guidance documents, which follow internationally agreed guidelines and take a case-by-case approach to assessing the safety of GMOs. For this approach, it is essential to update the guidance document as experience is gained. Dr Kuiper regarded the ongoing self-tasks of EFSA as a good way to update the guidance document regularly. EFSA confirmed its commitment to update its

[1] The Advisory Forum is a platform for consultation between Member States and EFSA on areas of high priority for the European work within the remit of EFSA.

guidance documents whenever necessary and provide more detailed guidance based on proposals from its working groups and from broader scientific consultation.

The expert from Austria expressed a general concern because of the uncertainties which are inevitable in risk assessment. Experts from two other Member States, Poland and Latvia, however, mentioned that we live in a world full of uncertainty.

The expert from Austria also stated that there is insufficient information in the current guidance document to perform a comprehensive risk assessment. The expert from Denmark found that the EFSA GMO risk assessment guidance is sufficient for a uniform and robust risk assessment of GMOs in Europe, which view was supported by the majority of the risk assessors present, and should not be more restrictive than risk assessment guidance for novel foods, for example. Many Member State experts expressed the need to continue the harmonization process for the GMO risk assessment across the EU. The consensus was that the EFSA approach is appropriate and that the guidance document provides a good common basis for the Member States.

EFSA's current procedures

The quality of the data from the applicant is checked by the national risk assessors and by the EFSA GMO panel. If they are unsatisfactory in any respect the applicant is requested to provide more information and/or additional data. Such requests are routine for almost all of the past and ongoing applications (see the table on the status of applications in Annex 4). The expert from Belgium mentioned that applicants should not provide arguments built on alleged benefits of the GMO products, since the assessment should address potential risks.

Member States' comments are now published with each GMO opinion and are considered helpful to facilitate better decision making across the EU. The expert from Belgium asked EFSA to evaluate the contributions of different national agencies and to identify more clearly the perceived relevance of the comments provided by the Member States (e.g. irrelevant, relevant but not changing the risk assessment, relevant for future applications/research, etc.). Dr Riitta Maijala suggested that the EFSA Advisory Forum would be asked for suggestions as to how to address this issue.

Biological relevance versus Statistical analysis

One important issue is the need to assess the biological relevance of statistically significant differences between a GM plant and its non-GM counterpart. Two years ago, a statistical working group was set up by EFSA to look at new statistical methods that could help risk assessment. The work has emphasised that statistical tools can support but not lead the biological assessment and that threshold values for variation of test endpoints which are used by statisticians to test for equivalence must be set by biologists. The majority of the Member State experts agreed with the need to define biological relevance, but no specific proposals were provided on how this should be done. Dr Harry Kuiper mentioned that for the current dossiers, EFSA looks at the range of biological variation estimated on the basis of experiments and data available from the scientific literature and databases. For example, in the case of MON863, six reference lines were included in animal feeding trials to provide information on biological variation. Furthermore, ILSI is building up high quality databases to quantify parameters and their variability.

The current EFSA guidance document specifies that the applicant has to replicate trials over years and sites and a number of Member State experts asked whether more details could be given for the design of field trials. The statistical working group of the EFSA GMO Panel is investigating the number of sites, the number of years, whether the same sites should be used, and the interpretation of all the factors and their interactions. It was clarified that there could be agronomic difficulties to use the identical plots year after year. An expert suggested specifying the statistical power within the definition of a field experiment. This idea was supported and EFSA would look at ways for the applicants to overcome possible difficulties.

Environmental risk assessment

In addition to their general support for the current guidance document, several Member State experts asked EFSA to work on the development of more detailed guidance, especially in the area of environmental risk assessment, and in particular for the field trials setup and test parameters, how to take bio-geographical regions into account, and to harmonise the data and methods for impact assessment on indicator non-target organisms. The environmental working group of EFSA's GMO Panel will address concerns about non-target organisms and regional specificity in its ongoing work on refining environmental risk assessment approaches, following the EFSA Scientific Colloquium held in June 2007[2]. The best way forward for regional specificity in the environmental risk assessment would be to calibrate existing knowledge with information from field trials and well-managed cultivation experiences in the specific regions. For example in Spain, there have been extensive studies of the biota occurring in GM*Bt* crops. It was suggested that a country could commission research in their own environments in order to provide information on specific interactions between GM crops and biota in their regions. Another approach is to evaluate ecological processes, which apply over a broad diversity of environments.

Agricultural practices

GM Herbicide Tolerant (GMHT) crops and their impact on biodiversity were discussed. GMHT crop cultivation will affect biodiversity in crops due to the effects of the herbicide treatments on botanical diversity and this should be indicated in the environmental risk assessment. Impacts on biodiversity and the development of resistance to the herbicides are herbicide management issues and thus are the responsibility of the risk managers of the Member States under the pesticides Regulation 91/414/EC. The EFSA GMO Panel has worked on this issue, together with the Panels on Plant Protection Products and Residues (PPR) and Plant Health (PLH). A document proposing a pragmatic approach to handle the environmental risk assessment of GMHT crops in a comprehensive way is now under consideration.

For GMHT crops, the appearance of other metabolites is considered under the pesticide Regulation 91/414/EC.

Member States were encouraged to perform the environmental risk assessment of cultivation dossiers under Regulation (EC) No 1829/2003.

Post-market Environmental Monitoring

The EFSA guidance on post-market environmental monitoring has been accepted generally by Member States as being appropriate and workable. General surveillance for adverse unanticipated effects should monitor relevant parameters. General surveillance monitoring is currently being conducted on GM crops grown in the EU and results are now becoming available.

Since many GMOs are imported together in bulk for food/feed processing, initiatives are being developed for monitoring GM crops collectively instead of individually, and this move is welcomed by EFSA. However, it is important that there is wide consultation and agreement on these procedures.

The expert from Ireland suggested that the work of the post-market environmental monitoring working group under Directive 2001/18/EC should be brought in conformity with the work of EFSA on post-market environmental monitoring. The expert from Ireland also suggested that the experience gained from the cultivation of GM crops in different EU MS over the last ten years and the independent post-market monitoring studies published in peer reviewed scientific journals should be used by risks managers in drawing up any future post-market environmental monitoring plans.

Risk/benefit analysis

Many Member State experts shared an interest in how risk/benefit analysis can be considered in relation to GMOs. During the EFSA Scientific Colloquium in 2007[2], it was concluded that a benefit assessment

[2] A detailed report will be available on the website http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178621343596.htm

could be conducted as part of the environmental risk assessment, particularly if adverse effects had been identified. EFSA will consider the feasibility of risk/benefit analysis.

Use of animal models for safety testing

The majority of risk assessors present were satisfied with the present guidance provided by the EFSA GMO Panel regarding the conduct of animal feeding trials, while some Member State experts requested more standardisation,. Questions included: "How to respect the nutritional requirements of test animals when feeding whole GM foods which are not part of their normal diet?" and "How to prescribe a general test that would fit the many different kinds of novel food?". Dr Kuiper indicated that careful preparation of animal test diets is needed and can be accomplished.

With respect to the prescription of defined parameters and endpoints for a particular animal feeding trial, it was noted that tests are done differently by different applicants, but the differences in the test set-up are relatively minor because all are based on the OECD protocol as cited by the EFSA guidance document. A new tabled report of the EFSA GMO Panel on animal feeding trials concluded that (1) animal feeding trials with whole GM food/feed should be performed on a case-by-case basis depending on the results of other molecular, compositional and toxicological analyses. These studies should not be performed routinely, and (2) further harmonisation in this area is possible. To implement this, the European Commission or a Member State would have to take the lead in making a proposal to the OECD for standardisation of the protocols of the animal tests.

With respect to the prescriptions of which tests should be performed, there are many short-term toxicity tests that can be used for GMO risk assessment and the 90-day feeding trial has sufficient capacity and sensitivity to predict long term effects of GM food consumption. Literature databases may be used to support this approach. At present, and for the crops assessed so far, animal feeding trials with the whole food do not add greatly to the safety evaluations, but for future GM crops this may be different.

It was suggested that EFSA could check these important conclusions with other Scientific Panels dealing with whole foods, since the findings of the tabled report go beyond the restricted area of GMOs and have wider application for other novel non-GM foods.

The expert from Austria pointed out that this report provides a good overview on scientific work done and that he was pleased with the recognition of the value of harmonization. However, the Austrian expert commented that it was important that the case-by-case approach is not used as an excuse for not giving further guidance. The consensus was that the tabled report would provide a major step forward in a mutual understanding of the work of EFSA and its mission to establish a harmonized risk assessment based on sound science.

The Member State experts were asked if they considered whether a (harmonized) 90-day feeding trail in rodents should be prescribed as part of a standard test-package for the whole food, or alternatively should be performed on a case-by-case basis. Almost all experts agreed with the EFSA approach of case-by-case, while the expert from Hungary suggested that a feeding study should be conducted routinely and considered that 90 days were not enough.

Impact of feeding studies of unconfirmed scientific quality

The expert from Poland enquired about the value of animal feeding trial reports published on the internet (e.g. by I. Ermakova). It was pointed out that as such studies did not go through a peer reviewed process, and no detailed datasets were published, the quality of the data could not be verified. Therefore the value of such Internet studies is very limited.

The opinion was expressed that risk assessment must consider possible combined exposure to several different GM products, which might potentially result in cumulative effects even if exposure was not simultaneous. Although these compounds may be present in low doses and potential effects difficult to detect, some models exist to explore toxicity testing from the pesticide literature. The EFSA GMO Panel is aware, but has not yet been in a situation where it was necessary to address this, unlike the EFSA Panels dealing with pesticides and chemicals.

Future developments

Profiling methods have been used during the last 10 years and are useful to map the level of natural variation. They are not yet ready to be used routinely in risk assessment for authorisation dossiers and more work is needed to allow interpretation of observed differences. Validation of profiling methods is to be encouraged.

GM animals: a special Codex task-force is considering foods from GM animals and EFSA intends to establish working groups to consider GM animals, probably starting with fish.

Novel GM crops, GM trees, GM pharmaceutical crops: an EFSA self-tasking working group is preparing an opinion on appropriate risk assessment criteria for such crops. Public and Member State consultation on this document will take place in the coming months.

Allergenicity testing: EFSA's working group on allergenicity is studying adjuventicity and immunogenicity and investigates test methods other than bioinformatics. Some MS stated that algorithms for allergenicity testing have substantially improved and computational assessments have increased in importance compared to *in vitro* tests, particularly for the pepsin test in which there seems a declining confidence. One expert found the EFSA guidance already too prescriptive in the area of allergenicity, when compared to risk assessments of conventional crops that are found to be allergenic, such as wheat.

Conclusions

(i) Member State experts agreed that EFSA's guidance document was a proper basis for risk assessment and that this should continue to be updated in step with scientific progress,

(ii) The overwhelming majority of the risk assessors of Member States are in agreement with the EFSA case-by-case approach to requests for 90-day feeding trials for risk assessment of GM whole foods, i.e. that 90-day feeding trials are requested only when needed,

(iii) Guidance on environmental risk assessment, should be continuously updated, especially in the testing of effects on non-target organisms (which is currently proposed as an EFSA self-tasking activity),

(iv) More guidance is needed on defining threshold values for variation of test endpoints that are used in statistical analyses to assess biological relevance (in conformation with EFSA's self-tasking statistics working group),

(v) Clarification is needed in the guidance on the experimental design of field trials in order to achieve more harmonised approaches,

(vi) EFSA should publish the mandates of its working groups, together with their composition,

(vii) EFSA will consider the feasibility and explore a scientific approach for risk/benefit analysis,

(viii) EFSA to assure the distribution of the animal feeding trials report to other Panel experts dealing with the same type of testing of whole foods.

As an outcome of the meeting this report and its annexes provides a comprehensive overview of regulatory GMO risk assessments in Member States, highlighting the many commonalities and few differences in risk assessments and providing suggestions for future work. This report will be submitted to the Advisory Forum for information and endorsement of the proposed follow-up actions at its meeting in January 2008 and will be shared with the European Commission, the Member States, and the Scientific Committee and Panels of EFSA. The report will also be published on the EFSA website.

Annex 1: list of participants
Annex 2: overview table of the MS answers to the questionnaire
Annex 3: compilation of individual MS responses to the questionnaire
Annex 4: overview status of the applications
Annex 5: presentation by Dr Djien Liem
Annex 6: presentation by Dr Reinhilde Schoonjans
Annex 7: presentation by Dr Harry Kuiper

Annex 8: presentation by Dr Joe Perry
Annex 9: presentation by Dr Jeremy Sweet
Annex 10: presentation by Dr Harry Kuiper

Further Actions

- Hungary to make its protocol for regional risk assessment available when ready to all Member States.
- Germany to make the report of the studies of Germany's Nature Conservation Organization available to all Member States.
- Austrian Agency for Environment to share with all Member States its experiences with cultivation dossiers (expected Summer 2008).