WORKSHOP ON THE RISK ASSESSMENT PRINCIPLES FOR GM PLANTS: BACK TO BASICS

BRUSSELS 14th-15th JUNE 2016

MEETING REPORT

On the 14th and 15th of June 2016 EuropaBio organized a workshop entitled: "Back to basics: risk assessment principles for GM plants". The objective of this workshop was to re-visit the way in which food and feed risk assessments for GM plants are conducted in the EU and to discuss whether these risk assessments are fit for purpose and are implemented according to general risk assessment principles. Over 90 participants from 22 countries registered for the workshop (83 in person, 16 via the livestream) representing academia, regulators from around the world (from agencies like EFSA, Food Standards Australia New Zealand, and Japanese secretariat of Food Safety Commission), the European Commission (EC), EU Member States (MS) and industry.
The workshop was divided into five sessions:

1. Risk assessment principles for GM plants.
2. Weight of evidence. Case study: Allergenicity.
3. Risk vs. Hazard and Exposure. Case study: protein safety.
4. Assessing unintended effects. Case study: Risk assessment of GM plants with stacked traits.
5. Conclusions of the workshop.

Presentations were given by the EFSA GMO Unit, third country regulators, international scientists, Member State representatives and industry. A panel discussion took place at the end of each session so attendees could pose questions to the speakers and engage in discussions.

The workshop was opened by Natalie Moll, secretary general of EuropaBio, and an introduction was given by Karen Holt (EuropaBio representative from Syngenta).

The first session (Risk assessment principles for GM plants), chaired by Dr. Joachim Schiemann (director Institute for Biosafety in Plant Biotechnology, Julius Kuehn Institute (JKI) included two presentations. Dr. Monica Garcia-Alonso (an independent consultant from Estel Consult Ltd.) initiated the session with the basic principles of risk assessment, stressing the key difference between risk and hazard. She also described how common risk assessment tools used in many different fields (e.g. risk assessment of chemicals and pesticides) can be applied to the risk assessment of GM crops (such as using scenarios, the weight of evidence approach and pathways to harm). Later, a presentation by Dr. Peter Kearns (Principal administrator at Organisation for Economic Co-operation and Development, OECD) presented the role of OECD in harmonisation of risk assessment procedures and how the risk assessment approach for food and feed derived from GM plants had evolved over time. During the panel discussion, participants discussed the extent of harmonisation of risk assessment guidelines at international level. Dr. Kearns highlighted the need to remember that some foods currently on the market contain toxins and allergens, for example cassava and only correct preparation (processing) does make the food safe for consumption, therefore the risk assessment is based on a comparison of the GM crop with its conventional counterpart and aims at establishing whether the GM food is "as safe as" the conventional food. There were some questions regarding current data requirements in the EU guidelines and how these differ from other international guidelines. It appears that most countries follow CODEX guidelines for food safety assessments, however the main difference appears to be in the implementation of these Guidelines. For example, in the EU additional studies are

required to answer the same question and there is highly detailed prescription on how the data must be generated, as stipulated in very detailed EFSA Guidance documents. Participants also asked what criteria could be used to establish "History of safe use (HOSU)". In addition, it was discussed whether a better understanding of the process followed by developers to select elite events would be helpful when determining the data requirements related to unintended effects. In particular, EFSA suggested that it could be useful to publish general information on the criteria used by developers to select and discard GM events (Candidate elite events), what sort of unintended effects are observed and what is the percentage of occurrence of these effects. Another point for discussion was agro-phenotypic data; although these data are not mentioned in CODEX as a data requirement for food safety assessments, in the EU these data are typically submitted in all applications, whether for food and feed import or for cultivation. This is probably because of historic reasons due to the fact that in the early days of GM risk assessment, there were great concerns regarding the possibility of unintended effects due to the genetic modification that could led to adverse effects. A weight of evidence approach was then introduced, using data that compared the GM crop with its comparator and this included agro-phenotypic comparisons. Participants questioned whether these data are useful for the assessment of GM food and feed and whether this should still be necessary (nice to know/need to know?).

During the second session (Weight of evidence; Case study: Allergenicity), Dr. Annabelle Capt (EuropaBio Industry Team expert from Bayer Crop Science) provided an overview of the industry opinion on the weight of evidence approach used in allergenicity assessments for GM crops and how the requirements have evolved over the years in the EU. Dr. Capt highlighted some of the challenges currently faced by industry in the EU due to the imposition of data requirements that are not required elsewhere in the world, such as deviations in simulated gastric fluid (SGF) studies to include physiological conditions and the quantification of endogenous allergens in compositional analyses. Dr. Lisa Kelly (GM team leader in the Chemical Safety and nutrition section, Food Standards Australia New Zealand, FSANZ) shared her experience of how allergenicity assessments for food derived from GM crops is conducted in Australia and New Zealand. She explained that the assessment is based on CODEX (2009)[1] and follows the recommended weight of evidence approach, however FSANZ do not require an assessment of the levels of endogenous allergens as this is not a clear requirement in CODEX and they consider that there is not enough knowledge to correlate changes in levels of endogenous allergens and risk. Dr. Jan Pedersen (Risk assessor at the National Food Institute in Denmark) discussed Denmark's perspective on GMO allergenicity, where the weight of evidence suggested by CODEX is also followed. Dr. Pedersen stressed the importance of taking into account the exposure levels in the risk assessment of GM foods, which sometimes does not seem to feature in the assessments performed by EFSA. Expression levels of GM proteins tend to be extremely low and the risk assessment should reflect this more adequately. The last speaker in this session was Dr. Antonio Fernandez (Scientific officer at EFSA) who described the current approach taken by EFSA for allergenicity assessments. Dr. Fernandez explained that EFSA follow CODEX recommendations and that CODEX foresee that some of the recommendations can be modified when scientifically justified. EFSA therefore consider that SGF studies should be conducted under conditions more representative of real physiological conditions and that the quantification of endogenous allergens is essential to protect vulnerable groups in the population. He also shared that EFSA have a working group working

[1] CODEX (2009) Principles and guidelines for food safety assessment of foods derived from modern biotechnology. Codex Alimentarius Commission, Rome

on further guidance and that this guidance will include further allergenicity assessments involving digestibility, measurement of endogenous allergens and non-IgE mediated responses. It is expected that this guidance will be adopted in spring 2017, after a consultation workshop with stakeholders at the end of 2016.

The information exchanged during these presentations was discussed during the panel session, led by the speakers and moderated by the session chair Dr. Kitty Verhoeckx (Netherlands organisation for applied scientific research, TNO). Participants discussed the importance of the weight of evidence approach to assess the allergenic potential of new proteins, since to date; there is no validated single test that can predict accurately that a protein will be an allergen. Some participants made the observation that although different countries claim to follow CODEX guidelines, it is clear that interpretations on the data requirements and their implementation obviously differ, leading to the question of whether CODEX guidelines should be reviewed. Some of the discussions centred on the usefulness of the additional studies requested by EFSA to comply with the CODEX guidelines. The requirement to measure endogenous allergens in compositional analyses was heavily contested as it is still unclear how endogenous allergens fluctuate in conventional varieties and how the amount of allergens correlate with elicitation and sensitisation. However, since these requirements are written in the Implementing Regulation (EU) No 503/2013, it seems that there is no longer a scientific forum in which to discuss the relevance of this. In line with CODEX, all regulatory bodies except EFSA accept search strategies differing from the one indicated by FAO/WHO (2001) when they are scientifically justifiable.

Session 3 (Risk vs. Hazard and Exposure. Case study: protein safety) was opened by a talk by Dr. Donald MacKenzie (Regulatory affairs lead for the golden rice project at the International Rice Research Institute). Dr. MacKenzie described the process that is commonly followed to assess the safety of GM proteins. He proposed that since this process has many commonalities in many countries and the same conclusions are reached, regulatory authorities could base their authorisation decision on the conclusions of the other authorities with similar regulatory requirements. Dr. Anna Lanzoni (Senior Scientific Officer at EFSA) described the protein safety assessment followed by EFSA, which in her view, is in line with international guidelines. Dr. Lanzoni explained that current EFSA requirements for 28-day toxicity studies are only requested when the toxicity of the new proteins cannot be established by other means. One of the key pieces of information that could determine the need for such studies on a case-by-case basis, would be detailed knowledge of the mode of action and structure of the protein. The next presentation was given by Dr. Marco Corvaro (EuropaBio Industry team expert from Dow Agrosciences), discussing the industry position on 28-day oral toxicity studies. Dr. Corvaro stressed that in view of the EU Directive 2010/63/EU, there is an obligation to minimise animal testing and tests should only be conducted when there is a good justification and a clear risk hypothesis.

A panel discussion moderated by Dr. Francesca Tencalla (independent consultant, ToxMinds) then followed. The discussion started with a discussion on the 28-day repeat dose toxicity study, where all appeared to agree that should only be conducted when necessary, based on a formulated hypothesis and depending on available knowledge of the protein. There was a comment that this is in line with the approach followed in other areas, such as chemicals, where structure-activity relationships are examined. This could be applied to proteins and data for a protein could be used for the assessment of similar proteins. The participants also discussed the importance of considering the levels of exposure in the assessments, although Dr. Lanzoni commented that, in her opinion, EFSA also needs

to look at potential future uses of products that may lead to higher exposure. Only EFSA requires repeated dose toxicity testing as all other regulatory authorities consider that acute toxicity tests are sufficient. The participants thought this was based on the fact that none of them were aware of any protein that would only show effects when administration was repeated while having no effects when administered acutely at a high dose. Dr. Lanzoni clarified that the absence of such an example does not exclude that specific proteins might only show responses when repeatedly administered.

The next day started with Session 4 (Assessing unintended effects. Case study: Risk assessment of GM plants with stacked traits). Dr. Kensuke Katsuta (Risk assessor at the Japanese secretariat of the Food Safety Commission) described past and current approaches for assessing the risk of GM plants with stacked traits in Japan. Dr. Katsuta explained, that based on the experience gained to date, the Japanese Authorities had decided that a reduction in the review process and data requirements for stacked products based on the trait and the category the fall into, under certain circumstances was warranted. The classification of single events falling into different categories is now based on the function of the traits expressed and its impact on the metabolism of the plant. This is used to guide the need for a risk assessment and determine which stacked events do not require specific data and which stacks do need further evaluation. Dr. Laura Privalle (EuropaBio Industry expert from Bayer Crop Science) presented a summary of the product development process that is followed by developers and how events are screened and selected for further development. Dr. Privalle explained some of the criteria used in the screening process of candidate events, which is mainly based on phenotypic characteristics. She acknowledged that unintended effects due to genetic modifications do occur, in the same way that they occur in conventional breeding, but most events likely to lead to unintended effects are counter selected during the development process and unlikely to become lead events. Dr. Esther Kok (Head of the department of novel foods and agrichains at Wageningen University in The Netherlands) summarised a publication describing the EU member states' perspective on risk assessments of GM plants with stacked traits. Dr. Kok explained that the current approach set out in EU guidelines differs from the rest of the world and that many member states urge for a revision of the requirements, in that no additional requirements for the risk assessment of stacks should be imposed for food and feed applications if there is no indication of interactions. This was followed by a presentation by Dr. Howard Davies (former director of the James Hutton Institute in the UK) describing past and current EFSA approaches for the risk assessment of stacks in the EU. Dr Davies pointed out that discussion on the requirements set out in the implementing regulation will be difficult as this is now legally binding and more rigid. However, certain analyses conducted by applicants are not required by the Implementing Regulation (EU) No 503/2013. The last presentation on this session was given by Dr. Penny Hunst (CropLife International industry expert from Bayer Crop Science) who summarised how GM plants with stacked traits are assessed in the EU and globally. Dr. Hunst highlighted that major differences in the requirements are observed between the EU and other countries leading to asynchronous review timelines.

The panel discussion for this session was moderated by Dr. Monica Garcia-Alonso and led by all the speakers in the session. Many comments suggested that there appears to be a need to revise the way in which GM plants containing stacked events are assessed in the EU, but that for that there needs to be a political will and scientific support. As described by Dr. Katsuta, Japan recently changed the assessment process for stacks, concluding that some stacks did not need any further assessment if the singles had been assessed and fall into a certain category. In addition, the Australian representative described that glycosylation and endogenous allergen studies used to be submitted to assess

allergenicity are no longer required. So there are precedents of countries making requirements fit for purpose once experience is gained. Many participants agreed with the approach proposed by The Netherlands and other Member States that contributed to the presentation summarised by Dr. Kok. There was a request to follow a pragmatic implementation of the Implementing Regulation (EU) No 503/2013. Representatives of the European Commission noted the comments. During the discussion, it was highlighted that one of the major obstacles during the assessment process of GM products is the fact that dialogue between EFSA and applicants is limited, whereas this is a key part of the process in other countries. There appears to be agreement that more dialogue would be beneficial and the absence of EFSA during the stack session was noted by several participants indicating a lack of dialogue on this subject matter.

After this session, Dr. Peter Kearns summarised the workshop and moderated the final panel discussion. The panellists for this session were: Dr. Howard Davies, Dr. Monica Garcia-Alonso, Dr. Penny Hunst, Dr. Donald MacKenzie and Dr. Jan Pedersen.

During this final discussion some of the issues raised during the workshop were re-visited for further discussion. One of the key themes was the difference in data requirements for food safety assessments imposed in the Implementing Regulation (EU) No 503/2013 from CODEX and how the flexibility which is within the legislation should be used to allow for a more science based approach. Discussions touched on some of the more specific requirements. It appears that differences of opinion also exist between member states and EFSA. Participants asked whether the European Commission could facilitate the discussion. The panel session also discussed whether current EU guidelines are in line with basic risk assessment principles. The views appear to suggest that although EFSA guidelines and the Implementing Regulation (EU) No 503/2013 are based on risk assessment principles, the current implementation of this regulation does not allow flexibility to follow a case-by-case and weight of evidence approach. The prescription on data generation and the requirements for stacks, stray from these principles, as they do not seem to take into account the low level of hazard associated with most GM stacked products. This led to the discussion of “proportionate” data requirements, where less data could be provided for products for which the hazard and exposure would be low and more data would be provided for products where there is more uncertainty regarding the hazard. It appears that some countries have rationalised and simplified their data requirements after years of experience, while in the EU the requirements are getting more complex. There were suggestions that there is room for improvement for food and feed risk assessments in the EU and that a dialogue between EFSA, member states and applicants is essential to move forward. The discussion also considered whether countries could cooperate more efficiently since the data package prepared for food and feed assessments is basically the same for all countries, rather than having all countries looking at the same data, reaching similar conclusions, could the assessment be done in a way that served multiple countries?

Dr. Feyza Selcuk (Chair of the regulatory operating committee in EuropaBio, from Monsanto) provided some concluding remarks and take home messages, officially closing the workshop.