

## EFSA's risk assessment on GMOs Case studies and lessons learnt

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The newly established European Food Safety Authority (EFSA) plays a central role in the European Union (EU) authorisation process for GMOs, as it is asked by the Commission to provide a scientific opinion whenever national scientific bodies raise concerns over the safety of a GM product. However, the EFSA GMO panel has failed to conduct a rigorous assessment of the data provided by companies and, in most cases, has even ignored some of the EU legal requirements on risk evaluation of GMOs. In particular, the EFSA has given scant regard to its legal obligations to consider long-term effects of GMOs on health and the environment<sup>1</sup>, to address differences in scientific opinions between member states and its own GMO panel<sup>2</sup>, and to clearly identify areas of scientific uncertainties<sup>3</sup>.

In the EU the scientific advice is clearly separated from the political decision, and the precautionary principle underpins decisions about health and the environment. However flawed scientific opinions do not enable politicians and policy-makers to take informed decisions, and the precautionary principle cannot be applied when scientific uncertainties or assumptions are not even identified. After repeated criticisms by NGOs and independent scientists about GMO authorisations and strong complaints from national Environment ministers, the Commission announced on 12 April 2006 an initiative aimed at improving the risk assessment of GMOs in the EU<sup>4</sup>. The Commission still has to present the detailed measures that it intends to propose.

This paper summarizes the flaws and shortcomings of three recently published opinions of the EFSA on some GMO applications (GM maize MON863 for food and feed uses, GM maize varieties Bt 11 and 1507 for cultivation, food and feed uses) and proposes some concrete measures to improve the work of the EFSA and the procedure for the risk assessment of GMO applications. It concludes that, in order to ensure a strict implementation of the EU legislation on GMOs and a practical implementation of the precautionary principle, a new comprehensive regime for the assessment of GMOs should be developed. This set of procedures should be mandatory, especially for EFSA. It should detail the quality and amount of data to be presented by the applicant company, as well as the way how these data are assessed, and include detailed mandatory procedures for immunological testings, toxicity and antinutrition tests. As an overall conclusion it is made clear that the ongoing opinion making process by the EFSA should be suspended until some significant changes are put into practice.

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<sup>1</sup> See article 14.4 of Regulation 178/2002, or Annex II of Directive 2001/18/EC

<sup>2</sup> Article 30.4 of Regulation 178/2002 states that: "*Where a substantive divergence over scientific issues has been identified and the body in question is a Member State body, the Authority and the national body shall be obliged to cooperate with a view to either resolving the divergence or preparing a joint document clarifying the contentious scientific issues and identifying the relevant uncertainties in the data. This document shall be made public.*"

<sup>3</sup> See Commission Decision 2002/623/EC, Guidance notes supplementing Annex II to Directive 2001/18/EC

<sup>4</sup> "Commission proposes practical improvements to the way the European GMO legislative framework is implemented", Brussels, 12 April 2006, IP/06/498

## Part 1: Case study on MON863

### 1.1. Background information on the case of genetically modified maize MON863

MON863 is a genetically modified (GM) corn which expresses a Bt-toxin (Cry3Bb1). This toxin, which stems from a micro-organism (*Bacillus thuringiensis*), is meant to protect the maize against a pest called corn rootworm. This GM maize is different from those Bt-plants (Mon 810, Bt11, Bt 176) already placed on the market, as they produce a different toxin (Cry1Ab), which is toxic to the European corn borer. In contrast, Cry3Bb1 produced by MON863 is toxic to another pest insect, the corn rootworm. The application was filed in the EU by US company Monsanto.

The first public authority which examined the data submitted by Monsanto was the German Robert Koch Institut<sup>5</sup>, which did not mention any problems with the health risk assessment in animal feeding studies. The EFSA filed its positive opinion on 3 April 2004<sup>6</sup>. The EFSA mentioned some significant findings in animal feeding studies, but did not consider them as "biologically relevant". This term of "biological relevance" is not a scientific concept, it does not have a clear definition and it is therefore a highly subjective criteria, as even some EFSA GMO panel members admit<sup>7</sup>. Moreover, this assumption might have been influenced by the fact that the German experts which were the first to examine the application are also member of the EFSA GMO panel.

But soon heated discussions started up in several member states, especially in France<sup>8</sup>, about the significant findings in blood and other parameters during the animal feeding studies with rats provided by Monsanto, and about their relevance for the risk assessment. On 23 April 2004, the French newspaper Le Monde revealed that the French expert body in charge of GMO evaluation (CGB, Commission du Génie Biomoléculaire) had expressed doubts about the safety of GM maize MON863.

On 22 June 2005, after one year of legal battle, Greenpeace got access to the original and complete data provided by the company, via a court case in Germany. The data were forwarded to several independent experts for them to evaluate. The complete analysis of the data and of the statistical analyses performed by Monsanto are still ongoing but in October 2005 independent experts, who have conducted a preliminary analysis of the statistical design of the animal feeding studies, sent their statements to Greenpeace<sup>9</sup>.

Since the full papers were sent by Greenpeace to several EU bodies, only some short quotations are presented in this briefing. These quotes clearly indicate that the experts came to the conclusion that the statistical analysis done by Monsanto was not performed in a way that fulfills the requirements a rigorous risk assessment:

<sup>5</sup> *Assessment Report of the Robert Koch Institut in Accordance with Directive 2001/18/EC, Insect-Resistant Maize MON863 and MON863xMON810*, 8 April 2003.

<sup>6</sup> [http://www.efsa.eu.int/science/gmo/gmo\\_opinions/381/opinion\\_gmo\\_06\\_en1.pdf](http://www.efsa.eu.int/science/gmo/gmo_opinions/381/opinion_gmo_06_en1.pdf)

[http://www.efsa.eu.int/science/gmo/gmo\\_opinions/383/opinion\\_gmo\\_07\\_en1.pdf](http://www.efsa.eu.int/science/gmo/gmo_opinions/383/opinion_gmo_07_en1.pdf)

<sup>7</sup> Le Monde, 23 April 2004, "*L'évaluation scientifique des risques est opaque, les dossiers parfois incomplets, les délais très brefs*"; Le Monde, 9 February 2006, "*Nouveaux soupçons sur les OGM*".

<sup>8</sup> Le Monde, 23 April 2004, "*L'expertise confidentielle sur un inquiétant maïs transgénique*"

<sup>9</sup> PRELIMINARY REPORT BY CRIIGEN ON THE "FIRST PUBLIC INVESTIGATION OF THE CRUDE DATA IN MON 863 TOXICITY TEST ON RATS", G.E. Seralini and D. Cellier  
<http://eu.greenpeace.org/downloads/gmo/MON863Seralini1.pdf>

*"The following findings clearly indicate major failures of statistical analyses as performed by Monsanto:*

- introduction of irrelevant variability sources as use of additional animal groups likely to dilute biological effects,*
- methodological errors such as wrong test system in general which is not suitable to detect very important effects,*
- statistical techniques not performed properly; such as the Student test with too small animal groups (...)." (G.E. Seralini and D. Cellier)<sup>10</sup>*

## **1.2 Some first conclusions on case MON863**

It seems that the EFSA did not check sufficiently the statistical design of the data provided by the company Monsanto. At least no reference is made to such an evaluation in its opinions. Since the statistical design of the study does not give a full picture of the effects which were caused by the GM maize during the feeding studies, there is no scientific basis for assessing the real risk for human and animal health in this case.

This is a major obstacle for the marketing of this product in food and feed. Despite the design flaws, there is no doubt that significant effects were observed during the feeding studies, such as an increased number of white blood cells in the males, reduced immature red blood cells in females, a significant increase in blood sugar in the females or a higher frequency of physical irregularities in the kidneys of the males, such as reduced weight and inflammation. Such effects can indicate indeed a severe impact on health of the test animals. The statement of the independent experts make it clear that these findings were rejected by the EFSA without sufficient scientific reasoning.

Coming from this background, the risk assessment of GM maize MON863 has to be restarted. A full reevaluation of the data is necessary and further new investigations might also be necessary.

## **1.3 Some general lessons learnt from the MON863 case**

In its risk assessment, the EFSA GMO panel follows the criteria outlined in the "Guidance Document of the scientific panel on genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed"<sup>11</sup>. Concerning the quality of the data there is a general standard given in these GMO guidelines, which has to be fulfilled by the applicant :

GMO guidelines, Annex 1, Part 1:

*"Data provided in support of an application should be of at least the quality expected of data submitted to a peer review journal. Particular attention should be paid to the sensitivity and specificity of methods employed and to the adequacy and appropriateness of controls."*

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<sup>10</sup> *idem*

<sup>11</sup> European Food Safety Authority, March 2005.

Apparently these standards were disregarded in the actual case.

Looking further to the requirements of the GMO guidance document, it is evident that there are no detailed standards for statistical analyses of data. Furthermore there is even no obligation for the applicant to conduct any feeding study with animals, like it was performed by Monsanto on rats in this specific case.

So the whole application might have passed without discussion if Monsanto had not filed its 90 days feeding study. On the other hand, at this point one can only speculate what might have been the outcome if further tests on other animals, or for a longer period of time, would be conducted with the GM product under discussion.

So as a first conclusion, the guidelines do not provide for sufficient mandatory testings. Even listed standards (such as a quality control of the paper) were disregarded in the case of MON863.

Coming from this perspective, there are some basic general criteria which should be seen as absolute necessary preconditions and laid down in mandatory written procedures to be followed by the EFSA before any more scientific opinions on GMO can be issued by the Authority. Some of these demands are also backed by the recently published scientific paper highlighting health risks of genetically modified peas<sup>12</sup> :

- The material produced by the applicant has to undergo a comprehensive quality review before use in any EFSA opinions or national scientific bodies assessment report;
- The Precautionary Principle has to be applied in a way that significant findings in health tests makes further investigations mandatory, and no positive opinion can be forwarded by the EFSA or national scientific bodies assessment report;
- Immunological testings as well as toxicity and antinutrition tests have to undergo a rigorous, comprehensive and mandatory testing regime (for example some scientists argue that testing regimes for toxicity should at least follow EU pesticide regulations). In addition there is a need for a broad ethical debate on the use of laboratory animals in this context. In all cases where sufficiently significant benefits derived from the GM crop can not be identified, animal testings and market authorisations should be stopped.
- Already published opinions on GM products such as NK603<sup>13</sup>, GT73<sup>14</sup> and MON863, which gave rise to significant findings in animal feeding studies, have to be withdrawn and these products should be submitted to a complete reassessment procedure.

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<sup>12</sup> Prescott, V.E., Campbell, P.M., Moore, A., Mattes, J., Rothenberg, M.E., Foster, P.S., Higgins, T.J.V. & Hogan, S.P. 2005. Transgenic expression of bean alpha-amylase inhibitor in peas results in altered structure and immunogenicity. *Journal of Agricultural And Food Chemistry* 53: 9023 - 9030 (published November 16, 2005).

<sup>13</sup> <http://www.eu.greenpeace.org/downloads/gmo/GPTechCritOnNK603.pdf>

<sup>14</sup> <http://eu.greenpeace.org/downloads/gmo/GT73Oct2004.pdf>

## Part 2: GM maize Bt 11 and 1507 for cultivation in the EU

### 2.1 Some findings from Syngenta's data and EFSA's opinion on GM maize Bt 11

On 20 May 2005 the European Food Safety Authority delivered a positive opinion on Syngenta's application for insect-resistant genetically modified maize Bt11<sup>15</sup>.

The Swiss company Syngenta applied for the approval to cultivate Bt11 maize in the European Union in 1996. Bt11 produces the Bt toxin Cry1Ab against Lepidoptera (moths and butterflies) to protect maize against the two insect pests European stem borer (ECB, *Ostrinia nubilalis*) and Mediterranean stem borer (MCB, *Sesamia nonagrioides*). In addition, Bt11 is herbicide-tolerant against glufosinate-ammonium (BASTA, Liberty). The notifier claims that Bt11 will not be marketed for its herbicide tolerance, but in other countries, such as the USA and Canada, Bt11 is marketed for both GM traits.

Greenpeace published a detailed report on the opinion of EFSA<sup>16</sup>, from which some elements are here presented in short. The general finding is that the data presented by Syngenta are of poor quality and of even lower standards compared to the material of other companies. Some other failures are also identified :

- **Genomic data:**

Information about the insertion site and the insert are classified as confidential business information. Independent assessments are therefore impossible.

- **Health:**

Syngenta provided the results of only short term feeding studies, which were not intended as toxicity or immunological studies.

EFSA is of the opinion that no long term studies should be performed because no drastic effects were seen in short term experiments.

- **Ecological risk assessment (ERA):**

Adverse effects of Bt11 on non-target organisms such as interactions between plants, herbivores and pests at different ecological levels (i.e. multitrophic) were not investigated in the ERA and are not included in the monitoring or general surveillance plan.

Effects on soil organisms, for example potential *Bt* accumulation, were disregarded in the ERA and are not included in monitoring or general surveillance plan.

- **Monitoring:**

no case-specific monitoring is requested by EFSA for:

- the exudation of *Bt* toxins into the soil
- the accumulation and persistence of *Bt* toxins in the soil
- the possible effects on non-target soil organisms
- the possible effects on non target insect species and the relevant food web.

<sup>15</sup> [http://www.efsa.eu.int/science/gmo/gmo\\_opinions/922\\_en.html](http://www.efsa.eu.int/science/gmo/gmo_opinions/922_en.html)

<sup>16</sup> Bt11 C/F/96.05.10 Notification for cultivation, Greenpeace, September 2005. Available on : <http://eu.greenpeace.org/downloads/gmo/ReportOnBt11GMmaize.pdf>

## 2.2 Pioneer's data and EFSA's opinion on maize 1507

Pioneer's 1507 maize is a GM maize containing two types of inserted genetic constructs. One insert produces a modified form of the *Bacillus thuringiensis* (Bt) Cry1F protein, which is toxic to lepidoptera (butterflies and moths), in order to make the GM maize resistant to larvae of the European corn borer (*Ostrinia nubilalis*) and of the Mediterranean corn borer (*Sesamia nonagrioides*). The second GM trait is tolerance to the herbicide, glufosinate ammonium, sold under brand names including Basta or Liberty.

Cry1F is a different Bt toxin than that produced by many GM insect resistant maize, such as Bt176, Bt11 and MON810, which produce Cry1Ab. There are very few peer-reviewed studies on the environmental risks and human and animal health risks of Cry1F. Therefore, the evaluation of GM maize 1507 requires considerable care. EFSA gave a positive opinion of GM maize in January 2005<sup>17</sup>. This is the first time that EFSA has assessed a GM crop, not only for the import and processing, but also for cultivation. EFSA's assessment is woefully inadequate and there remain many scientific uncertainties and unknowns regarding the safety of GM maize 1507 for the environment, human and animal health. Greenpeace published a report on the opinion of EFSA<sup>18</sup>, from which some elements are here presented in short:

- **Genomic data:**

Several unintended additional fragments were observed. These unintended fragments result in two open reading frames, a faint signal is indicating the presence of unintended RNA, but this was not investigated further.

- **Compositional data:**

Many statistically significant differences are seen in the compositional analysis of GM maize 1507. Despite this, the EFSA states that there is "*No indication that such a [DNA] deletion produces any phenotypic effect in the transformed maize line.*"

- **Health:**

Several significant differences with feeding studies were observed, but dismissed without sound scientific arguments (e.g. on the ground that the effects were observed only within one sex).

- **Ecological risk assessment (ERA):**

The toxicity of 1507 to non-target lepidoptera is, in general, unknown. There have been no studies of the toxicity of this GM Bt maize to European lepidoptera. No relevant long term studies, either of exudation by the roots, on persistence, on accumulation nor the toxicity of Cry1F have been undertaken.

- **Monitoring:**

no case-specific monitoring is requested by EFSA for:

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<sup>17</sup> [http://www.efsa.eu.int/science/gmo/gmo\\_opinions/827\\_en.html](http://www.efsa.eu.int/science/gmo/gmo_opinions/827_en.html)

<sup>18</sup> "EFSA fails again: insect resistant GM Bt maize 1507 (C/ES/01/01) should not be grown in Europe", Greenpeace, December 2005. Available on : <http://eu.greenpeace.org/downloads/gmo/BackgroundBriefingPioneer1507Dec05.pdf>

- the exudation of *Bt* toxins into the soil
- the accumulation and persistence of *Bt* toxins in the soil
- the possible effects on non-target soil organisms
- EFSA justifies even the exclusion of lepidoptera from the case-specific monitoring because they consider it too expensive.

## 2.3 Some lessons learned from cases Bt11 and maize 1507

EFSA's opinions lack scientific rigour, being based more on general assumptions than on scientific facts. Published scientific evidence has not been assessed adequately. Areas of scientific uncertainties are not even identified, even though this is a clear legal requirement<sup>19</sup>. For example, the fate of the Bt toxin from GM Bt plants such as Bt11 and 1507 and its lifecycle in the farming environment or its ecological surroundings has to be taken into account in terms of the multi-trophic and multi-layer effects on the ecological food web.

The failures in the risk assessment performed by the EFSA GMO panel do not occur occasionally, and at least stem partially from the GMO guidelines, which are clearly not in accordance with the complexity of the food web and make no mention of multitrophic effects:

***"If first tier tests do not identify sensitivity in exposed species then second and third tier test may not be required"***<sup>20</sup>.

As for example the work of Andow and Hilbeck shows, effects can be observed further up in the food chain, without being noticed at the first level<sup>21</sup>.

Coming from these observations, it is obvious that the work of EFSA GMO panel has to be reorganised, and its published opinions have to be reassessed in several aspects.

## 3. Some general conclusions and most urgent demands:

In a meeting with members of EFSA GMO panel on 22 of February 2006, some of the findings listed above were mentioned by Greenpeace. Other NGOs which were taking part in the meeting raised similar concerns regarding the risk assessment, monitoring, access to data, transparency and the independence of EFSA<sup>22</sup>. There was a general concern raised during the meeting that the work of EFSA GMO panel was biased, and that the general reputation of EFSA will be affected if the standards and procedures of risk assessment of GMOs are not changed significantly.

<sup>19</sup> Commission Decision 2002/623

<sup>20</sup> "Guidance Document of the scientific panel on genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed", March 2005, European Food Safety Authority, page 38.

<sup>21</sup> Andow, D.A. and A. Hilbeck. 2004; *Science-based risk assessment for non-target effects of transgenic crops*, Bioscience 54: 637-649

<sup>22</sup> "EFSA: Throwing caution to the wind", Friends of the Earth Europe, November 2004 ; <http://www.foeurope.org/GMOs/publications/EFSAreport.pdf>

In its answers during the meeting, the EFSA took the view that published opinions were still valid, and saw no need to re-examine any of its reports. It was acknowledged that standards such as of statistical evaluation and tests for allergenicity should be discussed and might be improved. It was accepted that the declarations of interests by the panel members so far are not fulfilling the required standards, but no need was seen by the EFSA for direct action. A new guideline for post marketing monitoring was presented, which is "*largely based on routine observation*<sup>23</sup>" and therefore is not likely to fill the gaps which appear in the EFSA opinions on 1507 and Bt11 for cultivation.

In conclusion Greenpeace considers that the concerns raised about the current practice for the risk assessment were not taken into account by the EFSA, which also dismissed the need to take action to resolve the already identified failures in published opinions.

Greenpeace urges the responsible political authorities of the EU, the Commission, member states and the European Parliament, to make sure that some most urgent steps are taken immediately and to ensure that the work of EFSA GMO panel is frozen until significant changes are implemented:

- **A new comprehensive, coherent and mandatory regime is necessary for the assessment of GMOs.** This regime should address the quality and amount of data to be presented by the applicant company, as well as the way how these data are assessed. The material produced by the company has to undergo a much more comprehensive quality check before being used in EFSA opinions.
- A rigorous, comprehensive and **mandatory testing regime** should also be set up for immunological testings as well as toxicity and antinutrition tests (for example testing regimes for the toxicity of pesticides are precisely defined in law). In addition, there is a need for a broad ethical debate on the use of laboratory animals in this context. No animal experiments should be conducted when sufficiently significant benefits derived from the GM crop cannot be identified. Greenpeace believes that every effort must be made to avoid the use of and reduce future reliance on animal testing.
- The opinions presented by the GMO panel of EFSA have to reflect **all unanswered questions, uncertainties and assumptions** without prejudice. This is essential in order to allow for a correct implementation of the precautionary principle.
- Direct, indirect, cumulative and **long-term effects** of GMOs on the environment have to be properly investigated, taking into account various stress conditions and different regional environments. All levels of the food web should be investigated.
- The **precautionary principle** has to be applied in a way that uncertainties regarding safety are seen as a basis for measures to be taken to prevent environmental degradation and protect human health, i.e. **rejection of the application**. At the very least, uncertainties should trigger an **obligation for further** investigations to be conducted, and the EFSA should not be able to file a positive opinion.
- **Monitoring and general surveillance** have to take into account all levels of complexity, interactions and potential effects regarding human health and environment. They have to be based on active scientific investigations, not merely on questionnaires

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<sup>23</sup> "Opinion of the EFSA GMO Panel on the Post Market Environmental Monitoring (PMEM) of GM plants", EFSA, opinion adopted on 25 January 2006.

for farmers.

- **Full and free access to data** has to be provided.
- In those cases where a declaration of interest or activities of a member of the GMO panel indicates a **conflict of interest**, this expert should be excluded from the GMO panel. Experts who are involved in the risk assessment at the national level should not be members of the EFSA GMO panel.
- **No further opinion on GM products should be delivered by the EFSA** as long the procedures for the risk assessment of GMOs are not reorganised and completed in order to resolve the failures pointed out by these case studies, and to ensure that the current EU legal framework is strictly and properly implemented.