

Draft guidance document for the environmental risk assessment of genetically modified plants

Motivation for ENSSER to comment on the EFSA Draft Guidance

The European Network of Scientists for Social and Environmental Responsibility (ENSSER) was founded with the aim to advance science and research for the protection of the environment, biological diversity and human health against negative impacts of new technologies and their products. Consequently, ENSSER promotes the critical European and international discourse on new technologies, their impacts and their regulation. One specific aim of ENSSER in this context is to improve the quality of basic and regulatory science used in the risk analysis of existing and emerging technologies and their products such as genetically modified organisms, chemicals, food technologies, geo-engineering, nanomaterials, and synthetic biology, including the risk of their military use.

Several of ENSSER's members are participating in GMO risk research, assessment and communication since many years. They also participate in the current debate within the EU, but also within the international Cartagena Protocol on Biosafety, on how to develop GMO and specifically GM plant risk assessment to base it on sound methodology that aims at effectively minimising or avoiding risks for the environment and human health.

The ENSSER GMO Consultation Task Force was formed to study the EFSA draft guidance document for the environmental risk assessment of genetically modified plants and to comment on its various sections. The ENSSER input which has been submitted on April 29 2010 to the EFSA. ENSSER will continue to participate in this process and to inform the public about outcome of the consultations.

EFSA documents for downloading: <http://www.efsa.europa.eu/en/consultations/call/gmo100305a.htm>

In general, the guidance document represents a considerable progress in moving the risk assessment towards the current state-of-the-art of scientific investigation – with exception of the parts on problem formulation and monitoring for which great room for improvement remain.

What would improve the overall approach is an introductory development of a system of hypotheses of potential effects departing from the genetic modification through all levels of biotic organisation as a starting point for the subject specific categories explained in Chapter 3. An overall elaboration of relevant cause-effect chains in which the GM organism is involved would make all subsequent steps more targeted.

However, also a number serious scientific deficits remain that we explain in detail. ENSSER considers as particularly worrying a number of serious cases of selective citing of scientific publications and the selection of studies that were favoured over others. We strongly urge EFSA to correct this serious deficit as it will jeopardize the entire guidance document and even overrule the recognized improvements.

Abstract

Summary

1. Introduction

208: Trait segregation (frequently discussed as coexistence) is an issue which needs to be considered since it can give rise to the formation of unintended and, thus, untested stacked hybrids which may occur inside cultivated fields or outside (as ferals). This can bear significant risks for the environment as well as human and animal health.

2. Strategies for ERA of GMO plants

253: It would be useful to quote here the "Biosafety Assessment Tool" in addition since it provides a lot of relevant information in the given context, see: <https://bat.genok.org/bat/>

2.1. Comparative safety assessment as a general principle for the risk assessment of GM plants

262-275: this section is too unspecific. We suspect that this means to maintain the old way of characterizing a GM plant by making crude comparisons between some basic parameters (such as water, ash, protein content, amino acids, etc.) and any such measurements ever recorded for that plant, including 'historic' records without clear rules for acceptable and unacceptable degrees of difference - when a plant is not considered substantially equivalent anymore. None of that exists to date and has not been included in this GD either. Hence, we assume that the 'old' lack of rules continues to apply. Any number of significant differences in the parameters is acceptable and, in reality, the possibility of a substantially 'inequivalent' plant does not exist as long as it 'looks like the crop, smells like the crop and tastes like the crop'. This approach has long been criticized as not scientifically sound and, apparently, will continue to do so. This approach has important repercussions for the entire proposed ERA as it actually questions fundamentally the validity and seriousness of the proposed improvements. Under the 'old' guidance, this approach served as general justification for exempting to test the whole GM plant and focussing the testing on very limited tests with the bacteria-produced transgene product. If these do not yield 'results of concern', the GM plant is considered safe and no more tests with the GM plant are deemed necessary for safety reasons. Interestingly, for agronomic and efficacy reasons, always the whole plant is tested. Here, the applicants never only rely on data with microbial transgene products on some surrogate species. This appears to remain unchanged in the new guidance and, thus, puts the entire ERA at risk of being again unacceptable to the science community concerned with biosafety issues outside of EFSA. In particular for eukaryotic proteins/genes it is quite critical to do a thorough post-translational characterization.

264: Data from different sites or environments cannot be pooled but have to be assessed separately.

278: Ecosystems and landscapes should be added as a protection unit, since it is covered as such by nature conservation regulations and in addition, is a biological organisation level above the ecosystem level.

276-280: Assessment endpoint should not only reflect protection goals set by EU legislation, but also those set nationally by EU member states. These can for example include the protection goals of the national biodiversity strategies.

287-288: When changes in the phenotype are assessed, ecological characteristics should be explicitly taken into account. Among others this includes frost and heat tolerance, resistance to abiotic stressors, and dormancy. The assessment should not only focus on agronomic aspects such as disease and pest resistance, growth performance and/or yields.

291: We disagree with this statement (291-293). Unintended effects may well be inconsistent effects for example when they are under environmental control. If the applicant were to pool the data from different geographic regions, e.g. Spain, Puerto Rico, Chile, US, temperate Europe, this could introduce so much variability that no 'consistent' effect can be seen anymore although there is one. It ignores G x E interactions that are well established in the scientific literature and considered critical to understand variability/plasticity in plant attributes and their evolution but are still little understood. In the past, various unintended effects of GM plants have been reported are associated with different environments: lignin production, stem splicing, boll drop etc – some were linked to heat and drought stress – hence a GM plant grown under moist conditions would not show the same effects and, thus, would exhibit 'inconsistent' effects and ignored in ERA.

While we agree that some unintended effects may be predictable, for example, if the site of integration in the genome is known, unintended effects may just as well be entirely unpredictable if, for instance, they are coupled to environmental triggers. Often, we do not understand these at the onset and only if we look, we find them and can engage in focussed research to understand the underlying reasons for the unintended effect. Hence, we strongly recommend, that the text includes provisions for unintended and unpredicted effects.

293: Two different means are given for the detection and identification of unintended effects (analysis of flanking regions followed by comparative analysis incl. compositional, phenotypic and agronomic traits). However these two means are not related. It is not specified how GM plants should be tested for unintended effects in regard to the considered parameters or environmental conditions. The applicants therefore should be requested not only to present their results but also to present and evaluate their efforts to detect unintended effects and to assess the remaining uncertainty.

"Unintended effects" can be predictable (and explainable) but unwanted, but they can also be unpredictable. They can also go beyond compositional factors. Prediction in the light of current knowledge seem to be too narrow as there are huge knowledge gaps.

2.2. Objectives of the different steps of the environmental risk assessment

305-315: "The ERA consists of the 6 steps described in the Directive 2001/18/EC ..." We note that the GD makes inconsistent use of the term 'steps' and 'tiers': technical and conceptual steps of the ERA process. Here, the ERA process is described to be a step-wise procedure consisting of 6 steps. The EU Directive 2001/18/EC, Annex II, speaks of 'points' that 'should be addressed' and then lists the 6 points, EFSA now calls them 'steps'. In contrast, the same EU Directive describes 'steps' in Article (24) as: 'containment of GMOs is reduced and the scale of release increased

gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken." – clearly relating to a physical degree of containment involving technical steps: closed environment (laboratory, glass house) – semifield – field. Article (24) follows the internationally accepted terminology of the "step-by-step approach". We recommend that EFSA clearly defines what are 'steps' in the sense of the EU Directive and what are other kinds of 'steps', e.g. of ERA or the later introduced stepwise nontarget organism selection procedure.

2.2.1 Step 1: Problem formulation (including hazard identification)

We note that neither in Dir. 2001/18/EC nor in the Commission Decision 2002/623/EC the term 'problem formulation' is being used. In 2003, this term was first introduced in the context of ERA of GMOs by Hill & Sendashonga. The concept was further operationalized and applied to specific cases of GM crops by Nelson et al. and published in 2004 (In: Hilbeck et al. 2004, Vol I, peer-reviewed book series published by CABI). In the following years, publications by industry representatives came out presenting an alternative concept of what Problem Formulation should entail (e.g. Raybould 2006). So, simultaneously, over the following years, several documents were published on this issue from industry and industry-aligned scientist on the one side and non-industry aligned scientists on the other side. (see below). Interestingly, in this new EFSA GD, we only find the contributions by industry and industry-aligned scientists and no mentioning of those publications by independent public sector scientist groups. We find this quite revealing regarding what thinking form the basis of this part of the EFSA GD.

Below we list the publications of a widely known, peer-reviewed CABI book series on 'Environmental Risk Assessment of Genetically Modified Organisms'. While the entire books of the CABI series are highly relevant to the EFSA GD, we only highlight here the chapters that should have been considered and formally included in the development of this section of the GD. We note that of the **11 citations** listed in relation to problem formulation on page 15, in footnote 19, **3** were solely written by industry, **6** with co-authorship of industry representatives and scientists mainly from the US, Argentina and Australia who develop ERA concepts for the regulatory context in these countries that differ significantly from those in the EU and do not recognize the Cartagena Protocol on Biosafety with its provisions for ERA. So, from this fact, one is reasonably lead to conclude that corporate thinking had a disproportionate influence on the development of this section. This finds further support in the fact of the total lack of citation of all of the pertinent references listed below that we know are well-known to several EFSA GMO panel members. Furthermore, while the EPA citation in footnote 19 is proper and important as this was the first significant introduction of the problem formulation step into ecological risk assessment, it did not have GMOs in mind and the US is not applying it to GMOs. This leaves only **1** references that indeed discusses problem formulation in the context of GMO ERA and in the context of the Biosafety Protocol on Biosafety that is also pertinent to the EU regulations (i.e. Hill & Sendashonga 2003). Storkey et al. 2008 (as the only other publication without industry participation) does not deal with problem formulation (it is not mentioned once in the paper) but with comparative experiments of farm management practices. Unsurprisingly, the industry-focussed goals differ significantly from the goals proposed by independent public sector scientist groups. All in all, the problem formulation step as obviously envisioned by EFSA and grounded in the cited industry-dominated concepts aims at justifying the **narrowing of the ERA** frame to the **minimum set of endpoints/data** (see below) necessary and places great **emphasis on desk exercises and heuristic argumentations**. For instance, the EFSA - industry approach to 'Problem Formulation' envisions a comparative assessment in relation to the current practice (selection of choice usually is a worst practice that is most likely to make the GMO option look good easily but is not at all future-oriented) and based on the concept of familiarity as discussed earlier already. In contrast,

the approach to problem formulation as developed by others envisions the comparison to include other alternative solutions options that aim to solve the same problem as the suggested GMO option and therefore includes an 'option assessment'. The aim here is to place problem solving at the center and allow a governmental risk assessor to make decisions not only in face of current 'worst' practices but also other, future practices under development and **future alternatives** that aim to solve the same problem. The approach suggested and extensively tested and written about in the bulk of publications listed below is **inclusive, broad based and devises a procedure that allows to reduce the ERA based on data obtained with the GMO** - not heuristic arguments and speculations derived from other applications (e.g. purified microbial proteins, other GM plant species) and environments **without additional studies** (see below).

For illustrative purposes, we list some cited aims for problem formulation found in the references listed in the EFSA GD:

Wolt et al. 2009: "Adopting a **harmonized** approach to problem formulation should bring about **greater uniformity** in the ERA process for GM plants among regulatory regimes **globally**."

Raybould and Cooper 2005: "If estimates of the test endpoints already exist, the risk assessment can be completed **without additional studies**." - notably the endpoints

Raybould 2006: "To reduce environmental risk, **the objective of problem formulation** should be to **identify the minimum quantity of data needed for risk assessment** to demonstrate the safety of a GM crop."

Raybould 2006: "**Standardization of data requirements** for risk assessments is suitable for products where the problem formulations are similar. Chemical pesticides are an example of a class of product for which standard data requirements for environmental risk assessment make sense"

In other words, business as usual - follow the guidelines for pesticide testing as is the current procedure for safety data on GMOs. Applied to the current applications of GM plants of which the vast majority carry a Bt and/or HR trait - no more testing, e.g. of stacked events if their parents events have already been commercialized.

In our view, these two elements – grounding the ERA in the concept of familiarity and narrow, exclusive approach to problem formulation (hazard identification) - undermine all improvements suggested in the rest of the GD, since, if applied, they make all the following testing obsolete or offer the grounds for complete exemption and releasing of new GMO events untested for environmental biosafety.

Neglected citations of relevant peer-reviewed publications & missing attribution of concepts that went into the proposed changes of the GD, namely the selection procedure of nontarget organisms:

Hilbeck, A. and D.A. Andow (eds.). 2004. **Environmental Risk Assessment of Transgenic Organisms, Volume 1**: A Case Study of Bt Maize in Kenya. CABI Publishing, Oxon, UK.

Relevant chapter in book:

Nelson, K.C., G. Kibata, L. Muhammad, J.O. Okuro, F. Muyekho, M. Odindo, A. Ely and J.M. Waquil. **Problem Formulation** and Options Assessment (PFOA) for genetically modified organisms: the Kenya Case Study.

Hilbeck, A., E. Fontes and D.A. Andow (eds.). 2006. **Environmental Risk Assessment of Transgenic Organisms, Volume 2**: Methodologies for assessing Bt cotton in Brazil. CABI Publishing, Oxon, UK.

Relevant chapter in book:

Capalbo, D.M.F., M.F. Sion, R.O. Nodari, S. Valle, R.F. dos Santos, L. Coradin, J. de O. Duater, J.E. Miranda, E.P.F. Dias, Le Quang Quyen, E. Underwood and K.C. Nelson. Consideration of **Problem Formulation** and Option Assessment for Bt cotton in Brazil.

Andow, D.A., A. Hilbeck and Nguyen Van Tuat (eds.). 2008. **Environmental Risk Assessment of Genetically Modified Organisms, Volume 4**: Challenges and Opportunities with Bt Cotton in Vietnam. CABI Publishing, Wallingford, UK.

Relevant chapter in book:

Nguyen Van Uyen, Phan Van Chi, Nguyen Van Bo, Hoang Thanh Nhan, Le Quang Quyen, Nguyen Xuan Hong, Le Minh Sat, A. Wals, D.M.F. Capalbo and K.C. Nelson. Consideration of **Problem Formulation** and Option Assessment (PFOA) for Environmental Risk Assessment: Bt cotton in Vietnam.

Additional publications:

Problem Formulation and Options Assessment Handbook: A guide to the PFOA process and how to integrate it into ERA of GMOs. pp. 237. Web based resource at <http://www.gmoera.umn.edu/public/publications/index.html>

Hilbeck, A., K. Nelson D. Andow and E. Underwood. 2004. **Problem Formulation** and Options Assessment (PFOA) to Assess the Ecological Risks Associated with a GM Crop. In: Breckling, B. and R. Verhoeven (eds.), Risk, Hazard, Damage - Specification of Criteria to Assess Environmental Impact of Genetically Modified Organisms. Naturschutz und Vielfalt 1, Bonn, pp 131 - 143.

357: "seeds of the GM plant during transportation and processing potentially leading to sporadic feral GM" Not only seeds can lead to feral GM plants but also other vegetative propagules (onions, tubers...). These need to be included as well.

392f: "In the problem formulation process, applicants should on a case-specific basis" The applicant should analyse which primary and also secondary effects could be involved (causal network analysis) and identify those which could be involved in direct, indirect, delayed, and combinatory effects.

398: "Define assessment endpoints being representative of the aspects of the environment that need to be protected from harm according to protection goals set out by EU legislation" We urge to also include 'national legislation' or it will not help the member states much.

However, this part should not be left to the discretion of the applicant alone. Endpoint definition as a normative process must be guided by national and EU laws and be agreed upon by other stakeholders and society at large. Sound and acceptable endpoint definition needs to be undertaken through public consultations and decision making procedures. This would be the case if the Problem formulation process as developed by the global IOBC working group and published in the CABI book series listed above was considered, as this is a broad and inclusive stakeholder based approach framing the risk assessment based on more than the interests and needs of industry.

409-411: "Set the limits of concern for each assessment endpoint in order to define the minimum relevant ecological effect that is deemed of sufficient magnitude to cause harm." This is entirely unacceptable – this is NOT a task of the applicant. Otherwise the applicant might as well just write its own rules and safety data. It can be safely stated that the 'limits of concern' for environmental harm by an applicant (more often than not chemical industries) differs enormously from those by anybody else. There is no justification why the applicant should be the only one deciding what

harm is acceptable and 'biologically relevant' – for whom? The applicant or society and environment? This has to be eliminated if it is not making the entire ERA obsolete from the start.

412: "Define relevant baselines." This is under no circumstance acceptable. Otherwise regulations may just as well be dropped altogether.

Defining baselines of comparison, limits of concern, biological significance etc are true value-laden, normative issues that can under no circumstance be left to the applicant with a vested interest alone. These things must be defined by society and follow laws.

420: In table 1 under "Ecological Functions the following issues should be mentioned as well: "pollination" and "pest control by antagonists".

2.2.2. Step 2: Hazard characterisation

2.2.3. Step 3: Exposure characterisation

464: "However, if quantitative terms such as "high", "moderate", "low" or "negligible" are used to express such likelihoods, then the link between likelihood and probability." The likelihood most likely will depend on the characteristics of the receiving environment and usually cannot be estimated without an environmental characterisation. This should be brought to the attention of the applicants in an adequate way.

2.2.4 Step 4: Risk characterization

In the assessment of the level of hazard, an evaluation of standard errors should be provided for all experiments carried out that lead to the final probability estimate.

487: "The risk is characterised by combining the magnitude of the consequence of the hazard multiplied by its likelihood." A few paragraphs above (464 ff), qualitative characteristics like "high, moderate ..." have been introduced. How could they be multiplied? This construction is largely unfeasible in ERA. Rather than recommending a pseudo-quantification, the effects that bring up risks are better described verbally.

2.2.5. Step 5: Risk management strategies

2.2.6. Step 6: Overall risk evaluation and conclusions

2.3. Cross-cutting considerations

2.3.1. Choice of comparators

558: "It is imperative..." but eventually not always. Therefore a better formulation would "It can be useful..."

542: Choice of comparators: The word "isoline" is not mentioned. Negative segregants are not allowed.

592: "The applicant should discuss potential risks arising from the genetic background of varieties which might subsequently include the GM event and how these might alter the conclusions of the risk assessment." This requires a more comprehensive metabolomic study. The GD should require such an investigation since it is 1. state-of-the-art and 2. an indispensable starting point for any risk consideration.

595: data may be required... different genetic backgrounds have never been be problem up to now, have not be discussed up to now.

573: standard farming practices: needs to include organic agriculture.

553: Negative segregants are not suited to detect unintended effects caused by genetic modifications outside the insertion locus. The document should consider this aspect and the applicant should be requested to include it when reviewing his efforts to detect and identify unintended effects (see comment on 291-303). When an additional comparator is included comparisons have to be made between a) the test and the comparator and b) the test and the additional comparator. It might be advisable to further compare the differences obtained from a) with b).

558: "The comparison of GM plant and comparator should also include a comparison under agronomic practices but cannot replace the comparison of the two plants as such because the use of agrochemicals such as insecticides can mask adverse effects on non-target organisms" The statement that for "insect-resistant GM plants, equivalence with a conventional counterpart is highly unlikely if the latter is managed without the pest control that would be typically applied to conventional, non-GM plant." is not correct. In Germany for example, insecticides are only applied in less than 3% of maize production. The comparison for Bt maize should therefore be maize production without insecticide application.

In general a fuller picture could be achieved if the insecticide producing plant would be compared to both a comparator with and without insecticide, and figures for the general insecticide use should be given in order to assess whether insecticides are used and to what degree.

564: The material produced without any weed management also needs to be considered.

569: The document here focuses on high-input agriculture with high use of pesticides, but even in such systems pesticide use can widely differ. For example in integrated pest management, the approach is to use as little pesticides as possible by defining thresholds. Such differences - or the general approach towards agricultural systems with lower agrochemical use - are not considered. In the ERA, national circumstances as requirements or best practise guidelines to apply IPM concepts and economic thresholds have to be stated and taken into consideration.

579: We appreciate that GM parental lines or GM lines containing previously stacked events should be included as additional comparators. However, this approach is contradicted by the lines 1143 that state that single parental lines may be included for comparison.

592: "The applicant should discuss potential risks arising from the genetic background of varieties which might subsequently include the GM event and how these might alter the conclusions of the risk assessment." This requires a more comprehensive metabolomic study. The GD should require such an investigation since it is 1. state-of-the-art and 2. an indispensable starting point for any risk consideration.

2.3.2. Receiving environment(s)

Here and in other cases the effects of GMOs on the microbial ecosystem should also be mentioned and tested as several studies have confirmed changes in the microbial flora in terms of species composition. Particular attention should be given to Mycorrhizae as they are an environmental component critical for plant growth and survival.

An assessment of the soil ecosystem including animals, plants both unicellular and multi-cellular, fungi, bacteria should be included in the guidance to applicants.

The document needs to contain clearer guidance on the conceptual basis of how receiving environments are integrated with the cultivation areas of the GM plant in question since this defines the number of field trials that will be needed to generate sufficient field trial data.

642: "Applicants should take into account interactions of the GM plant with any other GM plants that have been deliberately released or placed on the market in the same receiving environments, including interactions between the specific cultivation characteristics (e.g. use of plant protection products) associated with the different GM plants. In addition, applicants should consider likely and/or predicted" It is unclear why pesticides are emphasized here, while other cultivation practices and characteristics are not.

2.3.3. General statistical principles

The statistical analysis protocol proposed now by the GMO Panel of EFSA (1), termed power analysis and advocated by Joe Perry (2), claims that no means of quantification of substantial equivalence existed in previous ERA requirements. Therefore, in this concept, in order to establish a natural background value of any measured characteristic of a GM plant variety studied, they propose a number of comparators included besides the isogenic line that has been solely required previously in such experiments as control. Proposed comparators include different commercial varieties. According to the notion, the deviation among these comparators serves as a more realistic background value than that in the isogenic line, and meta-analyses or multivariate analysis reveal more reliable diversity indices for the GM variety studied. In reality, the use of different varieties (even possibly of different vegetation length or FAO number) simply broadens the standard deviation of the non-GM varieties, and therefore, makes the possible difference between the GM variety and its isogenic line, possibly significant statistically, disappear in this increased background. Moreover, such power analysis protocol could allow comparison among field experiments carried out at different locations globally, possibly further broadening the thus increased background.

1 European Food Safety Authority, Panel on Genetically Modified Organisms (GMO Panel) (2010) Scientific Opinion on the assessment of potential impacts of genetically modified plants on non-target organisms. EFSA Journal 2010; volume(issue):xxxx. [55 pp.]. doi:10.2903/j.efsa.20NN.NNNN. (<http://www.efsa.europa.eu/en/consultations/call/gmo100305-ax1.pdf>)

2 Perry JN, ter Braak CJF, Dixon PM, Duan JJ, Hails RS, Huesken A, Lavielle M, Marvier M, Scardi M, Schmidt K, Tothmeresz B, Schaarschmidt F, van der Voet H (2009) Commentary: Statistical aspects of environmental risk assessment of GM plants for effects on non-target organisms. Environ. Biosafety Res. 8 (2), 65-78. DOI 10.1051/ebr/2009009

794: "In medical science a level of 80% is usually considered to be an acceptable level for statistical power, but it is recognised that for ecological field trials this is an aspiration that may only

be achievable in exceptionally well-resourced and extensive experiments (Perry et al., 2003). Notwithstanding, optimal experimental design should be directed to attain power as high as possible." Yes, this statement can be accepted. It justifies a very high level of remaining uncertainty, i.e. actually existing effects which cannot be detected with sufficient security during ERA. However, if this is the case, then in ANY case an according case-specific monitoring would be mandatory where this applies. Otherwise, the monitoring would not make sense. See below.

814: in Table 3 "organisms tested under optimised conditions" This should be changed to "tested under 'defined' conditions." In lab testing, stress tests can also be executed.

822: "organisms for which testing in the laboratory is inappropriate (for example species that are highly mobile, such as bees; or species for which rearing methods are inadequate; see chapter 3.4)." In particular for bees, there are many relevant issues which can and must be tested under controlled (laboratory) conditions.

853: "representativeness across geography and climate. Unless explicit appropriate justification is given by the applicant, each field trial should be replicated over at least two years, within each of which, there should be replication over at least three sites. However, the explicit requirements above for replication to achieve representativeness do not apply to confirmatory field data for the assessment of unintended." To recommend 2 years for 3 sites – to achieve representativeness for the diverse European conditions seems entirely impossible. In particular because this excludes any studies of effects that occur in crop rotations. Two crop rotation periods would be far below a minimum of what is ecologically reasonable and required. Otherwise, practically ANY question under investigation would have to be assessed in case specific monitoring. The ERA should be an approach to clarify risks and not "to sweep them under the carpet".

860: The applicant should be given more guidance of what is required here in order to reflect sufficiently on the relevant meteorological, agronomic and soil conditions.

863: "In particular, the applicant must provide explicit reasons when data from field trials in EU Member States are not available. It is apparently not sufficient to provide reasons." It is apparently not sufficient to provide reasons. A reason would be that field trials may be costly. So if relevant information is not there, then data from within Europe must be presented.

908: A description of the biological conditions (e.g. pest and disease infestations as a baseline) should be added.

970: The applicant should be requested to reflect on whether their comparative safety assessment is complete and on the assumptions on which it is based.

In case of difficult statistical treatment of micro-flora and particularly of bacterial composition it should be suggested to carry out a meta-genomic analysis with the appropriate molecular tools.

2.3.4. Long-term effects (including techniques for their assessment)

Long-term effects also need to include synergistic effects.

2.3.5. Risk assessment of GM plants containing stacked transformation events

1126: replace "may be" with 'will be'. It has to be clear from the onset, that a stacked event is regarded as a new event with regards to regulation and RA, ie requiring a new and full RA with its own set of data. Data and information will be required from the applicant that are derived from experiments and field trials with the stacked event as a whole. These should cover a broad range of environmental conditions incl. exposure to biotic and abiotic stresses, as different conditions

may give rise to different combinatorial effects (including due to epigenetic changes). It has to be clear that submission of data, information and RAs from the parental transformation events alone is not sufficient.

1127: ... referring to "**single event(s) antagonistic effects**": Of interest are metabolic alterations. Metabolomic profiles are needed to assess this. Accordingly they must be presented.

1130: change c) to: 'potential synergistic, additive or antagonistic effects or any other effects resulting from the combination of the events' – or 'potential combinatorial effects, including synergistic, additive or antagonistic effects ...'. It should be made clear here, that interactions between 1) the modified or inserted genes, 2) the stacked proteins and 3) the stacked traits as well as interactions with 4) endogenous genes/proteins should be considered and assessed, and that 1) - 4) include influence on and interaction with metabolic pathways and physiological processes. Assessments should thus cover, for example, whether the different events affect the same biochemical pathways or physiological processes or may have any combinatorial effects that may result potentially in new or increased adverse effects compared to the non-modified comparator as well as the parental events.

1134: In the current draft GD it is left to the applicant whether the applicant wants to provide experimental data or give a rational justifying why there is no need for the assessment of all possible sub-combinations of the stacked event. If the applicant considers no experimental data necessary they need to show that the stacked event behaves the same as the single events and sub-combinations with respect to three different criteria (a, b and c) – yet the data requirements for a, b and c are not specified. In addition, the criteria for the rational are not elaborated any further. We regard it as paramount that the applicant should be required to provide a full RA of stacked events, and provide the full set of data for them, including for c). A 'scientific rationale' can not substitute for experimental data, particularly when dealing with uncertainty.

1142: As outlined in section 2.3.1, a conventional counterpart used as comparator should have a genetic background that is as close as possible to the GM plant, i.e. a (near)-isogenic line. The applicant should be required to provide data and rational as to why the comparator chosen is the closest possible to the stacked event crop.

1143: The document here states that single parental GM lines or lines containing previously stacked events for which a full risk assessment exist may be included as additional comparators. In contrast to that, it is stated in line 579ff that it should be done. The prior used term "should" is in line with the EFSA guidance document on stacked events.

1144: The 'may' used here should be replaced with 'should'. This is appropriate and in line with section 2.3.1 (line 581) and with the EFSA GD on stacked events.

1156: There is no paragraph covering gene flow, which may occur either as stacked event or in any sub-combination. This may give rise to increased persistence or invasiveness and requires assessment. Furthermore, the applicant should provide methods and reference material for detection and identification of the stacked event and also all the sub-combinations.

1157: The paragraph should make reference to all possible combinatorial effects, including antagonistic effects. Reference should also be made to any potentially new or increased endogenous toxins, harmful substances and/or antagonist that may arise from the combination of events. Assessments should be based on experimental data collected in field trials over a number of growing seasons and laboratory feeding studies over a number of generations using plant material derived from the stacked event. We fully agree with the requirements to assess resistance issues, including development of cross-resistance.

1166: The assessment of effects of stacked events on NTOs is crucial. Harm to NTOs may not only arise from the combination and interaction of biocidal events, but from the combination and interaction of any events, due to combinatorial effects on the various levels (gene expression, transcription, translation, biochemical & metabolic pathways, phenotypical processes). The applicant should be required to fully test and assess the stacked event GM plant for adverse effects on NTOs. Thus change 'may be' (line 1170) to "will be".

1178: "Post Market Environmental Monitoring Plan" This does not take explicitly into account intended or unintended synergistic effects. It may well require additional observations compared to the single events.

3. Specific areas of risk to be addressed in the ERA

3.1. Persistence and invasiveness including plant-to-plant gene flow

3.1.1. Step 1: Problem formulation

1227: "plants that colonize and invade semi-natural and natural habitats where they reproduce and establish self-perpetuating populations" Proposed addition: Self perpetuating populations can exist exhibiting intermittent occurrences (not constant at particular locations) involving persistent seed banks.

1283: "Figure 4: Questions defining four stages of information requirements to test formulated hypotheses concerning persistence and invasiveness of a GM plant itself, or of its wild relatives as a result of" Above (in line 794 ff) it was stated, that considerable uncertainty occurs. Thus it is inappropriate that Fig. 4 implies that all questions could be answered by yes and no. Instead, e.g. for Stage 1, a guidance should be provided how to handle "uncertainty remains". For stage 2: How is the likelihood, that "either" occurs under changed environmental conditions or under altered conditions concerning the genetic background?

3.1.2. Step 2: Hazard characterization

1351: "In GM plants with more than a single transgene (e.g. stacked GM plant events), the applicant should consider whether the combination of transgenes may lead to enhanced persistence or invasiveness that is more than the simple product of the single traits." In case that there is the risk of hybridisation with already marketed events that may stack in addition by cross-pollination, an inclusion of the additional possibilities may be mandatory. Otherwise, in the field (and on the table of consumers) could occur transgene combinations, which have not been tested for unintended combinatory effects.

1393: "Crops vary considerably in their ability to form feral populations and this is extensively recorded in the scientific literature (e.g. Bagavathiannan and Van Acker, 2008). If the conventional crop forms feral populations, then this will allow the GM trait to persist outside production systems, and the consequences of this will need to be assessed (stage 3). Similarly, there is extensive literature available on the sexual compatibility of crops with their wild relatives, and this was discussed earlier (see stage 1). Both of these routes allow potential persistence beyond the production site, and this leads to the next stage assessed (stage 3)": They also need to be assessed with regard to possible combinations with notified traits or traits under development.

1416: "habitats and over a minimum of two years." Does EFSA seriously believe that this will in any way fulfill the requirements of representativity? Representativity was considered a relevant issue above. With this approach the safety level would be brought down to an unacceptable level.

1433: How can seed bank behaviour be determined in 2 years? In our view, this is biologically and ecologically and statistically impossible.

1400-1469: "referring to Stage 3 information requirements" How can the requirements listed here investigate and determine how to secure against the occurrence and persistence of hybrids stacking not notified combinations which may persist in farm-saved seeds which may lead to products that appear on the market? A recent of example of why such information is important has been the detection of flax contamination with the event FP967/CDC (Triffid).

3.1.3. Step 3: Exposure characterization

3.1.4. Step 4: Risk characterization

3.1.5. Step 5: Application of risk management strategies

3.1.6. Conclusions

3.2. Plant to micro-organisms gene transfer

1. EFSA's definition doesn't enable identification of all potential hazards that may arise from the process of HGT. This is because EFSA only considers one outcome (incorporation) to be relevant, while ignoring other outcomes and hazards posed by the process (1). Many genes are mainly found on mobile elements that do not rely on vertical reproduction of their hosts. Without being part of a current host's evolution, these genes may have relevance to their host at a point in time and an environment they are in (2, 3). A more inclusive definition is used by Environmental Risk Management Authority of New Zealand (4):

[...] (HGT) is defined as the transfer of genetic material from one organism to another outside the context of parent to offspring reproduction

2. EFSA's definition uses the term "genetic material", but then focuses only on DNA, ignoring other substances that can cause heritable and infectious effects in exposed organisms. E.g., plant produced dsRNAs have been shown to act as pesticides, being transferred through the gut and spreading through the body of an animal eating them (5, 6, 7). This is independent of transfer or maintenance of the original DNA construct, but in some animals it is heritable (8, 9, 10). RNAi based GMOs are on the market and will increasingly come before regulators. Limiting RA to the effects of DNA transfer is insufficient and should be extended to the effects of all substances produced by a GMO on other organisms.

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3.2.1. Step 1: Problem formulation

The statement "exposure to a selection pressure would be critical for the dissemination and maintenance of horizontally transferred genes" is not true. Genes neutral or detrimental to a host can introgress. Genes may spread by HGT and later may adapt the host to a new environment. Examples are virulence determinants spread by viruses, and ABr and post-segregational killing (PSK) genes (1). PSK don't confer any advantage to the host - they kill cells hosting their competitors - still they are maintained in a population. DNA inserted into a mobile element with a PSK are maintained, at least temporarily, without selective pressure (2, 3).

The idea of '1 protein-1 function' isn't tenable. Knowing one biochemical function of a transgene product doesn't exclude presence of other functions (4) displayed in new environments (in different hosts, tissues, cell compartments) (5, 6). Statements about the selective pressure a gene may be under may thus be highly speculative.

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3.2.2. Step 2: Hazard characterization

3.2.3. Step 3: Exposure characterization

Frequency of transfer isn't the only important factor for RA because a) rare events are near certainties at the scale of biology on Earth and b) rather than frequency, the time it takes for an event to amplify through biological processes and the severity of potential adverse effects are crucial for harm (1).

Most studies focus on introgression of easily detectable, functional genes (table 1 ref. 2), leading EFSA to conclude that these events seem to be rare. It is far more likely that shorter sequences will be transferred. While more difficult to observe, it is not less relevant for RA because

a) insertion of short DNA segments may alter gene expression levels of microbial genes; most transgenes contain sequences designed to do that. This effect may easily be underestimated. E.g., a study using random chromosomal sequences of *S. cerevisiae* found that half of them lead to "considerable gene expression" in *E. coli* (3). Similar results were obtained using plant and viral promoters in bacterial hosts (4, 5).

b) Transfer of partial genes (gene cassettes) can alter protein function. E.g., HGT of cassettes and recombination events in the recipient *S. pneumoniae* lead to the emergence of mosaic genes, which substituted high tolerance to penicillin for low level tolerance. HGT of cassettes would on their own be insufficient to create a new phenotype (6). The same is true for Cry proteins, where exchangeable cassettes alter the toxicity range of the protein (7, 8).

c) An inserted short sequence may be a target for homologous recombination in consecutive HGT events.

References

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3.2.4. Step 4: Risk characterization

3.2.5. Step 5: Application of risk management strategies

3.2.6. Conclusions

3.3. Interactions of the GM plant with target organisms

Data needs to be requested from the applicant that shows the quantitative effect of the GM plant on the TO in terms of life table data of the TO. While this may sound trivial, the matter of the fact is that in almost all current application dossiers of Bt crop plants, the efficacy of the GM plant is delivered as a measured plant parameter, e.g. number of tunnels inflicted by a boring pest on the plant. Little or many times no data is delivered how the particular GM plant affects the TO in terms of mortality, development time or weight gain of the TO! Often such efficacy is assumed from other trials with either other GM plants carrying the same construct or a similar one or from test with the bacteria-produced toxin. Both will not deliver definitive data as to whether or not that GM plant for which approval is sought will actually work satisfactorily and express what is considered a 'high dose' (25x times the dose necessary to kill a homozygote susceptible target insect). Such data cannot be derived from other GM plants or trials with bacteria-produced toxins. But such data is essential to estimate the risk of resistance evolution in the TO.

3.3.1. Step 1: Problem formulation

3.3.2. Step 2: Hazard characterization

1717: This should be changed to "In some cases, the data might be obtained from the literature, but in many cases data sets will be incomplete." It should be also assessed that resistance might not only devalue the trait itself (and concurrent traits) but might also affect the use of conventional Bt products (if it is applied in the particular context or elsewhere against the same or related target organisms).

3.3.3. Step 3: Exposure characterization

In at least two cases (RR Soybean and maize MON 810) it has been shown that fusion RNAs can be transcribed covering part of the sequence where the transgenic sequence is inserted and part

of the transgene itself with unpredictable protein production and effects. Therefore this possibility should be evaluated when analysing the GMP

3.3.4. Step 4: Risk characterization

3.3.5. Step 5: Application of risk management strategies

3.3.6. Conclusions

3.4. Interactions of the GM plant with non-target organisms

Interestingly, we find that the EFSA GD has, in fact, drawn substantially from the material cited below regarding the NTO selection procedure but has failed to properly attribute this to the scientists who developed them and their publications.

Neglected citations of relevant peer-reviewed publications & missing attribution of concepts that went into the proposed changes of the GD, namely the selection procedure of nontarget organisms are:

Hilbeck A & DA Andow (eds) 2004. **Environmental Risk Assessment of Transgenic Organisms, Vol.1**: A Case Study of Bt Maize in Kenya. CABI Publishing, Oxon, UK.

Minimum number of relevant chapters in book:

Birch ANE et al. **Biodiversity and non-target impacts: Case study of Bt-maize** in Kenya. (Ch.5)

Hilbeck A, E Fontes & DA Andow (eds) 2006. **Environmental Risk Assessment of Transgenic Organisms, Vol.2**: Methodologies for assessing Bt cotton in Brazil. CABI Publishing, Oxon, UK.

Minimum number of relevant chapters in book:

Hilbeck A et al. **Methodology to support non-target and biodiversity risk assessment**. (Ch.5)

5 additional chapters on application of ERA concept to 5 functional groups of nontarget organisms (nontarget herbivores, predators, parasitoids, flower visitors and soil ecosystem processes)

Andow DA, A Hilbeck & Nguyen Van Tuat (eds) 2008. **Environmental Risk Assessment of Genetically Modified Organisms, Vol.4**: Challenges and Opportunities with Bt Cotton in Vietnam. CABI Publishing, Wallingford, UK.

Minimum number of relevant chapters in book:

Hilbeck A et al. **Non-target and Biological Diversity Risk Assessment** (Ch.5)

5 additional chapters on application of ERA concept to 5 functional groups of nontarget organisms (nontarget herbivores, predators, parasitoids, flower visitors and soil ecosystem processes)

In summary, the concept detailed in chapter 3.4 of the GD ERA document (and even more in the supplementing material on NTO risk assessment) and also onward was developed by a total of **> 60 international scientists** of a global working group of the IOBC published in a total of **3 peer-reviewed books** consisting of **13 relevant chapters**. **This large body of work** has not been attributed once in the GD on ERA and only almost negligibly in the supplementing document on

nontarget ERA. This is entirely unacceptable. The only citation found in the supplement document on nontarget effects were: Andow et al. 2006b, Birch et al. 2004, Hilbeck et al. 2008

Of the books and chapters listed above this includes only 1 chapter: Birch et al. 2004.

Hilbeck et al. 2008 is the publication of a project where the developed concept first published in the above listed CABI books were integrated into the EU ERA scheme and applied to a German case example in a multi-year project that is still on-going. So, citing Hilbeck et al. 2008 does not qualify as proper attribution of the original concept. Further, even in the supplementing material, the concept can hardly even be attributed to Hilbeck et al. 2008 in general. **An outsider would never understand that this part of the GD concept was NOT developed by EFSA.**

While we welcome and applaud EFSA for including the approach developed by the global IOBC working group in their new GD which constitutes a big improvement over the previous concept, we certainly expect proper attribution and recognition from EFSA on this issue.

Interestingly, we have official EFSA presentations wherein these improvements were presented to a larger public at an earlier stage of the development of the EFSA GD. These presentations contained the original figure of the selection scheme from Hilbeck et al 2008. In those presentations, of which we have copies, there is still an attribution to the Hilbeck et al. 2008 publication. Strangely, this attribution has disappeared from both the GD and the supplementing material. While the figure has graphically been altered (to also avoid copy-right issues presumably), the content is still the same as depicted in the graph published by Hilbeck et al 2008.

3.4.1. Step 1: Problem formulation

1778: "One environmental concern is that GM plants may have an adverse effect on biodiversity, through interactions with populations of other species associated with or sympatric with the GM plant" Through secondary effects unintended developments may also occur in a wider context.

1932: "Figure 6." Would it be possible that question 8 can have only one answer? For reasons of consistency, the NO alternative should be also considered – and stated what happens then ... would it require withdrawal of the submission?

1948: "it might necessary" to has to be "it might be necessary to"

1996: "explicit justification, under these circumstances, there is no requirement for a minimum number of sites and/or years" This is problematic since the absence of effects has to be shown under representative conditions and this is not feasible if no adequate standards are set.

3.4.2. Step 2: Hazard characterization

2042: "Once specific measurement endpoints are chosen, appropriate methods and criteria of measurement should be selected and described. This includes information on studies to be conducted, the appropriate tier for analysis, the design of protocols and statistical power (Marvier, 2002, Lövei and Arpaia, 2005, Perry et al., 2009) (see chapter 2.3.3)" Also indirect effects should be considered (along the food chain) – not only direct effects (GM-plant <> NonTargetOrganism NTO)

2144: "Design and analysis of field trials for NTOs should be performed according to the criteria explained in chapter 2.3.3." It should be also assessed, that there can be shifts in the pest spectrum – if one (or the) target species are eliminated, which others may change in abundance? If this cannot be assessed, it should be noted as an issue for case specific monitoring. This point

applies also to other issues: If it cannot be reasonably anticipated, it should be explicitly listed as a point for case-specific monitoring

3.4.3. Step 3: Exposure characterization

3.4.4. Step 4: Risk characterization

2187: "management measures where levels of risk exceed threshold levels (see step 3.4.5)." This is a so-far unexplained concept. Where are reasonable criteria for threshold levels defined?

3.4.5. Step 5: Application of risk management strategies

3.4.6. Conclusions

Proposed ecotoxicological approach to environmental risk assessment (ERA) of Bt plants in field trials

The ecotoxicological survey protocol proposed now by the GMO Panel of EFSA, upheld by Jorg Romeis (1), considers that if no toxicity is detected on a given non-target organism (NTO) in well-designed laboratory experiments, subsequent semi-field or field experiments may be skipped from the tiered step-wise approach in assessing toxic effects on that NTO. This notion has been criticised both from fundamental toxicological aspects (lack of acute exposure studies to predict ecologically relevant effects under field conditions) (2), and from the aspect of protected species, yet continues to be supported by the EFSA GMO Panel and by Romeis et al. (3). It is essential to emphasise that results in early tier studies in toxicology cannot warrant the outcome of tests at later tiers, due to the complex interactions existing in given ecosystems and ecosystem services. Therefore, the exclusion of later tier tests from ERA on the basis of favourable results at earlier tiers (e.g. laboratory) is unacceptable by the principles of environmental toxicology.

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3 Romeis J, Meissle M, Bigler F (2007) Reply to Early-tier tests insufficient for GMO risk assessment. *Nature Biotechnology* 25, 36-37.

3.5. Impacts of the specific cultivation, management and harvesting techniques

General remark: Impacts of potentially altered cultivation, management and harvesting techniques should not only be compared to techniques used in conventional agriculture but also to techniques used in organic agricultural systems.

2230: "Although information on the impact of cultivation in those countries is out of the scope of the present ERA, it may provide information on the impact of unintended release into the European environment(s)." It would be a pity to leave out of consideration cases in which through export options other countries ruin their biotic resources. To some extent, this is also a relevant issue for

the EU, if alterations in other countries might affect global biosphere processes. It may well be discussed, whether the soy-bean exports from Argentina and Brazil do not only disturb and destroy biodiversity on a continental scale in South America but also affect global climate regulations, if more and more natural ecosystems are converted into soybean monocultures or oil palm plantations.

3.5.1. Step 1: Problem formulation

3.5.2. Step 2: Hazard characterization

GM HT plants should be assessed (lines 2318 – 2319) not only for the effects of the changes in weed management on biodiversity (flora and fauna) in and around fields, but also for the effects on soil life and aquatic organisms.

3.5.3. Step 3: Exposure characterization

2372: "applicants are invited to consider the various scenarios which might occur in representatives receiving" representative

3.5.4. Step 4: Risk characterization

3.5.5. Step 5: Application of risk management strategies

Specific case of GM HT plants: Applicants should provide more detailed data on direct and long term effects of glyphosate, the active ingredient most often used with GM HT crops, on plant health, non-target crops, and on non-target organisms in terrestrial and aquatic environments. Glyphosate affects soil microorganisms and potentially favours fungal pathogens (1, 2, 3). It also impacts aquatic organisms (4, 5, 6, 7). As glyphosate is known to bind divalent cations such as manganese important for plant yield and health (8), impacts of glyphosate on plant micronutrient uptake and health should also be assessed (3, 9).

Glyphosate application may increase pathogen frequency in subsequent crops (10, 11, 12) and impede germination of non HT crops (13). Neighbouring non-resistant crops can be affected by glyphosate spray drift, leading to reduced weight, chlorophyll and micronutrient content (8). Therefore, impacts on subsequent crops and neighbouring non-target crops should be considered too.

References

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- 3 Kremer, R.J., Means, N.E. 2009. Glyphosate and glyphosate-resistant crop interactions with rhizosphere microorganisms. *Europ. J. Agronomy* 31: 153-161.
- 4 Perez, G.L., Torremorell, A., Mugni, H., Rodriguez, P. Solange Vera, M., Do Nascimento, M., Allende, L., Bustingorry, J., Escaray, R., Ferraro, M., Izaguirre, I., Pizarro, H., Bonetto, C., Morris,

D.P., Zagarese, H. 2007. Effects of the herbicide Roundup on freshwater microbial communities: a mesocosm study. *Ecological Applications* 17: 2310-2322.

5 Relyea, R. 2005a. The lethal impacts of Roundup on aquatic and terrestrial amphibians. *Ecological Appl.* 15: 1118-1124.

6 Relyea, R. 2005b. The impact of insecticides and herbicides on the biodiversity and productivity of aquatic communities. *Ecological Appl.* 15: 618-627.

7 Relyea, R.A., Jones, D.K. 2009. The toxicity of Roundup Original Max to 13 species of larval amphibians. *Environ. Toxicol. Chem.* 28: 2004-2008.

8 Cakmak, I., Yazici, A., Tutus, Y., Ozturk, L. 2009. Glyphosate reduced seed and leaf concentrations of calcium, manganese, magnesium, and iron in non-glyphosate resistant soybean. *Europ. J. Agronomy* 31: 114-119.

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10 Fernandez, M.R., Selles, F., Gehl, D., DePauw, R.M., Zentner, R.P. 2005. Crop production factors associated with Fusarium head blight in spring wheat in eastern Saskatchewan. *Crop Science* 45: 1908-1916.

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12 Fernandez, M.R., Zentner, R.P., Basnyat, P., Gehl, D., Selles, F., Huber, D. 2009. Glyphosate associations with cereal diseases caused by Fusarium spp. in the Canadian Prairies. *Europ. J. Agronomy* 31: 133-143.

13 Tesfamariam, T., Bott, S., Cakmak, I., Römheld, V., Neumann, G. 2009. Glyphosate in the rhizosphere – Role of waiting times and different glyphosate binding forms in soils for phytotoxicity to non-target plants. *Europ. J. Agronomy* 31: 126-132.

In general, glyphosate-based herbicides contain surfactants that may be biologically or chemically active and can influence the behaviour of active ingredients in the environment. Formulated herbicides, e.g. Roundup that contains surfactants such as polyethoxylated tallow amine (POEA), have been shown to exhibit higher toxicity than the active ingredient alone, in this case glyphosate (1, 2). Therefore, applicants have to provide data on the herbicide formulations and the surfactants that are supposed to be used with GM HT crops.

Biodiversity has declined in Europe and elsewhere within the last decades at an alarming rate. Change in agricultural land use and intensification of farming systems are a major cause of this decline (3). Current levels of biodiversity in agricultural systems can hardly be considered to be sufficient and sustainable. Management strategies to restrict the environmental impact to the levels currently found in equivalent non HT plants (lines 2470 – 2474) will therefore not be sufficient to guarantee truly sustainable agricultural systems. Instead, applicants should provide solid data whether and to what extent the introduction of GM plants will increase biodiversity.

1 Brausch, J.M., Smith, P.N. 2007. Toxicity of three polyethoxylated tallowamine surfactant formulations to laboratory and field collected fairy shrimp, *Thamnocephalus platyurus*. *Arch. Environ. Contam. Toxicol.* 52: 217-221.

2 Cox, C., Surgan, M. 2006. Unidentified inert ingredients in pesticides: Implications for humans and environmental health. *Environmental Health Perspectives* 114: 1803-1806.

3 Firbank, L.G., Petit, S., Smart, S., Blain, A., Fuller, R.J. 2008. Assessing the impacts of agricultural intensification on biodiversity: a British perspective. *Phi. Trans. R. Soc. B* 363, 777-787.

3.5.6. Conclusions

2481: There is one consideration lacking which should also be assessed in the context of risk assessment: Which measures are in place and how efficient are they to prevent the unintended (or eventually also illegal but intended) transfer of propagules to other countries (in particular to countries of origin of the particular plant species) with the possibility that they persist there and hybridise with components of the wild flora there. This means, how certain are EU states that they can prevent undesirable cross-boundary transfers of GM plants. An interesting example to discuss this: The development of herbicide resistant creeping bentgrass (for HR golf courses) is on the way in the US. Those who would like to devalue GM HT traits might well bring it elsewhere and let it hybridise with genetically compatible weedy varieties.

3.6. Effects on biogeochemical processes

Line 2501, lines 2527 - 2529, page 75, lines 2597 - 2598: The sentence that includes line 2501 sets the standard of comparison of the GM plants to be "conventional production (e.g. agriculture)". This leaves uncertainty about types of production practices that should be used for comparison, and therefore leaves the interpretation of what constitutes an adequate comparator to the applicant. Production practices used for comparison should include at a minimum widely used farming methods including high-intensity, high input farming (often referred to as industrial farming methods), and also organic production. Both are established commercial practices and therefore deserve inclusion for comparison.

It may be argued that because GM is not accepted by organic agriculture, it would not affect organic production. To the contrary, narrow economic considerations - net profit to farmers and input companies and net price to consumers, without including the costs of negative externalities - may allow GM crops to displace organic production or limit its expansion. Therefore the potential adoption of a GM crop may affect organic production, and the possible consequences should be considered by using organic as a standard of comparison.

3.6.1. Step 1: Problem formulation

2517: Applicants should be required to evaluate the impacts of the GM plant on biogeochemical processes rather than merely be "requested" to consider them. Biogeochemical processes in agriculture, such as nutrient and carbon cycling, have major impacts on the environment and human health, and therefore should be a mandatory part of the evaluation of GM plants. Because of the scope of adequate evaluation of biogeochemical processes, EFSA could consider a tiered mechanism for determining whether a thorough evaluation of biogeochemical processes is needed for a particular GM plant. But this process should be determined by EFSA or independent scientific bodies, and should be conducted in a transparent method.

2523: "ensure that detailed data are supplied when required, and that data requirements remain proportionate to the potential risk for biogeochemical processes." To determine what is proportionate should be made more explicit: As stated above (e.g. line 794ff, the uncertainties that remain are considerable, effects can accumulate, and the health and biotic resources of a population of more than 400 mill people represent the scale under consideration. The livelihood of an entire continent would have to be weighted against the individual economic interest of an

applicant. The argumentation – security cannot be achieved because this would be uneconomic and not proportionate to the gain achievable with the trait is not admissible.

2534: "II. Altered movement of other compounds from roots to soil, which may directly influence processes in soil fertility, nutrient transformations and soil food webs;" including soil characteristics e.g. pH and Redox (influencing nutrient mobilisation).

2548: A new section should be added that reads: "VII. The potential that the GM plant may alter the use of production inputs such as pesticides that are known or suspected to cause environmental harm and harm to human health."

3.6.2. Step 2: Hazard characterization

2559: The word "likely" should be replaced with a phrase such as "reasonable possibility". Prior to extensive commercial use for several years, there may be too few data to determine the likelihood that a GM plant will cause the listed changes in production practices or impacts. Therefore a lower standard of evidence is justified to prevent possible harm.

2567: The standard of "additional adverse effects" should be replaced with "significant adverse effects". Current predominant western high input agricultural practices are widely acknowledged to be unsustainable by consuming large amounts of non-renewable fossil fuels, causing greenhouse gas emissions, reducing biodiversity, and harming terrestrial and aquatic ecosystems through pesticide, and synthetic fertilizer effects. Therefore, practices that continue the net problems of current industrial agricultural practices should not be encouraged. By analogy, standards have been set to reduce the environmental impacts of previous harmful industrial practices. New highly polluting power plants, for example are typically not allowed. Plants using newer technology that are less polluting must replace older plants. Similar standards should be accepted for new agricultural practices and crops.

3.6.3. Step 3: Exposure characterization

2573: The production-site environments should also be the subject of this section, because some important biogeochemical processes - such as those that affect soil fertility - may primarily affect the production environment, and sometimes have little effect on the receiving environment. This is especially true because the definition of biogeochemical processes on page 73 lines 2495 - 2500 is broad and includes processes that are primarily local. Although the wider receiving environment is typically the focus of exposure for biogeochemical processes, and most changes in biogeochemical processes that are manifest in the production environment will also impact the receiving environment, some important impacts on the production environment may not have clear or significant impacts on the receiving environment. For example, reduction in soil fertility in the production environment may or may not have impacts on the wider receiving environment. Reductions in fertility may in some cases result in lower productivity with no clear impacts to the broader environment. On the other hand, reduced soil fertility may result in higher fertilizer inputs that then result in impacts on the receiving environment. Which scenario ensues may be determined by economic forces that do not consider biogeochemistry. Furthermore, since possible impacts on the receiving environment are removed in time and space, the direct impacts on the production environment, such as on soil fertility, may be more directly measured in connection with the GM plant, and may occur sooner than impacts on the receiving environment.

Therefore in line 2576, the word "both" should be changed to "either," and wording in the previous sentences should include production and receiving environments.

2581: Similarly, harm to some processes in the production environment should not be excluded.

3.6.4. Step 4: Risk characterization

2596: The word "major" should be changed to "significant" (that is, reliably measurable). Current predominant high-input agricultural practices are already having major negative impacts on the environment. Practices that cause any additional significant harm above the already unacceptable harm caused by these predominant practices should not be acceptable. Indeed, new practices should reverse the current harm caused by industrial agriculture.

Lines 2608 - 2611: should be deleted. The sentence beginning "It is accepted..." is unsupported and we believe, untrue. There is no evidence that this sentence is accurate, and it sets an unacceptable tension between it and the following requirements about biogeochemical loss estimates. That is, it is unclear why an application should have to determine this possible loss if it is unlikely to occur. To the contrary, for widely adopted GM traits for widely grown crops like maize or soybeans, which describes the current commercially successful GM crops, significant changes in biogeochemistry may occur. For example, supporters of GM crops contend that some of these crops (herbicide tolerant) have substantially increased conservation tillage practices that can have substantial biogeochemical effects. Drought tolerant maize may allow it to displace other crops in low precipitation areas (e.g. the western U.S. great plains and similar areas). Because maize often has different nitrogen requirements and retention properties than many other crops, such displacement could have significant consequences for nutrient cycling - an important part of a biogeochemical process.

3.6.5. Step 5: Risk management measures

3.6.6. Conclusions

2630: As a general point, biogeochemical processes often take considerable time to clearly manifest. While fluxes may be measured accurately on an instantaneous basis, the variability in the environment over time and space - including the large background effects of large pools of some chemicals such as soil carbon, organic matter, or indigenous nitrogen or phosphorus - means that processes that are of concern based on cumulative effects typically cannot be accurately revealed in one or even several years of measurement. This argues for the need for post-commercial monitoring of these processes in conjunction with the GM plant.

3.7. Effects on human and animal health

With respect to effects on human and animals health we would like to refer to the article "Genetically modified crops consumption at large scale: possible negative health impacts due to holes in assessment" by Seralini G-E., Mesnage R., Clair E., Gress S., Spiroux de Vedomois J. & Cellier D.

Abstract: Background, aim and scope Here we reviewed 19 studies of mammals fed with commercialized genetically modified soybean and maize, which represent per trait and plant more than 80% of environmental GMOs cultivated on a large scale since numerous years. From that we make new proposals for their evaluation. The concerned feeding trials have been mostly performed to obtain commercial release. Thus, these play a crucial role in health risk and environmental assessments with non target mammalian species. In addition, we have obtained the

raw data of several safety in vivo tests on rats, at least 90-day long, following Court actions or official requests. These include the analysis of biochemical blood and urine parameters of mammals eating GMOs, together with numerous organ weights and histopathology findings. We have thoroughly reviewed these tests from both a biostatistical and a biological point of view. Some of these tests showed controversial protocols which can be discussed, and statistically significant results considered as not biologically meaningful by regulatory authorities, raising the question of their interpretation. However, several convergent factors appear to indicate liver and kidney problems as endpoints of GMO diet effects in these experiments. This is confirmed by our meta-analysis of all in vivo studies published revealing that the kidneys are particularly reached, concentrating ~43.5% of all parameters disrupted for males. The data indicating no biological significance of statistical effects detected have been published mostly by companies from 2004, long after 10 years of commercialization in the world of comparable GMOs.

Main challenges: The transparency of crude data from toxicological studies is crucial. These can be put on the EFSA website in order to have a full review of these by the wider scientific community, and in order to inform better the citizen, and to implement a real scientific debate. Moreover, 90d long tests are insufficient to evaluate chronic toxicity. No minimal length is yet obligatory for all cultivated GMOs on a large scale; this has been discussed as socially unacceptable to protect consumers' health. We propose to improve and prolong the protocol of the 90-day studies which should be rendered obligatory, with sexual hormones assessed. A new 'SSC' statistical method is proposed in addition. This should not be optional overall if the plant is designed to contain a pesticide, which is the case for more than 99% of cultivated commercialized GMOs.

3.8. Overall risk evaluation and conclusions

4. Postmarket monitoring

2673: "4. Post Market Environmental Monitoring Plan" This is the overall weakest part of the document. It does not explicitly require to list any issue where uncertainties in the environmental risk assessment remain, It is a general issue, that for most of the questions dealt with in the ERA, it was not considered as a requirement to have (multi) crop rotation investigation time periods but only time periods of 2-3 years recommended. If this remains the recommendation, then more or less any question investigated that refers to soil fertility, biodiversity, non-target organisms, etc. needs to be investigated scientifically on a case specific basis in the context of monitoring.

4.1. General

2684: "(EC, 2002a, Wilhelm, 2003, ACRE, 2004)." Wilhelm 2003 is not in the reference list. Eventually, Wilhelm and Schiemann 2003 are meant. In the reference list, relevant concepts are missing. E.g. Züghart & Breckling <http://www.umweltdaten.de/publikationen/fpdf-l/2350.pdf> and the results of the SIGMEA workpackage 8 on monitoring, see <https://www.inra.fr/sigmea/deliverables> , in particular

- [D8.1](#) - Hypothesis based approach of monitoring strategies

- <https://www.inra.fr/sigma/content/download/2869/28620/version/2/file/SIGMEA+Project+n o+501986+-+DELIVERABLE+D8-1.pdf>
- [D8.2](#) - Intermediate report on European Monitoring approaches and implementation issues
- <https://www.inra.fr/sigma/content/download/2870/28623/version/2/file/SIGMEA+Project+n o+501986+-+DELIVERABLE+D8-2.pdf>
- [D8.3](#) - Biological indicators and sampling protocols for monitoring schemes
- <https://www.inra.fr/sigma/content/download/2872/28629/version/2/file/SIGMEA+Project+n o+501986+-+DELIVERABLE+D8-4.pdf>
- [D8.4](#) - Report: Concept for a long monitoring strategy

- <https://www.inra.fr/sigma/content/download/2872/28629/version/2/file/SIGMEA+Project+n o+501986+-+DELIVERABLE+D8-4.pdf>

2689: "Applications concerning only food/feed or ingredients (for example, imported into but not cultivated within the EU) will thus not normally be required to describe a detailed environmental monitoring plan if the applicant has clearly shown that environmental exposure is absent or will be at levels or in a form that does not present a risk to other living organisms or the abiotic environment." however, the applicant must inform about occurrences of unintended presence in the environment as a basis to facilitate the possibility to assess eventual negative environmental implications.

4.2. Interplay between environmental risk assessment and monitoring

4.2.1. Monitoring of effects: Foreseen and unforeseen

4.2.2. Monitoring framework

4.3. Case-specific GM plant monitoring

2744: "Such monitoring may be carried out at a limited number of sites ('local monitoring'), where exposure is greatest and intensive recording and data collection can take place." These sites must be representative for the regions in the EU and the GM cultivation pattern.

4.4. General surveillance for unanticipated adverse effects

2771: "an unusual effect has been observed" Hopefully, this does not mean to document ALL unusual effects. This would be entirely out of scope of what is feasible. Instead, it is required to assess effects which have any connection to the causal network of interactions the GMO is involved in. Such a cause-effect network must be established during environmental risk assessment. If anything "entirely" unforeseen should occur, it indicates, that the ERA procedure needs to be revised.

2787: "unanticipated adverse effects on human health is defined, according to Directive 2001/18/EC, as monitoring for unanticipated adverse effects that may result from handling of the GM plant." Here a hint (reference) would be necessary where health effects are monitored which occur in the course of consumption.

2791: "components, monitoring for health effects could be considered in conjunction with human population screening methods currently used by public health organisations (for assessing such elements as incidences of allergic reactions) and as part of the suggested plant production and farm questionnaires." Both types of monitoring plans must be science-based i.e. fulfil the criteria of providing scientifically relevant information which was acquired using scientific methods (and not limited to lay-person opinion-based statement collection)

4.4.1. Approach and principles of general surveillance

2819: "The EFSA GMO Panel is of the opinion that general surveillance is a general overseeing of the geographical regions where GM plants are grown without having any specific hypothesis on adverse effects on human health or the environment. As general surveillance is not hypothesis-driven, it is not conducted using directed experimental approaches (see also ACRE, 2004, Sanvido, 2005). However, robust scientific methodology should be applied wherever possible in order to evaluate empirical knowledge. This especially refers to defining sample sizes, sampling and recording methods, in order to produce statistically valid data for determining causes and effects." This has been already discussed frequently at previous occasions to a considerable extent and it does not get better by repetition. Anything that has a scientific relevance is required to operate on a hypothesis base. Otherwise it is not a scientific investigation. With this restriction of excluding the investigation of hypotheses, general surveillance would be nothing but operating an alert system that waits passively for anything to come in - i.e. to wait that someone else reports something. Not all uncertainties that remain from environmental risk assessment can be dealt with on a case-specific basis. For example, the hypothesis that unapproved stacked events occur through hybridisation with other approved events is in a strict sense not case-specific but involves several cases. If general surveillance is not hypothesis driven it is not executed on a scientific level. If it is not science-based, then it is not relevant for monitoring. In best case, it may inspire monitoring efforts by suggesting hypotheses.

2826: "Existing surveillance systems should be used where practical (e.g. routine farm recording systems) and any 'unusual' effect, not occurring in similar situations within conventional cropping, should be recorded (e.g. effects on soil)." To "record" implies a measurement. This implies a targeted action, and targeted action implies an underlying hypothesis. Otherwise it would be scientifically irrelevant (if something would be recorded without any reason and intention). Sorry, but this is fully across with fundamental aspects of scientific practice.

2829: "The establishment, persistence and spread of a GM plant is not an environmental hazard in itself." This normative sentence has been frequently stated in the monitoring context. Repeating it does not make things better and leaves the question unanswered: who has decided so on which basis and which stakeholder where involved? Persistence in the environment "in itself" i.e. without entering ecological and environmental relations is physically impossible. This implies at least that it increases uncertainty how the population could further develop. It increases the space for the occurrence of unintended genomic combinations, eventually the occurrence of additional stacked event and combination with other genomic backgrounds that could give rise to undesirable effects. This would have to be investigated in advance how the implications are. Well – it would make a nice task to do that with traits that are not yet developed. Further submissions would have to screen which "old" GM plants remain in the wild and could cause unintended and undesirable combinations. Such a plain and generalising statement like given in line 2829 is by far below reasonable scientific standards and should not occur in a guidance document. Its re-iteration devaluates other good achievements that have been made with this document.

2835: "Thus, an evaluation of how and where the GM plant will be grown and the associated environmental exposure is considered a good starting point in any general surveillance plan."

supported. In case of feral escape, it would be required to provide the information where and to what extent feral GM plants occur. Otherwise, the fate of the populations cannot be assessed.

2838: "be applicable, in a proportionate and cost-effective manner, for monitoring the GM plant in a range of representative environments, reflecting the range and distribution of farming and environments exposed to the GM plants and its cultivation." Just to remind the EFSA authors of the proportion: The environment on the continental level inhabited by more than 400 mill. people in the EU. Cost-effectiveness can never be an argument to postpone or ignore reasonable requirements of environmental safety. If this would be an argument, then General Surveillance is limited to what a company can afford. If this should be a criterion, then a transgenic construct cannot be admitted, if the submitting company should eventually state – sorry but from now on we are no more in the position to monitor since it goes beyond the capacity of what can be afforded in the context of cost-effectiveness. Safety of the citizens of the European Union and their environment cannot be made dependent on companies cost considerations. Therefore, generally this statement should not be used as a criterion to determine measures and should not occur in a guidance document. If scientifically reasonable and necessary investigations cannot be handled by the applicants, the general public will have to cover the issue.

2842: "Such additional studies would be case- specific monitoring studies as they would require an experimental approach to confirm the specific hypothesis that an observed effect is associated with the GM plant," Again as before – and where will be the investigation located whether unintended combinations of different notified traits occur? By definition, this is not specific for a particular case but it is a combinatory effect. Therefore, General Surveillance must be to a relevant extent hypothesis driven.

4.4.2. Main elements of general surveillance

2854: "define the methods and approaches that will be used to conduct general surveillance of regions where the GM plant occurs," occurs through cultivation or self-organised dispersal and/or hybridisation outside cultivated areas.

2910: "Issues of human health (e.g. due to exposure and handling of GM plants) may also be integrated into farm questionnaires." however, farm questionnaires usually cannot be used to detect quantitative changes in ecosystem services and biodiversity issues as this requires scientific observation and quantification. Assessment on this level serves hypotheses formation but not to decide presence or absence of an effect.

4.4.3. Importance of a baseline

2951: "Direct comparison with non-GM plant reference areas should be used if available, but reference can also be made to the historical knowledge and experiences of the "observer" (e.g. farmers, inspectors, wildlife surveyors) in relation to the situation prior to the introduction of the GM plant." Again, this requires in addition a scientific basis of observation and cannot be left to visual impression on a personal level.

4.4.4. Data quality, management and statistical analyses

4.5. Reporting the results of monitoring

3003: "If appropriate, the applicant should provide access to raw data for stimulating scientific exchange and co-operation." It is always appropriate to make existing environmental data available for independent scientific investigation.

4.6. Review and adaptation

3050: "also be adapted based on an assessment of the appropriateness and cost effectiveness of the monitoring plan. Implementation of the revised monitoring plan remains the responsibility of the applicant unless" Delete "cost effectiveness". If the safety level of the environment is made dependent on cost consideration, a notification will not be reasonably acceptable by the public.

References

Appendices

A Background information for the geographical zones in the receiving environment(s) in Europe

3488: "With reference to natural diversity, a broad range of various environments in terms of their flora and fauna, climatic conditions, habitat composition and ecosystem functions and human interventions: Include soils: Climatic conditions, soils, habitat composition..."

3544: "d. LANMAP" There is a comparable approach developed at the University of Vechta, see I. Hornsmann, G. Schmidt, W. Schröder <http://www.springerlink.com/content/np13640840545762/fulltext.pdf>

B Considerations fro Long-term effects

3567: "B. CONSIDERATIONS FOR LONG-TERM EFFECTS" It is not understandable why this part is not put into the monitoring chapter. It brings relevant guidance information that should not be hidden and buried in an annex. 'Would the authors of the guidance document seriously think that information as discussed in this annex would be accessible through "farmer questionnaires" as presented in the general surveillance part?

3644: "To gain greater credibility in GM risk assessment, impact models need to be assessed against hard, comparative data. Nevertheless, modelling should continue to be developed and adapted for use in future impact studies." and the results of General Surveillance should feed this process – by hypothesis driven investigations.

3665: "The monitoring plan might lay down how the possible effects of Bt maize can be judged in relation to contemporaneous effects of other agricultural change in the receiving environments." Is this Case Specific or General Surveillance? The authors of the Guidance Document should be explicit – and include this part in the Guidance Document and not in an annex.