Technical background for a complaint under Article 10 of Regulation (EC) No. 1367/2006 against the decision of the EU Commission to give market authorisation to stacked soy MON87701 x MON89788

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Content

Summary

Existing EU regulations foresee a high level of protection for consumers and the environment.

- For example Regulation 1829/2003 states that genetically engineered organisms “should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard.” (Recital 9 of Regulation 1829/2003).
- Annex II of Directive 2001/18 requires the examination of the direct and indirect, the immediate and delayed effects of the GMO on human health or the environment.
- Directive 2001/18 requires post-marketing monitoring “in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of GMOS as or in products after they have been placed on the market.”

In June 2012, the EU Commission issued a market authorisation for the genetically engineered soybean MON87701 x MON89788, based on an opinion from EFSA. Testbiotech examined EFSA´s opinion and the decision of the EU Commission. In this technical background, based on the analysis of the risk analysis as performed, we show that EFSA´s opinion and the decision of the Commission do not fulfil the requirements of current EU Regulations. The technical background is further underpinned by legal analysis and is based on scientific findings.

The four grounds of complaint are that:

- EFSA did not require Monsanto to submit evidence based on appropriate comparators and/or it erred in concluding that the genetically engineered soybean is 'substantially equivalent' to that comparator;
- EFSA failed to consider and/or require Monsanto’s environmental risk assessment to investigate the synergistic/ combinatorial effects leading to enhanced toxicity of the whole food/feed;
- EFSA failed to require Monsanto to undertake a sufficient assessment of the immunological risks posed by the Soy in issue and
- Failed to ensure that an appropriate monitoring plan was put in place.

In the detailed reasoning of the complaint, Testbiotech sets out some of the technical details behind this complaint, which may require further discussion. However, some of the deficiencies are self evident and crucial to Testbiotech's submission that the overall risk analysis is fundamentally flawed. Some of the most obvious deficiencies and failures are:

- The genetically engineered soybean was developed to be grown in Brazil in particular. However, no data were made available on the compositional analysis of the soybean grown in Brazil and the impact of the various geo-climatic regions in Brazil on the plants´ composition.
- Many of the dossiers prepared by industry do not fulfil basic scientific standards (such as Good Laboratory Practise), and were not peer reviewed by external scientists. This is also the case for crucial investigations into allergenic risks.
- The insecticidal protein as produced in the plants was never assessed as required under pesticide regulation.
- The residues from spraying with the complementary herbicide glyhopsate were not taken into account nor any combinatorial effects with the insecticide or any other combinatorial effects.
- Assessment of human and animal exposure to the insecticidal protein did not take into account very common usages of soybeans such as soybean sprouts, fermented products, baby food or milk produced from the soybeans.
- The assessment of allergenic risks was based on too few samples. It left aside specific risks which are highly relevant for infants. No other risks for the immune system besides allergenic diseases were explored.
- No feeding study was performed with the stacked soybeans to investigate potential health effects.
- The Commission did not request any monitoring of the effects of the Soy on health.

Art. 10 of EU Regulation 1367/2006, allows NGOs active in the field of environmental protection to request re-examination of Commission decisions. Based on this regulation we request the re-examination of the risk analysis by EFSA and the EU Commission as well as immediate withdrawal of market authorisation for soybean MON87701 x MON89788.

1. General Legal Framework

Regulation 1829/2003 on genetically modified food and feed ("the GM Regulation") states that, in order to protect human and animal health, food and feed that consists of, contains, or is produced from genetically modified organisms should undergo a safety assessment before it is placed on the market in the European Union.

"Genetically modified organism" is defined in Article 2(2) of Directive 2001/18 as "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination", where an "organism" is defined in Article 2(1) as "any biological entity capable of replication or of transferring genetic material".

Food and/or feed that consists of, contains, or is produced from, genetically modified organisms must not:

- "have adverse effects on human health, animal health or the environment": Articles 4(1)(a) and 16(1)(a) GM Regulation; or
- be placed on the market "unless it is covered by an authorisation granted in accordance with" the GM Regulation: Articles 4(2) and 16(2) GM Regulation.

In order to gain an authorisation, an application must be made to the competent authority of a Member State: Articles 5(2) and 17(2) GM Regulation. That application should include, among other things:

- "a copy of the studies, including, where available, independent, peer-reviewed studies, which have been carried out and any other material which is available to demonstrate that the food complies with the criteria referred to in Article 4(1) [/16(1)]": Articles 5(3)(e) and 17(3)(e) GM Regulation; and
- "either an analysis, supported by appropriate information and data, showing that the characteristics of the food are not different from those of its conventional counterpart, having regard to the accepted limits of natural variations for such characteristics and to the criteria specified in Article 13(2)(a), or a proposal for labelling the food...": Articles 5(3)(f) and 17(3)(f) GM Regulation.

The European Food Safety Authority was established by Regulation 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety ("the Food Safety Regulation").

Chapter II Section 1 of the Food Safety Regulation makes clear the "General Principles of Food Law" upon which European measures, such as the GM Regulation, should be based. These include:

- The "General Objective" of "a high level of protection of human life and health and the protection of consumers' interests": Article 5 of the Food Safety Regulation (reflected in Recital (3) ;
- The principle of "Risk Analysis". According to Article 6 of the Food Safety Regulation:

"(1) In order to achieve the general objective of a high level of protection of human health and life, food law shall be based on risk analysis except where this is not appropriate to the circumstances or the nature of the measure.

(2) Risk assessment shall be based on the available scientific evidence and undertaken in an independent, objective and transparent manner."

The GM Regulation was adopted with a view to achieving these General Principles by giving special weight to the precautionary principle. Recitals (2), (3) and (9) make clear:

> "(2) A high level of protection of human life and health should be ensured in the pursuit of [Union] policies.
>
> (3) In order to protect human and animal health, food and feed consisting of, containing or produced from genetically modified organisms...should undergo a safety assessment through a [Union] procedure before being placed on the market within the [Union].
>
> (9) The new authorisation procedures for genetically modified food and feed should...make use of the new framework for risk assessment in matters of food safety set up by [the Food Safety Regulation]. Thus, genetically modified food

and feed should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard, to be undertaken under the responsibility of the European Food Safety Authority (Authority), of any risks which they present for human and animal health and, as the case may be, for the environment. This scientific evaluation should be followed by a risk management decision by the Community, under a regulatory procedure ensuring close cooperation between the Commission and the Member States."

In the context of these General Principles, the European Food Safety Authority is mandated to issue guidance on the manner in which it will assess applications for authorisations under the GM Regulation. In particular:

- Under Article 23(b) of the Food Safety Regulation, one of its tasks is that it must "promote and coordinate the development of uniform risk assessment methodologies in the fields falling within its mission";

- Under Articles 5(8) and 17(8) GM Regulation, it "shall publish detailed guidance to assist the applicant in the preparation and presentation of the application";

It has issued two Guidance documents of particular relevance to the present application. These are the "Guidance on the submission of applications for authorisation of genetically modified food and feed and genetically modified plants for food or feed uses under Regulation (EC) No 1829/20031" (EFSA 2011 c), and the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the risk assessment of genetically modified plants containing stacked transformation events", adopted on 16 May 2007 ("EFSA Guidance (2007)").

These guidance documents outline the European Food Safety Authority's own view of how, in practice, it will discharge its obligation to conduct a "scientific evaluation of the highest possible standard" (Recital (9) GM Regulation), and to do so using a 'uniform methodology' (Article 23(b) Food Safety Regulation) and "based on the available scientific evidence and... in an independent, objective and transparent manner" (Article 6(2) Food Safety Regulation).

(a) Particular provisions of Directive 2001/18[1]

Directive 2001/18[2] requires that the placing on the market of a genetically modified organism (GMO) as or in a product may only take place after written consent by the competent authority has been given (Article 19). The application for such consent (notification, Article 13) must be accompanied by an environmental risk assessment, by other information, and by a monitoring plan (Article 13(2.b, 2.a, and 2.e)).

The environmental risk assessment

Recital (19) of Directive provides that "[a] case-by-case environmental risk assessment should always be carried out prior to a release. It should also take due account of potential cumulative long-term effects associated with the interaction with other GMOs in the environment." Moreover, "[n]o GMOs, as or in products, intended for deliberate release are to be considered for placing on the market without first having been subjected to satisfactory field testing at the research and development stage in ecosystems which could be affected by their use."

Recital 33 of the Directive indicates that the environmental risk assessment submitted as part of the notification procedure has to be "full". Recital 55 stresses the importance of following "closely" the development and use of GMOs.

Article 13 (2.b) provides that the notification shall be accompanied by "the" environmental risk assessment and the conclusions required in Annex II, section D. Annex II section D provides that information on the points listed in sections D1 or D2 should be included, as appropriate, in notifications with a view to assisting in drawing conclusions on the potential impact from the release or the placing on the market of GMOs. This information is to be based on the environmental risk assessment carried out in accordance with the principles laid down by sections B and C of Annex II to the Directive.

1 These chapters are mostly derived from Ludwig Kraemer Dossier, 2012, attached

2 Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ 2001, L 106 p.1. ("the Directive").

Accordingly, the principles with which environmental risk assessments should comply are laid down in Annex II to the Directive. Annex II indicates that the environmental impact assessment is not limited to an examination of the effects of genetically modified products containing GMO on the natural environment, it must also examine the effects on human health. This follows from the general objective of Directive 2001/18 as laid down in Article 1 – "[i]n accordance with the precautionary principle, the objective of this Directive is...to protect human health and the environment"[3], in Recital 5 of the Directive, and the reference to "human health or the environment" in Annex II itself, where this reference appears five times in the introductory remarks and in each of the four parts A to D of that Annex. Further, section A of Annex II states that:

> "The objective of an [environmental risk assessment] is, on a case by case basis, to identify and evaluate potential adverse effects of the GMP, either direct, indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have. The [environmental risk assessment] should be conducted with a view to identifying if there is a need for risk management and if so, the most appropriate methods to be used."

Finally, it is to be noted that it follows from Article 191(1) TFEU (The Treaty of the Functioning of the European Union) that in EU law, the "protection of the environment" includes the protection of human health[4].

The introductory remarks to Annex II of the Directive state: "A general principle of environmental risk assessment is also that an analysis of the 'cumulative long-term effects' relevant to the release and the placing on the market is to be carried out. 'Cumulative long-term effects' refers to the accumulated effects of consents on human health and the environment". Thus, the continued consumption of genetically modified plants, where herbicide residues might be present, should be submitted to risk assessment as a matter of course.

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3 The importance of the protection of human health is reinforced by the multiple references to it in the Directive – see: Article 13(6), in Recital 5 of the Directive, and the reference to "human health or the environment" in Annex II itself, where this reference appears five times in the introductory remarks and in each of the four parts A to D of that Annex.

4 Article 191(1) TFEU: " *Union policy on the environment shall contribute to the pursuit of the following objectives:... – protecting human health..."*

Section B sets out the general principles governing the performance of an environmental risk assessment, which include “identified characteristics of the GMP and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations.”

Section C.2 of Annex II describes the “Steps in the environmental risk assessment”. As a first step, that part requires the identification of characteristics that may cause adverse effects, and gives a general indication of what has to be done, noting that “it is important not to discount any potential adverse effect on the basis that it is unlikely to occur”. Section C.2 then alerts to “Potential adverse effects of GMOs will vary from case to case and may include: - disease to humans including allergenic or toxic effects…” Finally, Section C.2 outlines the steps involved in reaching an overall assessment of the risk posed by a genetically modified plant. These include the evaluation of the potential consequences of the adverse effects (for which the evaluation should assume that such an effect will occur), the evaluation of the likelihood of and the risk posed the occurrence of each potential adverse effect, and the identification of risk management strategies.

The conclusions of the risk assessment shall be part of the notification, in order to allow the competent authority to draw its own conclusions (Annex II, part D). The conclusions on the risk assessment shall include “Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMOs [GMHP] and persons working with, coming into contact with or in the vicinity of the GMO [GMHP] release(s)”[5].

It follows from these provisions that the environmental risk assessment has to include all effects which the placing of a GMO on the market may have on human health, including any possible cumulative effects. This also includes the potential effects of the use of herbicides or pesticides on the GMO plant or product. Of particular importance is the fact that the assessment of a particular potential adverse effect may not be excluded from the overall assessment on the basis that it is considered it is unlikely to occur. Although the likelihood of a potential adverse effect is one factor of the evaluation, the magnitude of its potential consequences and the risks it would

5 Directive 2001/18, Annex II, part D1 no.6 and part D2 no.6. Part D1 refers to GMOs other than higher plants, part D2 to genetically modified higher plants (GMHP). For reasons of simplification the two sections D1 no. 6 and D2 no. 6 were assembled in one text.

pose to the environment and human health must still be assessed, and both of these elements should be taken into account in the overall risk assessment.

Other information

"Other information" which has to accompany every notification under Article 13 of Directive 2001/18, shall include "considerations for human health and animal health, as well as plant health: (i) toxic or allergenic effects of the GMO and/or their metabolic products[6], furthermore "identification and description of non-target organisms which may be adversely affected by the release of the GMO, and the anticipated mechanisms of any identified adverse interaction"[7]and, as a catch-all formula "other potential interactions with the environment"[8]. For genetically modified higher plants (GMHP), Annex IIIB applies, this requires the notifier to supply, with his notification, the following information: "Information on any toxic, allergenic, or other harmful effects on human health arising from the genetic modification"[9]; "Information on the safety of the GMHP to animal health, particularly regarding any toxic, allergenic or other harmful effects arising from the genetic modification, where the GMHP is intended to be used in animal feedstuffs"[10]; and "Potential interactions with the abiotic environment"[11].

This wording with regard to the "other information" is thus again very broad and tries to cover all effects that the GMO product might have on human health or animal health. The choice of the terms "arising from the genetic modification" clarifies that information is to be supplied not only on the effects caused directly by the GMO, but also on all other harmful effects on human or animal health and which are, in one way or another, related to the genetically modified plant.

The monitoring plan

According to Article 13(2.(e), a monitoring plan has to accompany the notification; the plan shall be established in accordance with Annex VII to the Directive. Its objectives are underlined by recital 43 of Directive 2001/18 which states: "it is necessary to introduce into this Directive an obligation to implement a monitoring plan in order to

6 Directive 2001/18, Annex III A, section II, C.2(i)

7 Directive 2001/18, Annex IIIA, section IV B12.

8 Directive 2001/18, Annex IIIA, section IV B.16.

9 Directive 2001/18, Annex IIIB, section D no.7.

10 Directive 2001/18, annex IIIB, section D no.8.

11 Directive 2001/18, annex IIIB, section D no11.

trace and identify any direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of GMOS as or in products after they have been placed on the market". The use of the word "any" both in the Recital 43 and in Annex VII itself demonstrates that the purpose of the monitoring plan is to discover all possible impacts of adverse effects of GMOs, including those effects not foreseen in the environmental risk assessment ("unforeseen").

This interpretation is confirmed by the provisions in Annex VII on the design of the monitoring plan: the plan has to

I. be detailed on a case by case basis (Annex VII, C.1);
II. take into account the relevant environmental conditions where the GMO is expected to be released (C.2);
III. incorporate general surveillance for unanticipated adverse effects (C.3);
IV. provide for case-specific monitoring, though routine surveillance practices that "were already established" are allowed in appropriate cases (C.3.1 and C.3.2);
V. facilitate the observation "in a systematic manner" of the release of the GMO in the receiving environment and the interpretation of these observations "with respect to human health or the environment" (C.4).

In 2002, the Council adopted, by way of a Decision, guidance notes "supplementing Annex VII"[12]. The guidance notes "shall be used as a supplement to Annex VII of Directive 2001/18/EC" (Article 1). The guidance notes repeat in the introduction that the purpose of the monitoring plans is to "trace and identify any direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of GMOs as or in products after they have been placed on the market".

The guidance notes first repeat the objective and general principle of the monitoring plan of Annex VII to Directive 2001/18 and then add: "In addition, monitoring of potential adverse cumulative long-term effects should be considered as a compulsory part of the monitoring plan"(part B). They clarify what is to be understood by by the terms "direct effects", "indirect effects", "immediate effects" and "delayed effects".

With regard to unforeseen effects, the guidance notes indicate: "it is very difficult if not impossible to predict the appearance of potential, unforeseen or unanticipated

12 Decision 2002/811/EC of 3 October 2002 establishing guidance notes supplementing Annex VII to Directive 2001/18/EC, OJ 2002, L 280 p.27.

effects that were not highlighted in the risk assessment. General surveillance for potential unforeseen or unanticipated effects should, therefore, be considered as a part of the monitoring strategy" (part C). This statement indicates that notifier may not limit his monitoring plan to those risks identified in the environmental risk assessment which had to be made according to Article 13(2.b) and Annex II section D to Directive 2001/18.

The guidance notes also expressly state that the time-period for monitoring would depend on the circumstances, but could extend to a number of years (part C- 1.5). This is another indication that potential cumulative effects of genetically modified plants hand herbicide residues are to be controlled.

Case-specific monitoring (part C-1.3.1) should focus on "all the potential effects on human health and the environment identified in the risk assessment". It should begin with determining the case-specific objectives of the monitoring strategy, which "include" the identification of the occurrence and impact of potential adverse effects of the GMO or its use that were made in the environmental risk assessment. The strategy should indicate that these assumptions are to be confirmed by the case-specific monitoring. With regard to potential effects on human health, the guidance notes specify that such effects will depend on the inherent nature of a GMO and its specific genetic modification.

For unforeseen adverse effects that were not predicted in the risk assessment, the guidance notes make provision for a "general surveillance" (part C- 1.3.2) which consists of "routine observation ("look – see") approach". Such surveillance should be carried out over a longer period of time and possibly a wider area than the case-specific monitoring, though the type of general surveillance would depend on the type of unforeseen adverse effects. The notes indicate that the general surveillance could make use of established routine surveillance practices "where compatible"; then the established routine surveillance practice should be described in the plan, including any necessary alignment to the general surveillance. "Food surveys" are expressly mentioned (part C -1.7) as one example of existing systems.

The guidance notes contain a number of other indications, such as the monitoring methodology (part C- 2) and analysis, reporting and review (part C-3) which will not be set out here.

Overall, the main purpose of the monitoring plan is to confirm the assumptions that were made in the environmental risk assessment on (the absence of) potential adverse effects. However, the guidance notes expressly indicate that the monitoring strategy should also include a strategy with regard to unforeseen events not assessed in the environmental risk assessment.

(b) Particular provisions of Regulation 1829/2003

Regulation 1829/2003 applies to genetically modified food and feed. Articles 3 to 14 apply to genetically modified food, Articles 15 to 23 to genetically modified feed. The placing on the market of genetically modified food or feed requires an authorisation (Article 4 for food, Article 16 for feed).

Article 5(5) of Regulation 1829/2003 provides that an application for GMOs or food containing or consisting of GMOs must be accompanied by, amongst other things, "information and conclusions about the risk assessment carried out in accordance with the principles set out in Annex II to Directive 2001/18/EC or, where the placing on the market of the GMO has been authorised under part C of Directive 2001/18/EC, a copy of the authorisation decision". Furthermore, such an application shall be accompanied by "a monitoring plan for environmental effects conforming with Annex VII to Directive 2001/187EC..." (Article 5(5)(b)).[13]

Article 6(4) provides: "In the case of GMOs or food containing or consisting of GMOs, the environmental safety requirements referred to in Directive 2001/18/EC shall apply to the evaluation to ensure that all appropriate measures are taken to prevent the adverse effects on human and animal health and the environment which might arise from the deliberate release of GMOs..."

The European Food Safety Authority (EFSA) which has to give an opinion on the application, has to include in its opinion where applicable "post market monitoring requirements based on the outcome of the risk assessment" (Article 6(5)(e)) where such a risk assessment had been requested by EFSA[14]. In cases, where Article 5(5)(b)

13 For such cases, Articles 13 to 24 of Directive 2001/18 are declared inapplicable.

14 See Article 6(3.c) of Regulation 1829/2003.

applies, EFSA also has to give an opinion on the monitoring plan where appropriate (Article 5(5)(g).

The authorisation of a genetically modified food is granted by the Commission by way of the so-called comitology procedure (Article 7 and Article 35). The authorization has to include the particulars referred to in Article 6(5), which includes where appropriate a monitoring plan. In its decision, the Commission is not bound by the opinion of EFSA. Instead, the Commission has to take the EFSA opinion into account, as well as "any relevant provision of Community law and other legitimate factors relevant to the matter under consideration" (Article 7(1)).[15] In other words, the Commission has to determine, whether the monitoring plan has to include the control of potential adverse effects of the genetically modified plant during the use and consumption stage. Even when the EFSA, in any of its opinions, does not comment on the need for such a control, the Commission was obliged to decide on that issue.

The provisions on feed containing or consisting of GMOs mirror the provisions on genetically modified food: A provision corresponding to Article 5(5) of Regulation 1829/2003 is laid down in Article 17(5), a provision corresponding to Article 6(4) is found in Article 18(4). In addition, where appropriate EFSA also has to give the particulars of the relevant monitoring plan (Article 18(5.g)). The Commission, when authorising the genetically modified feed, also has to also refer to the monitoring plan (Article 19(2)).

It follows from these provisions that for genetically modified food or feed, information and conclusions about the risk assessment must be given. This risk assessment must have been carried out in accordance with the principles set out in Annex II to Directive 2001/18 (Article 5(5.a) and Article 17(5.a) see section 2 above). Also a monitoring plan has to be submitted with the application for authorisation (Article 5(5.b) and Article 17 (5.b)). Where EFSA expresses an opinion in favour of the authorisation, it has to address the monitoring plan (Article 6(5.g) and Article 18(5.g)) and indicate "post-market monitoring requirement based on the outcome of the risk assessment" (Article 6(5.e) and Article 18(5.e)).

The European Commission has the responsibility for authorising the placing on the market of genetically modified food or feed. Accordingly, it has an obligation to attach

15 Further, under Article 7(1) the Commission has to provide an explanation for the difference, where its decision is not in accordance with EFSA's opinion.

the necessary conditions to the authorisation in order to ensure that the food or feed has no adverse effects on human health, animal health or the environment (Article 4(1)). It has its own responsibility in this regard and may not rely on the – non-binding – opinion of EFSA; in the past, the Commission occasionally did add supplementary conditions on the placing on the market of genetically modified food products[16].

Under Regulation 1829/2003, genetically modified food or feed placed on the market, must be monitored according to the principles laid down in Directive 2001/18 (see section 2 above). The monitoring plan must attach greater importance to potential adverse effects and to the unforeseen effects of the genetically modified food or feed on human or animal health than in the application of Directive 2001/18 alone, as it is the very purpose of Regulation 1928/2003, expressed in Recitals 2 and 3 and its Articles 1, 4 and 16, to protect human health. Further, the information and conclusions concerning the risk assessment must take into consideration this need to protect human and animal health.

The Court of Justice confirmed this interpretation and stated that[17]:

> "Regulation 1829/2003 applies to the specific field of food and feed. As regards food, its first objective, referred to in article 4(1), is also to avoid adverse effects on human health and the environment. However, Directive.. 2001/18 [was] drafted primarily from the angle of the concept of 'deliberate release' which is defined in article 2(3).. as an intentional introduction of a GMO into the environment, without specific containment measures designed to limit their 'contact' with the 'general population and the environment'. That approach thus appears to be more general, including with regard to the placing on the market of a GMO as a product. In this respect, … recitals 25, 28 and 32 in the preamble to Directive 2001/18 link the need to introduce an assessment and authorisation procedure to the situation in which the placing on the market includes a deliberate release into the environment. Although Regulation 1829/2003 also includes, in particular in Articles 5(5) and 6(4), aspects of environmental risk assessment of food, it is, as regards food, based overwhelmingly on an appraisal emphasizing protection of human health which is linked to the specific

16 See for example Commission decision 2010/135/EU, OJ 2010, L 53 p.11, Recital 18 and Article 4(e), where additional monitoring measures were requested.

17 Court of Justice, case C-442/09 *Bablok,* Judgment of 6 September 2011, paragraphs 97 – 102.

> fact that that food is, by definition, intended for human consumption. Thus, in accordance with recital 3 in the preamble, in order to protect human health, foods containing, consisting or produced from GMOs must undergo a 'safety' assessment. Regulation 1829/2003 thus introduces an additional level of control. That regulation would be rendered nugatory, if the view were to be taken that an assessment carried out and an authorisation issued pursuant to Directive … 2001/18 covered all subsequent potential risks to human health and the environment".

The least which one can conclude from these remarks by the European Court of Justice is that the safety assessment – in other words the environmental risk assessment and the post-marketing monitoring evaluation – must be, under Regulation 1829/2003, at least as strict as under Directive 2001/18, if not stricter.

Conclusion

It follows from all these provisions, that under Directive 2001/18, a notifier's documentation must contain a comprehensive environmental risk assessment of the GMO, which includes all potential adverse effects on human and animal health. Unlikely occurrences must also be included in the assessment and evaluated. The monitoring plan must also contain a strategy for monitoring events that were not foreseen in the environmental risk assessment.

The purpose of Directive 2001/18 is also to protect human and animal health, and as GMO plants are consumed by humans, the environmental risk assessment and the monitoring plan must, therefore, also contain an assessment of such potential effects (risk assessment) and a strategy to verify whether such adverse effects actually occur. Indeed, the development of allergies or other adverse effects, due to the consumption of genetically modified plants which are herbicide-resistant, and which possibly contain herbicide residues, are not so unlikely that the monitoring of such effects can be omitted.

The competent authority has to give written consent for the placing on the market of a GMO as or in a product (Article 19). The consent has to specify, among other things, the monitoring requirements in accordance with Annex VII to the Directive (Article 19(3.f)). This provision clarifies that the competent authority is not bound, in the monitoring conditions, which it puts on the consent with regard to monitoring, by the

monitoring plan of the notifier. Rather, this plan is, legally, a mere proposal. Thus, the competent authority, which gives written consent, has a responsibility of its own to ensure that all direct and indirect, immediate and delayed, cumulative and unforeseen effects of the GMO on human and animal health and the environment are properly monitored.

2. Factual background

The genetically modified soybean “MON87701 x MON89788”, the “Soy”, is a hybrid product. It is created by using traditional breeding methods, to combine the genetic material of two parent plants: Soybean MON87701 and soybean MON89788 (“the Parents”).

Both Parents are themselves genetically modified:

a. MON87701 is a soybean, which has had a DNA sequence for insecticide proteins “Cry1Ac” inserted into its genome. It was authorised by Commission Decision 2012/83/EU of 10 February 2012.

b. MON89788 is a soybean which has had a DNA sequence for glyphosate herbicide resistant protein “CP4 EPSPS” inserted into its genome. It was authorised by Commission Decision 2008/933 of 4.December 2008.

“Cry” proteins are toxins derived from the bacterium *Bacillus thuringiensis*. This is a gram-positive soil dwelling bacterium which is also used as a biological pesticide. The Cry toxins – in their natural crystal form - can be used as a pesticide. These toxins are also commonly referred to as “Bt toxins”.

EPSPS proteins (enzymes) can also be derived from soil dwelling bacteria. They confer tolerance to glyphosate-based herbicides.

The Soy thus combines the insecticide traits of MON87701, and the herbicide tolerance traits of MON89788. As it combines more than one modified gene, it has “stacked genes” and is called a “gene stacked event” or “stacked event”.

Monsanto Europe SA (“Monsanto”) filed application EFSA-GMO-NL-2009-73 seeking authorisation under the GM Regulation for the Soy and its derived products for food and feed uses, import and processing in the European Union. The Application excludes cultivation within the EU.

The Soy and the derived products, that Monsanto has applied for to bring into the EU, are genetically modified organisms, or food/feed containing genetically modified organisms, within Article 2 of Directive 2001/18 and Article 2(5) of the GM Regulation. The grains are biological entities capable of replication or of transferring genetic material, and are therefore “organisms” within Article 2(1) of Directive 2001/18. Their genetic material has been altered in a way that does not occur naturally, within Article 2(2) of Directive 2001/18.

The European Food Safety Authority (“EFSA”) considered the Application, in order to determine inter alia whether the Soy would have adverse effects on human health, animal health or the environment, contrary to Articles 4(1)(a) and 16(1)(a) GM Regulation, if its placing on the Union market were to be authorised.

In accordance with Articles 6(4) and 18(4) of the GM Regulation, EFSA consulted the competent national authorities of Member States on the Application.

Following that consultation, EFSA adopted an Opinion on the Application on 26 January 2012 (EFSA 2012, “EFSA Opinion”). It concluded:

> “In conclusion, the EFSA GMO Panel considers that the information available for soybean MON 87701 × MON89788 addresses the scientific issues indicated by the guidance document of the EFSA GMO Panel and the scientific comments raised by the Member States, and that soybean MON 87701 × MON 89788 is as safe as its comparator with respect to potential effects on human and animal health or the environment in the context of its intended uses. In addition, the EFSA GMO Panel is of the opinion that crossing of single soybean events MON87701 and MON 89788 to produce soybean MON 87701 × MON 89788 does not result in interactions between the events that would affect the safety of soybean MON 87701 × MON 89788 with respect to potential effects on human and animal health and on the environment, in the context of its intended uses.”

In the absence of a decision by the Council, and on the basis of the EFSA Opinion, the Commission decided on 27 June 2012 to grant the market authorisation (Commission decision 2012/347/EU, published on 28 June 2012[18]).

The Commission decided (Article 1 of the decision):

> "The following products are authorised for the purposes of Article 4(2) and Article 16(2) of Regulation (EC) No 1829/2003 in accordance with the conditions set out in this Decision:
>
> (a) foods and food ingredients containing, consisting of, or produced from MON-877Ø1-2 × MON-89788-1 soybean;
>
> (b) feed containing, consisting of, or produced from MON- 877Ø1-2 × MON-89788-1 soybean;
>
> (c) MON-877Ø1-2 × MON-89788-1 soybean present in products other than food and feed containing it or consisting of it, for the same uses as any other soybean with the exception of cultivation."

The Commission agreed with the plan of the applicant on the monitoring plan for environmental risks. Further, the Commission decided upon the monitoring plan for food consumption (point I of the Annex):

> "Post-market monitoring requirements for the use of the food for human consumption: Not required."

18 http://ec.europa.eu/food/dyna/gm_register/index_en.cfm

3. Grounds of the complaint

Ground A: Failures in EFSA's assumption the Soy is 'substantially equivalent'

Introduction:

Ground A is that EFSA committed a manifest error of assessment in concluding that the Soy is 'substantially equivalent' to its conventional counterpart apart from the insertion of the Proteins. EFSA concluded the substantial equivalence without sufficient scientific evidence. Thus, the whole risk assessment of EFSA is manifestly flawed because the following steps in risk assessment and all final conclusions are based on this assumption.

In comparison to their conventional counterparts, both the stacked event and the parental plants show a number of significant differences. By referring to unspecific reference material and the ILSI database, which is known to be unreliable, differences in phenotype and in plant composition were interpreted as having no biological relevance.

Reasoning

A1 Weakness in assumptions concerning parental plants

The statement of EFSA that the parental plants are substantially equivalent to its isogenic comparators is rather questionable. As it is shown by the data and also as is evident from EFSA´s opinion (EFSA 2011 a), there is no doubt that for example MON87701 shows several significant and unintended effects such as a change in content of Vitamin E.

However, despite significant and unintended effects in parental plants, EFSA declared MON87701 and MON89788 to be equivalent in comparison to their conventional counterparts. For the purpose of demonstrating equivalence, EFSA and Monsanto

refer to the ILSI database. But as recent statement by an expert on EFSA´s GMO Panel shows, this database is known to be unreliable (see A4).

Although it is not possible to run a complaint about the market authorisation of the parental plants at this stage, the existing uncertainties regarding the substantial equivalence of the parental plants should have been taken into account by EFSA during the risk assessment of the stacked Soy. Since EFSA did not discuss the relevant uncertainties issue in detail, the risk assessment of the Soy is founded on an assumption about equivalence, which is not based on sufficient scientific evidence.

A2 Missing comparators

Since there are justifiably severe doubts in the substantial equivalence of the parental traits, a detailed investigation of the plants components of the stacked Soy would have been necessary.

As also EFSA Guidance (2007) proposes:

> "In line with the EFSA Guidance Document [2006], the most appropriate comparator(s) for the GMO plant containing the stacked event should include the GM parental materials as well as appropriate non-transgenic genotype(s). A genetic background comparable to the GMO containing the stacked events should be chosen... The applicant should provide detailed information justifying the choice of comparators."

Accordingly, the investigation of the differences between the stacked Soy and its comparators should include the isogenic and the non transgenic parental plants (as well as the crossings) in direct comparison of the field trials. However the applicant chose to use only one comparator (A5547) which is qualified as "conventional line that has a similar genetic background to the test substances" (Berman et al., 2008).

As a result, EFSA´s assumption of equivalence of the stacked Soy is founded on a flawed assumption of substantial equivalence of the parental plants (see A1) and is, furthermore, not based on sufficient and reliable data from the appropriate comparators.

A3 Wrong references

Instead of using appropriate comparator lines, many other soybean varieties were grown in parallel as “reference substances”, some of them even genetically engineered[19]. By following this approach, the applicant generated a broad range of data that are not related to the genomic background of the Soy and are likely to produce a broad range of data 'noise' that is likely to mask the specific differences between the Soy and its comparator.

Further, the ILSI data base was used as a further reference for historical data. Even the EFSA recognises the unreliability of this database. As Joe Perry, the current Chair of EFSA’s GMO Panel said:

> "I think we're in a situation where we would be unwise at the present time (maybe in the future this will be different), but at the present time we can't trust the ILSI database. There is not sufficient environmental information from where these trials were done and that's why we insist that the commercial reference variety should be planted simultaneously with the GM and the non-GM. Otherwise I think we are in an unsafe situation and I would worry that the limits would be too wide.“[20]

In section 4.1.3 of EFSA’s Opinion, it noted that the evaluation of the data obtained from the US field trial sites showed that statistically significant differences between soybean MON 8870 x MON 89788 (treated) and its comparator (not treated) was found for 20 analytes: including the proximate protein; the amino acids alanine and a number of fatty acids. In relation to the data obtained from the Argentinean field sites, the analysis revealed that there were 11 statistically significant differences between MON 8870 x MON 89788 and its untreated comparator. An analysis of the compositional data obtained from forage and seed samples from the field trials in Argentina in which both MON 8870 x MON 89788 and its comparator were not treated revealed statistically significant differences between the two soybean materials for 12 analytes.

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19 EFSA did not accept the data from the other genetically engineered plants for the purpose of comparison.

20 Observations of Mr. Joseph Perry, Vice-Chair, at EFSA’s consultative workshop on its draft guidance for the selection of Genetically Modified (GM) plant comparators, held in Brussels on 31 March 2011, http://www.efsa.europa.eu/en/events/event/gmo110331.htm

This large number of statistically significant differences was explained away either by reference to the amount of trial sites at which the differences were found, the range provided by the reference substances and/or literature contained in the ILSI Database.

Instead of setting aside the observed significant differences from compositional analysis, EFSA should have explored them in much more detail by subjecting the plants to defined environmental conditions and conducting investigations into gene activity and metabolic profile.

In the case of the Soy, there is a specific need for these more detailed investigations into changes in the plants´ composition since the expression of Cry1Ac was recently shown to disrupt regeneration, in vivo growth and development of transgenic tobacco and cotton (Rawat et el. 2011).

As a result, EFSA´s assumption of equivalence of the stacked Soy is founded on a flawed assumption (see A1) and is not based on sufficient and reliable data (A 2 and A3).

A4 Wrong approach for interpretation of phenotypical data

EFSA also failed to properly assess the data stemming from field trials concerning agronomic data and phenotypical differences. The significant differences from these trials (such as higher stand count) were interpreted only in regard to potential invasiveness and persistence (see Ahmad, et al., 2009, decision making tree on page 19). So for example, Ahmad et al., (2009) conclude on page 20 of the Monsanto report:

> “Thus, the statistical differences detected in early stand count, lodging, final stand count, grain moisture, 100 seed weight, test weight and yield are unlikely to be biologically meaningful in terms of increased weed potential of MON87701 × MON89788 compared to the conventional soybean control.”

This interpretation of the data does not take into account that a change in the phenotype is also an indication for unintended effects in the plant´s genome and a change of its components which can be relevant for food safety. The fact that phenptype changes can indicate the existence of unintended effects is recognised by EFSA in its 2007 Guidance in relation to stacked events at section 3.2.2. In addition,

EFSA notes that such unintended effects could include modified susceptibility to biotic and abiotic stresses.

Hence, EFSA´s assessment of equivalence lacks an adequate interpretation of the agronomical and phenotypical data.

A5 Missing data on impact from relevant geo-climatic regions

EFSA's 2007 Guidance Document states at section 3.2.1 that in relation to the compositional assessment of stacked events, "at least one year of field trial data is required, with trials performed together with appropriate controls in geographical localities representative of the climatic conditions under which such crops will be cultivated." Further, "possible differences in phenotypic characteristics and agronomic properties of stacks must be assessed in field trials over at least one season, as indicated [in relation to the compositional assessment). Again, on a case-by-case basis, additional information on agronomic traits of the stacked events may be required from additional field trials."

However, in relation to MON87701 × MON89788 the number of field trials and the data from the relevant geo-climatic regions is too low to draw any final conclusions about equivalence. Monsanto announced the Soy was developed for and will be sold under the brand name "Intacta" on the Brazilian market.[21] Therefore, the Soy intended for use in food and feed within the EU will be imported from Brazil. However, no data were generated under field conditions in Brazil. The field trials for compositional analysis and phenotypcial data were only conducted in Argentina and the US. It is also likely that other varieties were used in the field trials in Argentina and the US than the ones which are commonly planted in Brazil.

As a result, risk assessment of the Soy did not take into account any data from the most relevant geo-climatic regions where the Soy will be grown.

21 http://news.agropages.com/News/NewsDetail---6533.htm

A6 Missing data on the impact of specific abiotic stressors

Several investigations show that genetically engineered plants can exhibit unexpected reactions under stress conditions (see for example: Matthews et al., 2005, Zeller et al., 2010). These unexpected reactions can impact the plants compositions and give rise to unintended biological active substances such as micro RNA (see Zhang et al., 2011) or can cause a higher burden of fungal toxins (Zeller et al., 2010). The functional stability of the transgene under various defined environmental conditions, therefore, has to be investigated to assess safety for food and feed.

Section 7.4 of the 2006 Guidance recognises this by stating that (emphasis added) "the comparison between the GM plants and their most appropriate comparators should address also plant biology and agronomic traits, including common breeding parameters (e.g. plant morphology, flowering time, day degrees to maturity, duration of pollen viability, response to plant pathogens and insect pests, **sensitivity to abiotic stress**). As noted above, the 2007 Guidance also refers to the possibility of the unintended effects of the stacked event including modified susceptibility to biotic and abiotic stresses.

Ahmad, et al. (2009) give an overview of the reaction of the plants to specific environmental stressors such as drought, flooding and pressure from pathogens (page 41). However, the criteria relating to how these data were generated and evaluated are not given. According to the dossier, no statistical analysis was performed at all (at page 41). Therefore, no conclusions can be drawn from these data.

In order to perform the necessary risk assessment, the impact from specific stress factors should have been explored under defined environmental conditions, followed by appropriate statistical evaluation and including more recent scientific methods such as metabolic profiling.

As a result, no reliable data are available to show how the composition of the Soy will be impacted by abiotic stress conditions.

A7 Missing data on the impact of biotic stressors

As mentioned, several investigations show that genetically engineered plants can exhibit unexpected reactions under stress conditions. These unexpected reactions can impact food safety, for example, through a higher concentration of fungal toxins in the plants (Zeller et al., 2010). Therefore, the reaction of the transgenic plant to specific biotic stressors under various environmental conditions has to be investigated properly. Again this is recognised by EFSA in its 2007 Guidance at section 3.2.2.

There are significant findings on damage posed by plant pathogens and abundance of pest insects that indicate unintended effects of the Soy that also can be relevant for food safety (see for example Zeller et al., 2010 who found a higher infection rate with fungal toxins in the genetically engineered plants).

However, Ahmad et al., (2009) declare these findings as non-relevant. Their assumption (also adopted by EFSA), is based on reference data that do not stem from the comparison with the related isogenic comparators. For example, Ahmad et al. (2009) state concerning the higher damage caused by the soybean mosaic virus in Soy:

> "One difference was observed between MON 87701 × MON 89788 and the control for soybean mosaic virus at SF2 site during observation 2 (none vs. slight). However, the observed damage to MON 87701 × MON 89788 from this disease was within the reference range (none-slight)."

Concerning a lower abundance of the stink bug in the Soy, Ahmad et al., (2009) explain:

> "However, the mean value for MON 87701 × MON 89788 for stink bug damage was within the reference range. Thus, the statistical differences detected in arthropod damage are unlikely to be biologically meaningful in terms of increased pest potential or an adverse environmental impact."

From these more or less occasional data and their interpretation which is largely based on comparison with non-isogenic references, no conclusion can be derived if and under which environmental conditions the Soy might be more or less vulnerable to biotic stressors than its comparators. For example, targeted experiments should have been performed to investigate whether the soybean mosaic virus may affect the Soy under particular environmental conditions to a higher degree. In general, the reaction

of the transgenic plant to specific biotic stressors has to be investigated in much more detail and under defined environmental conditions before any conclusion can be drawn on food safety. For example it is also necessary to examine how the Soy reacts to extreme weather conditions as they occur under ongoing climate change.

A8 Missing scientific standards

The investigations concerning interaction with the environment, phenotypical characteristics and also some investigations concerning the plants´ composition do not meet basic standards for GLP (Good Laboratory Practice). This is explicitly stated in several of Monsanto´s dossiers dealing with the stacked Soy and its parental plants (Dunn & Kendrick, 2009; Giovannini et al 2008; Dunn et al., 2009; Elrod 2011).In several other dossiers there is no mention of the GLP standards at all (for example, Ahmad 2009; Berman, 2008). In others it is stated that GLP standards were not fully met (for example, Bermann et al., 2009; Lundry et al., 2006). Thus, most of these data were only subjected to the internal quality standards of Monsanto and are not in line with basic standards of scientific investigations. EFSA should have rejected these dossiers. There is, in any case, no reliable scientific basis to judge the safety of the plants.

The EU Commission does acknowledge the lack of sufficient scientific standards in the presented dossiers. In its recent proposal for implementing regulation on applications for authorisation of genetically modified food and feed (EU Commission, 2012), the Commission proposes requiring quality assurance for studies such as Good Laboratory Practice (GLP) or ISO for toxicological studies. But, of course, sufficient scientific standards have to be requested for each and every risk assessment of genetically engineered plants. According to existing EU Regulation, all products placed on the market have to be investigated in accordance with “the highest possible standard” (Regulation 1829/2003, recital 9).

In conclusion, the data from industry as mentioned should have been rejected by EFSA because they are not in accordance with internationally adopted scientific standards and therefore can not be regarded as being of “the highest possible standard” (Regulation 1829/2003, recital 9). As a consequence, the market authorisation of the Soy should be withdrawn.

A9 Incomplete data check of Soy sprayed with glyphosate

EFSA (2012a) concludes some significant compositional changes across all locations, especially in the stacked Soy sprayed with glyphosate, but only some of them were regarded as being relevant:

> "In conclusion, the only statistically significant differences across locations between soybean MON87701 × MON 89788 and its comparator that were consistently observed in both the USA and Argentina across the seasons were changes in the level of some fatty acids and increased levels of daidzein and genistein. These differences were small and not considered biologically relevant. Moreover, the values reported fell within the range defined by the natural variation of these constituents in commercial non-GM soybean varieties grown in the same field trials."

Increased levels of daidzein and genistein might well be of relevance as these substances are known to exhibit hormonal activity and are considered to be the major phytoestrogens in soy (see for example De Lemos, 2001). So further studies under other environmental conditions should be performed to find out more about the possible range in the content of these compounds.

Other studies not mentioned by EFSA (Barbosa et al., 2012; Bellaloui et al., 2008, 2009a, 2009b; Bott et al., 2008; Ducke te al., 2003; Reddy et al., 2000, 2003, 2004; Serra et al., 2011; Zablotowicz & Reddy, 2007; Zobiole et al., 2010a, 2010b, 2010c., 2010d, 2010f, 2010g, 2011a, 2011b, 2012) show that spraying the glyphosate tolerant soybean with the complementary herbicide can change the composition of the soybeans in several compounds (see table 1). EFSA also did not discuss the possible effects of glyphosate acting as a potent chelator (binding ions) and its impact on food safety and quality. Overall there is no scientific basis for claiming substantial equivalence of the Soy treated with glyphosate.

Table1: publications showing significant changes in components of glyhposate tolerant soybeans compared to isogenic lines after treating with glyphosate.

Study	Compound	Result
Barbosa et al., 2012	Protein: malondialdehyde, ascorbate peroxidase, glutathione reductase, and catalase	Elevated (seed)
	actin fragment, cytosolic glutamine synthetase, glycinin subunit G1, and glycine-rich	Expressed differently (seed)

Study	Compound	Result
	RNA-binding protein	
Bellalui et al., 2008	Protein	Protein elevated (seed)
	Oil	Reduced (seed)
	Oleic acid	elevated (seed)
	Linolenic acid	Reduced (seed)
	nitrogen assimilation, as measured by in vivo nitrate reductase activity (NRA) in leaves, roots, and nodules	Reduced
Bellalui et al., 2009a	Protein	elevated (seed)
	Amino acids	elevated (not significant) (seed)
	Oil	Reduced (seed)
	Oleic acid	elevated (seed)
	Linolenic acid	Reduced (seed)
	Prolin	Elevated (seed)
	nitrate reductase activity (NRA)	Reduced
Bellalui et al., 2009b	Ferrum	Reduced (seed)
Bott et al., 2008	root biomass and root elongation	depressions of plant growth in the GR soybean cultivar Valiosa strongly dependent on the selected culture conditions
	Shoot biomass	In soil culture, shoot biomass production declined by approximately 15–30% in glyphosate treated plants grown on an acidic Arenosol but not on a calcareous Loess sub-soil, while root biomass was not significantly affected
	nitrogen fixation	no effect of glyphosate application on nitrogen fixation as measured by acetylene reduction assay, soybean yield, or seed nitrogen content
Duke et al., 2003	daidzein	Elevated (seed)
Reddy et al., 2000	shoot and root dry weights	Reduced (greenhouse)
Reddy et al., 2003	chlorophyll content, root and shoot dry weight, or nodule number	no effect
	nodule biomass	reduced by 21 to 28% 14 d LPOST Soybean recovered by 14 d.
	Seed protein	Reduced when two applications were made (seed)
Reddy et al., 2004	AMPA, Shikimate, glyphosate levels in plants	Chlorosis, effects measured till 22 DAT
Serra et al., 2011 Greenhouse	Mn	No effect V8 (20 days after application)
	N, Mn, Cu, Zn and Fe	reduced
	Nodes	reduced
	Dry mass	reduced
Zablotowicz et al., 2007	seed nitrogen	reduced, when high doses of glyphosate were applied (seed)
Zobiole et al., 2010a	Number and weight of seeds	reduced by 25% and 13% (seed)

Study	Compound	Result
	per plant	
	17:1n-7 (not essentiell)	increased (by 30.3%) (seed)
	18:1n-9 (not essentiell)	increased (by 25%) (seed)
	linoleic acid (18:2n-6)	Decrease (2.3%) (seed)
	linolenic acid (18:3n-3)	Decrease (9.6%) (seed)
Zobiole et al., 2010b	Photosynthetic parameters	Decrease
	biomass production	Decrease
	water absorption	Decrease
	photosynthesis	Decrease
	water use efficiency	Decrease
Zobiole et al., 2010c	Shoot and root dry biomass	Decrease
	Photosynthetic parameters	Decrease
	Micronutrients (Zn, Mn, Fe, Cu, B) in leaves	Decrease
	Macronutrients (N, P, K, Mg, Ca, S)	Decrease (but no effect on N)
Zobiole et al., 2010d	photosynthetic parameters (A, SPAD, Fo, Fm)	Linear decrease R1 growth stage → long-term physiological impacts
	Macronutrients (N, P, K, Mg, Ca, S)	Decrease: effects in the following order: Ca > Mg > nitrogen (N) > S > K > P
	Micronutrients (Fe, Co, Zn, Mn, Cu, Mo, B)	Effects of single application in the following order: Fe > Mn > cobalt (Co) > Zn > Cu > boron (B)> molybdenum (Mo) two applications:Fe > Co > Zn > Mn > Cu > Mo > B
	shoot, root and total biomass dry weight	Reduced proportional to glyphosate dose.
Zobiole et al., 2010e	photosynthetic rate	Severely decreased RR2 more sensitive than RR1
	Leaf area and shoot biomass production	Severely decreased RR2 more sensitive than RR1
Zobiole et al., 2010f	photosynthetic rate	1800 dose: reduction 33 and 31%.
	lignin and amino acid content	Reduced (linear)
	height and total (shoot and root) dry weight	Reduced (linear)
Zobiole et al., 2010g	Nodule number	reduced
	Ni concentration	reduced
	Chlorophyll (SPAD units)	Lower in RR soybean even lower when treated with glyphosate
		Chlorotic symptoms, non persistent
Zobiole et al., 2011a RR1 and RR2	Fusarium spp.	Increased in RR1 and RR2 soybean
	Mn reducers /Mn oxidizers ratio	Decreased in RR1; The greatest reduction in the ratio of potential Mn reducers /Mn oxidizers occurred when glyphosate was applied at early (V2) compared with later

Study	Compound	Result
		growth stages (V4 and V6
	root and shoot dry weight	Decreased in RR1 and RR2 soybean Earlier glyphosate applications caused greater decreases in root dry weight Shoot dry weight of both varieties was most reduced when glyphosate was applied at the V6 growth stage and least at V4 and V2 stages, with the GR2 cultivar affected more than the GR1 cultivar (Fig. 6). In general, GR2 produced less biomass (shoot and root) than GR1 when glyphosate was not applied
Zobiole et al., 2011b RR1 and RR2	chlorophyll	decrease
	macro and micronutrient accumulation	Decrease All macro- and micronutrients, with exception of N and K, accumulated more in RR1 than RR2 (Figs. 2 and 3 and Table 1). This result may be an individual cultivar characteristic, but it suggests that the RR2 cultivar was inefficient in nutrient uptake and translocation or was unable to rapidly recover from potential chelating effects of glyphosate In the present experiment, glyphosate apparently remained active in soybean through R1 growth stage or later as indicated by decreased nutrient accumulation. It is known that glyphosate and its metabolites can remain within the plant until complete physiological maturity.
	Nodule dry weight and number	Reduced tendency for late applications to have less effect than early applications
	Shoot biomass	decrease higher percent reduction associated with late than with early glyphosate applications
	chlorosis	The new generation RR soybeans also showed undesirable glyphosate effects as “yellow flashing”.
Zobiole et al., 2012 RR2	photosynthetic rate	severely depressed
	macro- and micronutrient accumulations	Proportionally reduced as glyphosate rates increased and applications were delayed Macronutrient and all micronutrient concentrations except Cu were within the nutrient-sufficiency ranges for soybean Concentrations of Ca, Mg, S, and Cu were significantly ($p <$ 5%) lower in glyphosate-treated soybean yet all values were within the sufficiency ranges for those nutrient concentrations to provide acceptable soybean growth. Concentrations of P and Fe appeared to be increased by glyphosate.
	nodule number and dry weight	significantly decreased In contrast with other results, a tendency was noted for reduced effects at late applications compared with early applications
	root dry weight	more severely depressed with glyphosate applied at V2 growth stage compared with V6 growth stage
	leaf area and shoot dry weight	More strongly decreased at the late growth stage than at the early stage

In conclusion and even in accordance with EFSA´s Guidance, a much more comprehensive risk assessment must be applied if the comparative approach shows that equivalence with isogenic lines cannot be shown. Thus EFSA´s opinion is wrong in regard to its overall approach as well as in its conclusions.

A10 Missing data on processed food and feed

There are no data on the equivalence and quality of the products that are processed such as soybean sprouts, milk and baby food, or for products undergoing fermentation and heat treatment. Without such data, no conclusion can be drawn upon equivalence and food safety:

Data are necessary to assess effects of processing on the naturally occurring antinutrients such as the trypsin inhibitor. Its degradation can be impacted due to unintended effects in the plants. Other antinutrients should also be considered.

The composition of soybean sprouts need particular attention: The production of soybean sprouts is a highly dynamic process that involves many different gene activities and gives rise to a lot of transient products in the beans that are not relevant for other food usages. Further processing by heat is not applied in this case. Thus this product needs detailed and specific investigation including metabolic profiling.

A11 Some comments from Member States

Several experts from Competent Authorities of the Member States have raised concerns regarding the compositional equivalence of the Soy with its conventional counterparts. These concerns were not sufficiently taken into account in the final EFSA opinion. Some of the relevant statements were made (EFSA 2012b):

> “For some of the assessed parameters (ADF, glutamic acid, leucine, stearic acid, linoleic acid, arachidic acid, ash, vitamin E, stachyose, daidzein, genistein) the results established for GM soybean MON87701xMON89788 and the used non-transgenic control were significantly different. The notifier should discuss these

differences in more detail and further assess why they were not considered to be biologically meaningful."

"On the whole, the compositional differences between the seed samples of MON87701xMON89788 and the control showed a clear consistency concerning higher contents of amino acids and isoflavones (mainly daidzein and genistein) in the GM variant, whereas the contents of fatty acids (mainly palmitic and stearic acid), vitamin E and ash were lower. The conclusion would therefore be that these differences are inherent in GM soybean MON87701xMON89788 as compared to the A5547 control, even if they were not considered biologically meaningful when compared with commercial soybean varieties and with the ILSI database."

"Firstly, changed C:N ratios have effects on all metabolic and gene expression levels of plants. Secondly, the same trends were seen in the USA and Argentinian field trials, despite different fertility managements."

"Micronutrients were not measured, only ash content, which was lower in the GM variant. This is unfortunate, since indications for a "decreased uptake of micronutrients and subsequent development of deficiency symptoms in some GR soybean cultivars" exist (Johal and Huber 2009; Yamada et al. 2009). It seems therefore advisable to broaden the comparative analysis including certain micronutrients (e.g. Mn, Fe), in order to reveal potential deficiencies in the micronutrient uptake of GM soybean MON87701xMON89788."

Conclusions on Ground A:

- It follows that there is no basis upon which EFSA could have concluded that the comparison made was "appropriate" under the terms of Articles 5(3)(f) and 17(3)(f) GM Regulation. It should also be noted that in a number of respects EFSA failed to follow and/or comply with the terms of its own Guidance Documents.

- Further, and in consequence, contrary to the requirements of and Articles 6(3)(a) and 18(3)(a) GM Regulation, either EFSA has failed to consider whether

Monsanto's analysis was supported by "appropriate information and data", or EFSA has unlawfully and manifestly incorrectly concluded that the information provided by Monsanto was "appropriate".

- This error is also potentially highly material to the conclusion that the Soy does not present a risk of adverse effects on humans and/or animal health, contrary to Articles 4(1) and 16(1) GM Regulation.

- EFSA critically failed to consider the biological significance of any or all of the significant differences between the Soy and its conventional counterpart (to proceed further analyses). EFSA's conclusion that the Soy is safe depends on the assumption that the Soy is substantially equivalent to its conventional counterpart. As such, it is fatally flawed. In particular, on the basis of its conclusion that the Soy and its conventional counterpart are substantially equivalent EFSA concluded that it was not necessary to conduct a toxicological assessment of the whole food/feed. A properly conducted comparison of the field trial results with properly analysed literature might well have demonstrated that the statistically significant differences observed were biologically relevant, and required much more detailed analysis at the following steps.

- As such, EFSA's conclusion that there would not be an adverse effect on human health and/or animal health from the Soy, under Articles 4(1)(a) and 16(1)(a) GM Regulation, is not reliable.

- In addition, EFSA failed to ensure that Monsanto submitted information and conclusions about a risk assessment carried out in accordance with Annex II to the Directive as required by Article 5(4) of the GM Regulation.

Accordingly, the Commission should not have granted the authorisation of the Soy in this case. In particular, it has failed to comply with its obligations under: (a) Articles 4(1)(a) and 16(1)(a) to ensure that that food and feed that would have an adverse effect on human health, animal health, or the environment "must not" be placed on the Union market; (b) Articles 7(1) and 19(1) GM Regulation to take into account not only the EFSA Opinion but also "any relevant provisions of [Union] law", including the provisions of Union law that require Union institutions to comply with their own

guidance and (c) Article 168 TFEU and reflected in Recital (2) GM Regulation to ensure a high level of protection for human health.

Furthermore, so far as relevant, the Commission has unlawfully defeated a legitimate expectation that EFSA would act in accordance with its own guidance in advising the Commission on applications for authorisation under the GM Regulation, and that the Commission would ensure such compliance by EFSA before reaching its authorisation decisions.

Ground B: Failure to consider synergistic/combinatorial effects

Introduction

The potentially toxic effects of a particular genetically modified food/feed are one of the primary matters requiring investigation by EFSA in determining whether it will have adverse effects on human health, animal health or the environment, contrary to Articles 4(1)(a) and 16(1)(a) GM Regulation.

In the case of the Soy, EFSA did not present a risk assessment as legally required and sufficiently based on scientific findings: No feeding studies for investigating health effects were conducted with the stacked Soy, no acute, subchronic, long term and multigenerational study was requested. The only feeding study that was performed with the Soy was a feeding study with broiler to gain nutritional data – this is unsuitable for the detailed investigation of potential health effects.

No tests were performed to determine potential combinatorial or accumulated effects of the toxins, nor of any other factors such as other toxic compounds, bacteria, plant enzymes (trypsin inhibitors) and especially the residues from the complementary herbicide. No investigations were conducted to assess the impact of a permanent ingestion of these plants on the intestinal microbial composition in human and animals.

Further, the effects of different methods for processing the Soy and risks associated with particular usages of soybeans in human nutrition was not assessed.

All in all EFSA´s risk assessment of the Soy does not fulfil the legal requirements of current EU regulations.

Detailed reasoning

B1: False conclusion stemming from the comparative approach

EFSA concluded that there was no need to carry out any further animal safety studies of the whole GM food/feed, for three reasons:

- According to the previous opinions of EFSA, no adverse effects had been observed in the 90-day rat feeding studies involving the parents;
- The Soy had been found to be substantially equivalent to its conventional counterpart; and
- EFSA considered interactions among the additional produced proteins “unlikely”.

The first point might be a matter of further controversial debate (which will not be discussed in detail in this complaint about the stacked Soy). The second of these reasons is flawed, for reasons given in Ground A above: On the basis of existing data, substantial equivalence cannot be concluded for the Soy. As already shown in the complaint, EFSA was wrong even according to its own Guidance not to request further investigations with the whole food and feed.

Additionally, the third point of EFSA´s reasoning is substantially flawed, as the following paragraphs show.

EFSA´s approach is also wrong from a general point of view: Due to its reasoning that no further investigations would be necessary if compositional equivalence was assumed, EFSA did not take into account serious criticism of its overall concept of comparative risk assessment as, for example, expressed by some experts of the Member States (EFSA 2012b):

> “Moreover, the concept that nutritional equivalence can be assumed once compositional equivalence has been established is out-dated. In modern nutritional science this assumption has long been abandoned, since there is increasing evidence that compound interactions within the organic system

cannot be predicted by compositional data (Vivekananthan et al. 2003; Gitenay et al. 2007).”

B2: Insufficient investigation of selectivity of the newly expressed toxin

The mode of action of Bt toxins is a matter that is not presently scientifically understood. It is even a matter of controversial debate (Pigott & Ellar, 2007). For example, Zhang et al (2005), Soberon et al (2007), Broderick et al (2009), Johnston & Crickmore (2009), Mason et al., (2011) reach different conclusions as to the mode of action in target organisms. In addition, Frankenhuyzen (2009) shows that selectivity of Cry proteins is something that has to be disputed further.

Regarding potential health effects, Ito et al. (2004), Huffmann et al. (2004), Thomas & Ellar (1983), Gallagher (2010) and Mesnage et al. (2012) show that toxins that belong to Cry-classification (such as Cry1Ac) might cause health effects in mammals.

Since these questions were not investigated during risk assessment of MON87701, EFSA should not have been setting aside these questions when it came to risk assessment of the stacked Soy.

B3 The Cry toxin lacks authorisation under pesticide regulation

It also should taken into account that the Cry1Ac toxin in the plants was never assessed under standards as foreseen by pesticide authorisation 91/414 EEC. There are several important differences between the Cry toxin as produced in the plants and its usage in traditional mixtures (for general overview on these issues see Hilbeck & Schmid, 2006; Szecaks & Darvas, 2012): So far the Bt toxin was only used in traditional mixtures and in crystallized (inactivated) form. But in the plants the Cry1Ac toxin is solubilised (activated). Further, it is applied throughout the whole period of vegetation, while the traditional sprays are used a very targeted way. To be effective, it has also to be exposed in higher concentration than it is the case in the traditional mixtures: In the mixtures, additive and synergistic effects require only a low level of the single compound. Further, some details of the DNA sequence were changed during the process of transferring the DNA into the plants´ genome. For example, the Cry1Ac toxin contains four additional amino acids at its N-terminus compared with the Bt

toxin produced in Bt Cotton MON531. In comparison with the native protein, more changes were necessary to optimise the codon and length of the DNA.

All in all, without full authorisation of the Cry toxin (as it is produced in the plants) under pesticide Regulation, the placing of the Soy in the market clearly establishes double standards for the safety of pesticides within the EU: Under GMO regulation a much lower standard is applied than under pesticide regulation.

Since these questions were not investigated during the risk assessment of MON87701, EFSA should not have set aside these questions when it came to risk assessment of the stacked Soy.

It also should be acknowledged that in the Council Conclusions on Genetically Modified Organisms (GMOs) of the Council meeting on 4 December 2008, Member States demanded a revision of current EU regulations to close the loopholes between the pesticide regulation and the regulation on genetically engineered plants. This demand is in no way confined to the usage of the genetically engineered plants in agriculture but includes all relevant products, which might be authorised on the market[22]:

> "(...) the mandate includes examination of the criteria and requirements for assessing all GMPs, including GMPs that produce active substances covered by directive 91/414/EEC and herbicide-tolerant GMPs with a view to reviewing them if necessary; (...) RECALLS that the use of plant protection products implies authorisations at national level and EMPHASISES THE NEED for competent authorities involved with the implementation of Directive 2001/18/EC and of Council Directive 91/414/EEC concerning the placing of plant protection products on the market, within the Commission and at national level, to co-ordinate their action as far as possible;"

B4: Not assessing the interactivity of the Bt toxin with plant constituents

Not only is the mode of action of the Cry1Ac proteins not fully understood, EFSA also has no basis for assuming that they will not interact with other compounds. On the contrary, there are several publications that show that Bt proteins are highly likely to show synergies and interactions with other stressors and plant enzymes (for overview see Then, 2010).

22 http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressdata/en/envir/104509.pdf

For example, it is known that co-stressors such as cadmium and nematodes can cause toxicity of Cry toxins in slugs (Kramarz et al., 2007; Kramarz et al., 2009), which can be seen as important model organisms. Other combinatorial effects are known to enhance the toxicity of Bt toxins from investigations with pyrethroids (Khalique & Ahmed, 2005; Saleem et al., 1995), Azadirachtin, (Singh et al. 2007), Avidin (Zhu et al., 2005), Bacteria (Mason et al., 2011), Nosema (Reardon et al. 2004) and other Bt toxins (Sharma et al., 2010).

Since the Soy will contain residues from spraying with glyphsate formulations, the possible interaction between Bt toxins and co-stressors such as pesticides are highly relevant for the risk assessment of this product.

Other examples include the powerful effect that some plant enzymes that diminish the digestion of proteins (protease inhibitors) can have on the toxicity of Bt toxins, where toxicity has been found to increase up to 20 times even in the presence of very low levels of protease inhibitors (Zhang et al., 2000, Pardo Lopez et al., 2009). In the case of Soy products, the interactivity with protease inhibitor is highly relevant. All soybeans have high levels of these inhibitors their degradation depends on the method of heat processing. Even the presence of very low levels of protease inhibitors can multiply the insecticidal activity of Cry toxins. Since soybeans, for example, are also used as soybean sprouts, differing methods of processing have to be discussed case by case to assess all potential synergies.

Even EFSA´s own Guidance (EFSA 2007) requires these tests (see section 3.3.1):

> “An assessment of any potential for increased toxicity and/or allergenicity to humans and animals or for modified nutritional value due to the stacked events should be provided. These potential effects may arise from additive, synergistic or antagonistic effects of the gene products or by these produced metabolites and may be particularly relevant where the combined expression of the newly introduced genes has unexpected effects on biochemical pathways. This assessment will clearly require a case-by-case approach”.

But no tests were performed to determine potential combinatorial or accumulated effects of the toxins, nor of any other factors such as other toxic compounds, bacteria,

plant enzymes and pesticides in mammals. The relevant proteins (Cry1Ac and EPSPS) were only fed in separate feeding trials, the aspect of interactivity with protease inhibitors and residues from spraying with complementary herbicides were left aside completely.

Since these plants will be used in food and feed and might be mixed with other genetically engineered plants, further tests need to be carried out to determine potential accumulative or combinatorial effects. Without such investigations the market authorisation should be withdrawn.

B5: Insufficient assessment of expression of the Bt Toxin

One of the prerequisites of risk assessment is sufficient data on the expression of the newly expressed proteins. But in the case of Bt toxins, standardised protocols to measure the content of Bt toxins in a way that the results can be reproduced by other laboratories are missing (Székács et al., 2011).

Further, it is not clear how these plants and the expression rate of the newly introduced proteins will be influenced by more extreme weather conditions relevant in times of climate change such as drought. Several investigations show that genetically engineered plants can exhibit unexpected reactions under stress conditions. This can also impact the Bt content in the plants (Then & Lorch, 2008).

Viewed from this perspective, much more detailed investigations would be necessary. Only investigations under defined environmental conditions can reveal which impact factors are mostly relevant for the content of toxins within the plant´s tissue. Functional genetic stability has to be shown under defined stress conditions and not just in reactions to occasional environmental conditions from only one year as presented by Monsanto (see for example Deffenbaugh & Niemeyer, 2009). In this case no data were included into the risk assessment from the most important geo-climatic region Brazil (see A5).

Furthermore, in comparison to the parental plants the stacked Soy has a substantially higher content of the newly expressed proteins in its tissues, sometimes even above factor 2 (Deffenbaugh & Niemeyer, 2009). This effect clearly shows emerging genomic effects in the stacked Soy that cannot be predicted from the parental plants. Thus,

these effects would have needed further investigation. This was also requested by the experts from Member States (EFSA 2012b):

> “Since protein expression in plants can be affected by climatic conditions, soil fertility, agricultural practice or unknown gene-environment interactions, data from single season give a rough estimate of expression levels only. A more robust and reliable data basis should, therefore, include data from at least three field seasons at the same location (with six locations representing different environmental conditions) to integrate possible differences in expression values triggered by differences in ecological conditions.”
>
> “Values for the expression of Cry1Ac and CP4 EPSPS in some tissues of MON 87701 and MON87701 x MON89788 differ considerably between the single study sites. This suggests that the expression level in MON87701 and in MON87701 x MON89788 soybean depends on site-specific ecological factors. Hence, a thorough statistical analysis comparing expression values at the different sites should be provided to address this suggestion.”

B6: Failure to assess risks from residues of spraying

Several experts warn that a higher toxicity can be expected for glyphosate than previously thought (Benachour, et al., 2007; Paganelli et al., 2010; PAN AP 2009). Further, several studies indicate particular health risks from genetically engineered soybeans tolerant to glyphosate formulations and the residues from spraying with the complementary herbicide (Malatesta, et al. 2002, 2005, 2008; Cisterna et al., 2008, Magana Gomez et al., 2008).

In this context, the additive POEA (polyethoxethyleneamine) also has to be taken into account, as it is even more toxic than glyphosate. In 2010, German authorities prohibited the use of certain glyphosate formulations with a high content of POEA for the production of animal feeds in order to avoid the risk of toxins being passed through the food chain[23]. If other additives are used their residues would have to be considered too.

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23 www.bvl.bund.de/DE/04_Pflanzenschutzmittel/05_Fachmeldungen/2010/psm_anwendungsbestimmungen_tallowamin-Mittel.html

In general, the GMO panel leaves all questions concerning the risk assessment of residues from spraying to the EFSA pesticide panel. There are, however, several reasons why the risk assessment of genetically engineered plants with herbicide tolerance cannot leave aside the issue of residues from spraying:

- Commercial large scale cultivation of these plants means there is a strong selective pressure on weeds to develop glyphosate resistance, this increases the amount of sprayed herbicides and the load of residues. The complementary herbicides are likely to be sprayed several times during crop growth, thus the pattern of usage and the level of residues can be significantly higher compared to non-resistant crop plants.
- Herbicide tolerant plants are meant to survive the application of the complementary herbicide while most other plants will be killed after short time. Thus, residues of glyphosate, its metabolites and the additives can accumulate and interact in the plants that survive due to their additional genetic information.
- In the case of stacked events, a combination of specific plant constituents is fixed in the genetically engineered plants. The combination of the residues from spraying and of insecticidal proteins (as it is the case in MON87701 x MON89788) causes a unique and unavoidable exposure of the feed and food chain with very specific residues. Possible interactions have to be investigated in detail.

In conclusion, the residues and their combinations are inevitable constituents of the plants composition leading to specific pattern of exposure of the food chain. A basic prerequisite for risk assessment in this context is reliable data on residue loads from spraying with glyphosate formulations. The amount of these residues depends on the specific agronomic management used in the cultivation of the herbicide resistant plants. However, reliable data covering the actual range of residue load in the plants are not available (Kleter et al., 2011). Without such data, there can be no sound risk assessment of this product. A recent legal dossier, commissioned by Testbiotech (Kraemer, 2012[24]) also shows that from a legal point of view, the residues from spraying with complementary herbicides have to be taken into account in the risk assessment of genetically engineered plants.

24 attached

It also should be acknowledged that in the Council Conclusions on Genetically Modified Organisms (GMOs) of the Council meeting on 4 December 2008, the Member States demanded a revision of current EU regulations to close the loopholes between the pesticide regulation and the regulation on genetically engineered plants. This demand is in no way confined to the usage of genetically engineered plants in agriculture, but includes all relevant products which might be authorised on the market[25] (see point B3).

The need for taking the residues from spraying into account is underlined by the fact that a significant proportion of consumers seem to have a substantial load of pesticide residues in their blood. As EFSA (2011) wrote in a letter to the European Commission (DG Sanco) asking for an opinion on the publication by Aris & LeBlanc (2011):

> "From the consumer health perspective, the observations described by the authors on the presence of glyphosate and glufosinate in non-pregnant women blood (5% and 18% of the subjects, respectively) and of 3-MPPA in non-pregnant women, pregnant women and the fetal cord blood are not unexpected. It is known that pesticides are generally well absorbed by the gastrointestinal tract and that an exposure to the two herbicides investigated through the consumption of food commodities is plausible."

It is known that the microbial community in the soil can be changed by frequent application of glyphosate during cultivation. But EFSA completely overlooks that permanent ingestion of the soybeans that might carry a burden up to 20 mg/ kg of residues from spraying (as allowed by pesticide legislation), may in turn also affect microbial flora in the gut. There are, for example, concerns that permanent ingestion of glyphosate might be a cause of chronic botulism through interfering with the ecology of microorganisms in the gut (http://www.pan-germany.org/deu/~news-1102.html). The data from soil organisms, gives these scenarios sufficient plausibility and cannot be omitted from risk assessment. In any event, as outlined above Annex II to the Directive provides that a potential adverse effect cannot simply be ignored because it is considered unlikely. The magnitude of the risk must be evaluated and taken into account in the environmental risk assessment.

25 http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressdata/en/envir/104509.pdf

There might be also be other relevant issues in relation to changes in the intestinal flora of human and animals related to the ingestion of these soybeans. Thus, targeted feeding studies should be conducted.

B7: Not assessing interactivity with residues from spraying

Seen from the perspective of the technical background presented under B4 and B6, it is evident that glyphosate and the residues from spraying glyphosate on the Soy have to be considered as a potent co-stressor. Its combinatorial impact needs to be assessed during risk assessment.

The fact that no such investigations were requested has to be considered as a substantial and crucial failure of EFSA´s risk assessment, which affects the reliability of the opinion in general.

B8: Insufficient assessment of exposure and effects of processing

As EFSA points out in its opinion (EFSA, 2012a), the Soy might be used in a broad range of feed and food products:

> "The scope of application EFSA-GMO-NL-2009-73 is for food and feed use, import and processing of soybean MON 87701 × MON 89788 within the EU. Thus, soybean MON 87701 × MON 89788 will be imported into the EU mixed with other soybean varieties and used as food or feed or for the production of a large number of derived products, in the same way as any commercial soybean variety. The main product for human use is soybean oil. Around 10 % of the heat-processed (toasted) defatted soybean meal goes into soybean products for human consumption, including flours, soybean protein concentrates and various textured products simulating meats, seafoods and cheeses. The rest of the toasted defatted soybean meal goes into animal feed, mainly for poultry, pigs and cattle in the EU (OECD 2001). Whole soybeans are used to produce soy sprouts and baked and roasted soybeans. There is also a limited direct use for soybeans as animal feeds."

However, when it comes to effects of processing on the derived products, there have only ever been investigations in which soybeans were subjected to one specific kind of

heat processing, chosen by Monsanto without any clear justification. As Bell et al. (2008) state:

> "The temperature (~190° C) and duration (~15 min) used in this assessment were selected to represent a baking treatment that might be employed in the production of foods that contain soybean flour (Coward et al., 1998)."

Since there are no data on the effects from any other technical treatments that are commonly used to process soybeans, no conclusions can be drawn about the factual exposure of consumers and animals if the Soy is used in food and feed. This constitutes a major basic deficiency for the overall risk assessment.

B9: Further relevant issues: endocrinological studies

Targeted endocrinological studies should have been performed to investigate potential impacts on the reproductive system, since soybeans are known to produce several hormonally active substances that might have been changed unintentionally. As mentioned, for example, increased levels of daidzein and genistein might well be of relevance as these substances are known to exhibit hormonal activity (De Lemos, 2001).

B10: Further relevant issues: transfer of biologically active compounds

Since DNA and RNA are known to be transferred from genetically engineered soybeans to animal tissue (see for example Ran et al., 2009, Tudisco et al., 2010) and biological activity of the transferred plant RNA in animals was shown (Zhang et al., 2011), these issues should have been taken into account in EFSA risk assessment.

Some conclusions on Ground B:

The Commission's Decision and the opinion of EFSA are flawed. In this case, it is clear that EFSA had no sound basis for concluding that no further investigations would be required and the Soy could be considered safe. Consequently, the Commission fell into manifest error by failing to require a proper risk assessment that was of the "highest possible standard" and included a toxicity test.

In this case, therefore, the Commission has granted Monsanto's application without ensuring that:

- the authorisation was issued on the basis of a risk assessment of the "highest possible standard": Recital (9) GM Regulation.

- Monsanto had submitted information and conclusions about a risk assessment carried out in accordance with Annex II to the Directive as required by Article 5(4) of the GM Regulation.

- EFSA had complied with its duties, under Articles 6(3)(a) /18(3)(a) GM Regulation, to ensure that Monsanto had provided to it, and to EFSA, "appropriate" information and data to support the comparative analysis submitted with the application under Articles 5(3)(f) / 17(3)(f) GM Regulation;

It has also failed to act in accordance with its duties:

- under Articles 4(1)(a) and 16(1)(a) GM Regulation to ensure that food and feed that would have an adverse effect on human health, animal health, or the environment "must not" be placed on the Union market;

- under Articles 7(1) and 19(1) GM Regulation to take into account not only the EFSA Opinion but also "any relevant provisions of [Union] law", including the provisions of Union law that require Union institutions to comply with their own guidance;

- under Article 168 TFEU and reflected in Recital (2) GM Regulation to ensure a high level of protection for human health.

Furthermore, so far as relevant, the Commission has unlawfully defeated a legitimate expectation that EFSA would act in accordance with its own guidance in advising the Commission on applications for authorisation under the GM Regulation, and that the Commission would ensure such compliance by EFSA before reaching its authorisation decisions.

Ground C: Insufficient assessment of immunological risks

Introduction

Insect-killing Soy MON87701 is engineered to produce the insecticidal protein Cry1Ac. This is a Bt toxin which is known to enhance immune reactions and able to bind to epithelial cells in the intestine of mice (Vázquez-Padrón et al., 1999, Vásquez-Padrón et al., 2000).

Experts from Norway raised concerns already during the risk assessment of MON87701 (EFSA, 2011b):

> "According to the applicant the epitope test shows that Cry1Ac protein does not share structurally and immunologically relevant amino acid sequence similarities with known allergens, and that the Cry-protein has no similarities to IgE epitopes of allergenetic proteins. However, this Cry-protein has immunogenic potential to elicit strong IgG-response (Vazquez et al.1999) and the induction of IgG antibodies to food antigen and even crosspriming against a bystander antigen may be of biological significance (Brandtzaeg, 2010). Experimental studies both in vitro and in vivo have demonstrated that IgG antibodies that are not balanced by a mucosal IgA response can enhance the epithelial penetration of bystander proteins (Brandzaeg, 2010). Due to remaining uncertainty that Cry1Ac may enhance systemic and mucosal immune responses to co-administrated antigens, the Norwegian GMO Panel still sees the need for further clarification on the possible role of Cry proteins as adjuvants."

And experts from Belgium were upholding similar concerns in the case of the stacked Soy (EFSA 2012b):

> "If Cry1Ac is not likely to be an allergen itself, it should be emphasized that Cry1Ac has been proposed as an adjuvant for vaccines (Esquivel-Pérez and Moreno-Fierros, 2005; Moreno-Fierros et al., 2003; Vásquez et al., 1999; Vásquez-Padrón et al., 1999; Verdin-Terán al. 2009), which means that this protein is able to enhance the immune responses against antigens that are co-administered. This is not uncommon for a bacterial protein. The consequence of the presence of such immuno-stimulant in a plant destined to human consumption is not known. Particularly the adjuvant effect via intestinal route is poorly documented. It is not known whether the presence of Cry1Ac might elicit

sensitization against the other plant proteins upon ingestion. It might be relevant to study in mice the immune responses against soya proteins when the animals are fed Soybean MON87701 x MON8978."

Soy is one of the most potent allergenic food plants, consequently, from a precautionary perspective the introduction of this protein in soybeans is highly problematic.

C1 Insufficient testing of allergic reactions

As noted above, EFSA Guidance (2007) states that:

"An assessment of any potential for increased toxicity and/or allergenicity to humans and animals or for modified nutritional value due to the stacked events should be provided. These potential effects may arise from additive, synergistic or antagonistic effects of the gene products or by these produced metabolites and may be particularly relevant where the combined expression of the newly introduced genes has unexpected effects on biochemical pathways."

The findings in blood samples from individuals with a known allergy to soybeans should have already triggered more investigations assessing the parental plants (MON87701)[26] such as some investigations with a much larger number of blood samples. Instead, EFSA (2011a) stated very vaguely:

"The EFSA GMO Panel requested the applicant to comment on the observed differences (…) between the (…) MON 87701 and the control, in particular, when more spots can be seen with MON 87701 (…) and to identify (…) the spots corresponding to the known major soybean allergens. The applicant gave general comments that did not raise concern."

EFSA should have at least requested further testing for the stacked Soy. This should have been done not least for the following reasons:

- uncertainties remain from risk assessment of the parental plants
- the content of Cry1Ac is much higher in the stacked Soy
- combinatorial effects in the stacked Soy can also cause unpredictable reactions of the immune system.

26 which will not be discussed in detail in this complaint about the stacked Soy

These points are also supported by statements from the experts of Member States in relation to the authorisation of the stacked event, for example (EFSA 2012b):

> “The notifier does not regard an assessment of the allergenicity of the whole GM soybean MON87701 x MON89788 necessary, because "there are no reasons to believe that the allergenicity potential will be different in MON87701 x MON89788 since no changes in endogenous allergenicity of MON87701 x MON89788 are expected during the traditional breeding process that has been widely adopted and used in the development of new varieties across all crops in agricultural production systems". This argumentation misses the fact that an increased potential for allergenicity to humans and animals caused by additive, synergistic or antagonistic effects of the gene products or by these produced metabolites cannot be ruled out a priori (EFSA 2007).”

Internal documents from EFSA brought to the notice of Testbiotech fuel the substantial doubts on the quality of the risk assessment as conducted. As the minutes of a meeting of the working group (WG) “Self Task on Allergenicity” from 24 September 2007 shows, EFSA itself has serious doubts about the reliability of investigations with sera from patients with known allergic reaction to soybeans as performed in this case. According to the minutes (attached),

> “More sera from patients are needed but they also need to be well-characterised. Statistical calculations have been done showing that 60-70 well-characterised sera are needed based on variability. Since this might not be feasible, the WG has to consider the reliability of studies with a lower number of sera.”

However, in the case of MON87701, only 13 sera from patients were used, and similarly, in the case of MON89788 only 16 sera from patients were used for the investigations. These investigations were carried out with far too few sera, but nevertheless, constituted one of the crucial findings to conclude the safety of the parental plants as well as the stacked Soy.

Further, these investigations should also have been rejected because none of the studies fulfil the standards of Good Laboratory Practise (GLP). This is explicitly stated by Finessey et al., 2009, McLain et al., 2009, Rice et al., 2006 as well as by Geng et al. 2008. In addition, Rice et al. (2008) do not make any statement on GLP. Investigations

such as those of Finnessey et al (2009) and McLain et al (2009) have also never been published in any peer-reviewed magazine.

C2 Missing investigations on the impact on infants

As the cited internal document (minutes from meeting on 24 September 2007) from EFSA shows, the authority is also aware that specific investigations are needed to exclude risks for children:

> "Infants are more susceptible towards allergenic reactions as their gastro-intestinal tract differs from adults. A specific assessment for children might therefore be recommended. It needs however to be discussed how this specific pre-market assessment needs to be performed. It might for instance be recommended that more research is needed on young animal models."

Similarly, the need for more detailed investigations is expressed in EFSA (2010) at section 1.10.1:

> "The specific risk of potential allergenicity of GM products in infants as well as individuals with impaired digestive functions (e.g. elderlies, or individuals on antacid medications) should be considered, taking into account the different digestive physiology and sensitivity towards allergens in this subpopulation." (page 46)

However, these specific risks for infants were left aside during EFSA risk assessment, also disregarding relevant publications that indeed show specific immune reactions in infant mice to Bt plants (Finamore et al., 2008).

C3 False assumption on the digestibility of Cry proteins

Besides the test with sera from patients, potential allergenicity in parental plants was assessed by applying a pepsin digestion assay. As a result, the Cry protein is thought to be degraded quickly in the gastrointestinal tract. However, Chowdhury et al., (2003) as well as Walsh et al. (2011) have found that Cry1A proteins can frequently and successfully be found in the colon of pigs. Thus, the Cry1A proteins can show much higher stability in monogastric species than predicted by current in vitro digestion experiments. These findings should have triggered much more detailed risk

assessment by EFSA already on the level of the parental plants[27]. This issue is even more relevant for the stacked Soy that contains a higher content of the Cry protein. If, for example, the stacked Soy is mixed with other components in food and feed, the Cry1Ac could trigger immune reactions to compounds other than the Soy after ingestion.

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C4 Missing assessment of further immunological effects

Examples showing that Cry toxins can trigger the immune system include fish (Sagstad et al., 2007), pigs (Walsh et al., 2011), mice (Finamore et al., 2008), and rats (Kroghsbo et al., 2008, Gallagher 2010). Despite these findings, EFSA did not request immunological studies to assess this health risks in detail.

Some conclusions on Ground 4

The assessment of risks for the immune system as performed by EFSA does not give sufficient weight to the precautionary principle. It does not obey the necessary scientific standards and is even insufficient according to internal documents from meetings of EFSA´s own experts. For example specific risk assessment for allergenic risk to infants was left aside completely.

In conclusion, the Commission has failed to perform its duties and obligations under the GM Regulation and/or the general principles of EU law as set out above in relation to Ground B.

Ground D: Failure to request monitoring of health effects

In its decision to give market authorisation to the Soy, the Commission decided also upon the monitoring plan for food consumption (Annex at (i):

> "Post-market monitoring requirements for the use of the food for human consumption: Not required."

However, as a recent legal dossier compiled by Professor Ludwig Kraemer and commissioned by Testbiotech shows, the decision not to monitor any health effects

27 which will not be discussed in detail in this complaint about the stacked Soy

violates the requirements of EU regulations. As concluded in the dossier (attached), by taking into account Directive 2001/18 as well as Regulation 1829/2003:

I. The present practice does not monitor the potential adverse effects on human health of genetically modified plants at the use and consumption stage and therefore does not comply with existing EU legislation.

II. Directive 2001/18 and Regulation 1829/2003 require both that potential adverse effects on human health of genetically modified plants are controlled during the use and consumption stage, including in those cases where such effects are unlikely to occur.

III. The objective of both Directive 2001/18 and Regulation 1829/2003 is to avoid any adverse effect on human health from genetically modified plants. Therefore, the risk assessment must make sure, in both cases, that the cumulative effect of herbicide residues on genetically modified plants during the use and consumption stage is controlled.

IV. Wherever the monitoring plan for a genetically modified plants does not include the control of the cumulative effect of herbicide residues and genetically modified plants on human health during the use and consumption stage, the authorisation should be amended in order to provide for such a control.

Thus the decision of the EU Commission must be withdrawn or supplemented by a monitoring plan that is organised in a way that allows the discovery of all potential adverse effects of the plant on human or animal health. It also has to include the examination of effects that are unlikely to occur and unforeseen effects. Such effects might occur by the consumption of the genetically modified plants alone or in combination with residues of herbicides, or other residues found in the genetically modified plants themselves or which exist in other food or feed. Therefore, the effects from residues of the complementary herbicides must also be included.

So far, systematic data are not available on the impact on human and animal health of any of the genetically engineered plants that are authorised for commercialisation within the EU. Consequently, we have the same situation within the EU that the Commission described in a dossier compiled for the WTO in 2005 (European Communities, 2005):

> “As regards food safety, even if some GM products have been found to be safe and approved on a large scale..., the lack of general surveillance and consequently of any exposure data and assessment, means that there is no

> data whatsoever available on the consumption of these products – who has eaten what and when. Consequently, one can accept with a high degree of confidence that there is no acute toxicological risk posed by the relevant products, as this would probably not have gone undetected – even if one cannot rule out completely acute anaphylactic exceptional episodes. However, in the absence of exposure data in respect of chronic conditions that are common, such as allergy and cancer, there simply is no way of ascertaining whether the introduction of GM products has had any other effect on human health."

There is no doubt that the situation as described by the Commission (European Communities, 2005) is in contradiction with the requirements of current EU regulations.

Conclusion

Since the failures and deficiencies in risk analysis of EFSA and the EU Commission have to be regarded as severe, we request the withdrawal of the decision of the EU Commission.

Art 10 of EU Regulation 1367/2006 allows NGOs active in the field of environmental protection to request re-examination of decisions of the EU Commission.

Based on this regulation we request the re-examination of the risk analysis by EFSA and the EU Commission and until this re-examination has been completed, market authorisation for soybean MON87701 x MON89788 must be withdrawn.

The requested measure is necessary to reinstall the high level of protection for consumers and the environment as required by current EU regulations, and to prevent the erosion of EU standards safeguarding the implementation of the precautionary principle.

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Attachments:

- Legal dossier prepared by Professor Dr. Ludwig Kraemer
- Minutes of the meeting of the EFSA working group (WG) “Self Task on Allergenicity” from 24 September 2007