

The Austrian experiment with mice fed with a hybrid GM maize from Monsanto

Klaus Ammann, AF-5 20100407 open source

klaus.ammann@ips.unibe.ch

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The Issue:

The Austrian study published by the Austrian Ministry of Health in a preliminary report (Velimirov et al., 2008) is summarized by the main scientific author Prof. Dr. Jürgen Zentek as follows:

“Mice fed with GM maize had less offspring in the third and fourth generations, and these differences were statistically significant. Mice fed with non-GM maize reproduced more efficiently”.

The study makes several unconfirmed claims and has not been published in a peer reviewed journal. Prof. Jürgen Zentek himself declares his study as a preliminary draft which needs to be scrutinized and does only partially delivers conclusive results (personal communication 2008).

1. Summary:

The Austrian study which has been prematurely published as a report by the Austrian government does not stand to the review of peer experts. The principal scientist Prof. J. Zentek himself declares the study as a preliminary draft with partially inconclusive results, which needs to be corrected in some points. He is not happy with the present situation and the premature press conference of the Austrian ministry, and particularly he is refuting the conclusions drawn by [Greenpeace](#), requesting the immediate retraction of GM maize in Europe, since there is a real risk that consumers of this maize could become sterile.

Andrew Apel, webmaster and author of www.gmobelus.org, a new and excellent website, provides a lot of information, summarizing the case in several features and giving ample background [information](#) and lots of links. The study has been refuted by Monsanto in several statements, recently also by [EFSA](#) (European Food Safety Authority), see also chapter 7 below.

A German text can be found under the newspoints, written by Jan Lucht, on the [Internutrition website](#).

2. Background:

It is well known that the Austrian Government maintains for years a critical position regarding GM crops, this latest press conference in Vienna is not astonishing in the light of the transatlantic rift over risk perception and regulation of GM crops. Despite of hundreds of peer reviewed publications on risk assessment GM crops still have a bad reputation in Europe, and any kind of publication with seemingly negative results regarding environmental or food safety gets press attention way out of proportion, and activists with a negative agenda build up a culture of concern built on flawed data.

[See link for more pages](#) on the launch of questionable publications, the transatlantic rift, European regulatory politics etc. [▶](#)

It has become sad routine that advocacy groups like [Greenpeace](#) publicize reports which have [not undergone peer review](#) using their typical inflammatory language:

“An explosive study published by the Austrian government, on Tuesday November 11, identified serious health threats of genetically engineered (GE) crops. Mice fed with GE maize were severely impaired in their fertility, and produced fewer children than mice fed with natural crops. This study shows how little we know about GM products and their long-term impacts on our health and the environment. It also shows how flawed the current EU risk assessment system is.”

It is also alarming to see, that the number of papers published in scientific journals grow steadily, reporting seemingly negative results about GM crops. A closer scrutiny reveals flaws and questionable conclusions. There are also a few reviewed papers which stress negative potentialities related to impact on environment and health of GM crops (Miller et al., 2008). However, those cases published in a peer reviewed journal are nevertheless highly controversial.

Information about the authors of the Austrian study, more details about the regulatory background and a series of recently published papers critical about GM crops can be seen [here](#) including a brief discussion.

A closer look at this preliminary, not yet peer reviewed Austrian report reveals serious mistakes in data analysis and methodology, putting into question all the negative conclusions drawn by Greenpeace.

4. Data analysis

4.1. Data comparison GM- and non-GM feed

A comparison between the data for GM and non-GM feed does not show any effects on the mice used in the experiment.

However, there are considerable differences between the two non-GM lines used for the experiment: Several data sets (body mass in various generations) differed significantly, and the conclusion is simple: Non-GM maize seems to be an unhealthy feed for the mice in the experiment. Unfortunately, in some cases the two non-GM line data are lumped, a lost opportunity to study natural variation.

4.2. Confusion in terminology of pups

Table data comparison is hampered due to an inconsistent denomination of litter: Table 59: Despite the fact that the same terminology (pups per 'pair') was used as in Tables 36 and 40, most of the values in this table were appropriately expressed as numbers of pups per litter rather than per co-housed pair. Unfortunately, there appeared to be three major exceptions, all in the GM groups: pups at weaning for the 3rd litter, pups at birth for the 4th litter, and pups at weaning for the 4th litter. Resulting calculation errors and erroneous conclusions as a consequence under 3.2.

4.3. Organ weights: few conclusive results

The same picture for the organ weights: High variation, inconclusive results for the comparison between GM- and non-GM maize, but again the two non-GM maize lines demonstrated considerable differences, although this could not be corroborated by the microscopical comparison, which are in their methodology questioned by the [Monsanto-analysis](#) p. 6 paragraph 2.

4.4. Inconclusive immunochemistry results

The immunochemistry was inconclusive by the statements of the authors themselves: The differences were inconsistent between the two sexes and were not found in all segments, and specific immune populations did not show feed effects or there was too much individual variability or there were no statistically significant differences seen between the groups.

5. Methodological flaws

5.1. Unusual high mortality of mice populations used

Data analysis shows that the experiment suffers under an unusual high mortality of the mice used: Instead of the 1% mortality you can see a mortality of 8%. And, if you look closely in the tables, you can discover that the GM mice survived better than the non-GM mice. This means in fact, that the GM mice used in the Austrian experiment died 8 times more often than mice used for correct experimentation schemes. More details, explanation and graph [here](#) in the GMO Pundit of David Tribe:

There is no explanation given about the fact, that there were five instances of total litter loss after birth in the 3rd litter and one instance in the 4th litter. The reason for the total litter loss was not discussed, but it would probably be most appropriate to use the total number of surviving litters as the denominator when expressing number of pups at weaning, not the numbers of litters at birth. This is – among other reasons, important for the explanation of the lowering of fertility in the whole experiment.

5.2. Calculation errors

There are some calculation errors in the tables of the report (Velimirov et al., 2008), this has been found out and recalculated by Dr. James Lamb, who [reviewed](#) the study as an experienced independent scientist from a consulting company on request of Monsanto, the major statements:

*“The statistics cannot be tested appropriately without the individual animal data. The computational errors in such critical tables (Tables 36 and 59) raise serious questions about the other data in the report and the quality assurance methods that were or should have been applied before the conclusions were drafted and the report was released. When properly analyzed, **these data do not appear to support an effect on fertility or reproduction from consumption of GM corn.**”*

Details about the calculation and the two tables separately reproduced [here](#).

Dr. Lamb is, together with his colleagues Morrissey, Chapin and Gulati, a leading and independent expert on mice studies in toxicology, he co-authored important methodological papers on long-term mice experiments, which have contributed in an important way to the standard procedure later (Morrissey et al., 1989).

5.3. Study authors not specialized in experimentation with mice

Prof. Jürgen Zentek is according to his [bibliography](#) extracted from the Web of Knowledge a specialist on live stock feeding, with a prolific publication activity in excellent peer reviewed journals on animal feed science. The first author [A. Velimirov](#) is a specialist on organic food with three reviewed publications available on the Web of Knowledge (Mader et al., 2007; Velimirov et al., 1992) (Velimirov, 2005). She is also the author of an often by opponents cited paper on feed preference of rats (Velimirov, 2004) Some more, not peer reviewed papers can be seen under the [following link](#), a full bibliography of mainly non-peer reviewed publications reaching until 2006 can be seen [here](#). She also tried to demonstrate, that

organic food is better than conventional food in a conference paper, but the experiments are likewise not convincing, e.g. the origin and composition of feed in all its complexity is not clear. She is also the author of an often by opponents cited paper on feed preference of rats (Velimirov, 2004), claiming that rats prefer organic feed: the same analysis can apply: origin and composition of the feed is not clear, international standards of the Oecd AND EPA are not respected. Overall, it can be said with all this documentation, that Velimirov is a clear and uncompromising defender of organic farming. C. Binter has one conference paper on animal feeding (Binter et al., 2007). So it is fair to say that the authors have no extensive experience in experimenting with mice. This is why, although following with minor deviations the usual procedures of such studies with mice, their data calculation and interpretation is flawed due to lack of experience and leads to the wrong conclusions, the negative judgment is based on facts, see the [Monsanto analysis](#) p.2 second paragraph.

6. Specific long term problems in experimentation with mice

Reproductive Assessment by Continuous Breeding (RACB) have their own rules: RACB involves a set of parent mice who give birth to a series of 'litters' of baby mice. The mice in each litter from these parents are counted, measured, and evaluated in other ways. Guidelines are published by [EPA](#) (EPA Guidelines Food Toxicity, 1996) in all details in Chapter 3.1.5, p.8: (not cited in (Velimirov et al., 2008))

"Because the parental and subsequent filial generations have different exposure histories, reproductive effects seen in any particular generation are not necessarily comparable with those of another generation. Also, successive litters from the same parents cannot be considered as replicates because of factors such as continuing exposure of the parents, increased parental age, sexual experience, and parity of the females."

Also other documents point to the same 'normal' long term fertility problems. According to [Chapin](#) (Chapin & Sloane, 1997), the same text also given in a website of the [National Toxicology Program](#) of the USA stress the following facts:

With RACB, the successive generations of mice born to one set of parents, are necessarily born to parents of increasing age. As a result, a decline in the number of mice born in later generations is expected as a matter of course.

Unless offspring were allowed to grow and reproduce (as they are routinely in the more recent version of the RACB protocol) (Gulati et al., 1991), little or no information will be available on postnatal development or reproductive capability of a second generation.

Differences in the ages of the parent mice at the beginning of the experiment can have a significant impact. According to the University of North Carolina, on the very informative website '[Mouse Breeding Advice](#)' it is confirmed again that there are long term/multigeneration effects which need to be considered:

"Delayed breeding was associated with smaller litter sizes, both at birth and at weaning, a higher bodyweight of pups at weaning, a higher percentage of litters with at least one newborn pup cannibalized, earlier cessation of female reproductive life and a higher mortality rate of dams during the breeding period."

The Austrian study duly cites all advice of authorities related to Bt toxicity biosafety assessment, but seems to ignore the long term problems of multi-generation experiments with mice displayed in many websites and scientific papers, last but not least detailed also in comprehensive reviews of ILSI (Chassy et al., 2007; Chassy et al., 2004).

There is an additional problem with mice studies in general: there are considerable differences in the performance of various mouse stocks used for breeding, as is again shown by the [‘Mouse Breeding Advice’](#), the differences in breeding performance are remarkable and need to be taken into account in the study.

The summary of another study from Dr. John DeSesso, Senior Fellow at the non-profit group Noblis and editorial board of the journal Reproductive Toxicology, commissioned by Monsanto, comes to the same [conclusions](#):

“The report by Velimirov et al describes investigations into potential health effects in mice after long-term feeding of diets that contain several sources of corn. The studies have not been peer-reviewed and have not been published in the open literature. The methods and description of the electron microscopic findings are presented in insufficient detail to support the authors’ claims. The reproductive studies (multigenerational versus continuous breeding) resulted in conflicting results. The results from only the continuous breeding study had findings that appeared to indicate an effect on reproduction. However, the continuous breeding study used a non-standard study design, collected data that are not typically measured in these types of studies, and presented data in displays that are both difficult to understand and have mathematical errors. If data for individual animals were available for inspection, it may be possible to re-analyze the results and draw defensible conclusions. In the absence of such a re-analysis, the data are inconclusive, at best and provide no evidence of an adverse effect on reproductive performance in mice.”

It is interesting to note that both experts J.C. Lamb and Dr. DeSesso are not mentioning the long term problems in RACB studies, the results can be debunked by pointing to the calculation errors and other interpretation flaws.

Notable is the critique that the mice experiments have been conducted under rather poor health standards and questionable procedures have been applied related to the control of litters.

7. EFSA statement on Austrian mice study Dec. 4, 2008

Finally, EFSA also published, as part of their minutes from the 46th plenary meeting on December 4, 2008 the following [statement](#), which is given here in extenso:

Adopted part of the minutes of the 46th plenary meeting of the Scientific Panel on Genetically Modified Organisms held on 3-4 December 2008 GMO Panel deliberations on the Austrian report “Biological effects of transgenic maize NK603 x MON 810 fed in long term reproduction studies in mice” as adopted at the plenary meeting of 3-4 December 2008.

“On 11 November 2008 the Austrian Federal Ministry of Health, Family and Youth released a research report on studies in mice, which were conducted to assess the impact of genetically modified (GM) maize NK603 x MON 810 on reproduction (Biological effects of transgenic maize NK603 x MON 810 fed in long term reproduction studies in mice, Dr. Alberta Velimirov, Dr. Claudia Binter, Univ. Prof. Dr. Jürgen Zentek).

The report includes three studies, a life-time study, a multigeneration study (MGS), and a reproductive assessment by continuous breeding study (RACB). According to the authors the life-time study showed no statistically significant differences in survival between mice fed with kernels of maize NK603 x MON 810 and the controls. They also reported that, in the MGS study, no significant differences in reproductive traits were found between mice fed with kernels of maize NK603 x MON 810 and the controls. In the RACB study, the authors used a modified protocol of the original RACB study developed at the U.S. National Toxicology Program (NTP) for the testing of chemicals. Male and female mice were housed as breeding pairs for approximately 20 weeks and allowed to produce litters continuously throughout the cohabitation period. The authors identified differences in reproductive parameters between mice fed with the GM maize and the controls. They reported that there were statistically significantly fewer pups born in the GM group in the 3rd and 4th delivery and fewer pups weaned in the 4th litter compared with

the control group. The GMO Panel considered this report and came to the following conclusions. Regarding the RACB study, the summary Table 59 contains calculation errors and inconsistencies in the treatment of the data regarding the 3rd and 4th litters. In addition, it seems that the authors have calculated the number of pups at birth per pair and not per delivering pair, which is standard practice. Also, there appears to be methodological deficiencies in the statistical analysis that seriously compromise the interpretation of the data. For the reasons stated above, individual data are required for a proper assessment. In addition, more detailed information regarding the breeding scheme is needed. In particular, it should be clarified whether in the 3rd and 4th pairing the same or different pairs failed to reproduce.

Information regarding the normal variation of the parameters examined in this study for the mouse strain used (historical control data) is required before any conclusion may be drawn on possible alterations in reproductive performance. In addition, further information on the estrous cycle and histopathological parameters including spermatogenesis, follicle and oocyte counts is essential for assessing the claims of reduced fertility.

The GMO Panel also notes that information on the genetic identity and characteristics of the tested materials is not sufficient. On the basis of the data presented the GMO Panel is of the opinion that **no conclusions can be drawn** from the report.”

Published at http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902199319.htm. The complete minutes will be adopted at the 47th plenary meeting (28-29 January 2009) and will be published shortly afterwards. *EFSA/GMO/457 – part of the Minutes 46th Plenary Meeting of the GMO Panel*

8. EFSA opinion and confirmation on the MON810 maize from July 2009

Again, EFSA is repeating its positive opinion on the transgenic maize from Monsanto MON810. The summary is again given here in full extent:

Summary

This document provides a scientific opinion of the Scientific Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) on 3 applications submitted under Regulation (EC) No 1829/2003 for renewal of the authorisation of (1) existing food and food ingredients produced from genetically modified (GM) maize MON810 (Unique Identifier MON-810-6); (2) feed consisting of and/or containing maize MON810, including the use of seed for cultivation; and of (3) food and feed additives, and feed materials produced from maize MON810, developed by Monsanto to provide resistance to lepidopteran target pests.

The scopes of the 3 renewal applications cover the continued marketing of: existing food and food ingredients produced from maize MON810 (Reference EFSA-GMO-RX-MON810[8-1a]) that have been placed on the market in accordance with Article 5 of Regulation (EC) No 258/97; feed consisting of and/or containing maize MON810 that were authorised under Directive 90/220/EEC (Commission Decision 98/294/EC), including the use of seed for cultivation (Reference EFSA-GMO-RX-MON810[20-1a]); food additives produced from maize MON810 that were authorised under Directive 89/107/EEC, and feed produced from maize MON810, i.e., feed additives lawfully placed on the market under Directive 70/524/EEC and feed materials (Reference EFSA-GMO-RX-MON810[8-1b/20-1b]).

After the date of entry into force of the Regulation (EC) No 1829/2003, the products mentioned above were notified to the European Commission according to Articles 8 or 20 of this Regulation and subsequently included in the Community Register of GM food and feed.

*Maize MON810 expresses a Cry1Ab insecticidal protein, derived from *Bacillus thuringiensis* subsp. *kurstaki*, which confers protection against lepidopteran target pests such as the European corn borer (*Ostrinia nubilalis*) and species belonging to the genus *Sesamia*.*

In delivering its scientific opinion, the EFSA GMO Panel considered the 3 renewal applications (EFSA-GMO-RX-MON810[8.1.a], EFSA-GMO-RX-MON810[20.1.a] and EFSA-GMO-RX-MON810[8.1.b/20.1.b]); additional information supplied by the applicant; the scientific comments submitted by Member States; the report of the Spanish Competent Authority and its Biosafety

Commission; and relevant information published in the scientific literature.

The EFSA GMO Panel assessed maize MON810 with reference to the intended uses and appropriate principles described in the guidance document of the EFSA GMO Panel for the risk assessment of GM plants and derived food and feed. The scientific assessment included molecular characterization of the inserted DNA and expression of target proteins. A comparative analysis of agronomic traits and composition was undertaken, and the safety of the new protein and the whole food/feed were evaluated with respect to potential toxicity, allergenicity and nutritional quality. An assessment of environmental impacts and the post-market environmental monitoring plan were undertaken.

Maize MON810 was generated by particle acceleration technology. Maize MON810 expresses a cry1Ab coding sequence that encodes an insecticidally active Cry1Ab protein. The molecular characterization data established that a single insert is integrated in the maize genomic DNA. Appropriate analyses of the integration site including sequence determination of the inserted DNA and flanking regions and bioinformatic analysis have been performed. Updated bioinformatic analysis of junction regions demonstrated the absence of any potential new open reading frames coding for proteins known to be toxic for humans and other mammals and/or allergens. The expression of the genes introduced by genetic modification has been sufficiently analysed and the stability of the genetic modification has been demonstrated over several generations. The EFSA GMO Panel is of the opinion that the molecular characterization of the DNA insert and flanking regions of maize MON810 does not raise any safety concern, and that sufficient evidence for the stability of the genetic modification was provided.

Analyses carried out on materials from maize MON810, including stacked GM maize events where maize MON810 was one of the parental lines, and their comparators indicate that maize MON810 is compositionally, phenotypically and agronomically equivalent to the non-GM counterparts and conventional maize, except for the newly expressed trait.

The Cry1Ab protein shows no homology with proteins known to be toxic for humans and other mammals and/or allergens. In addition, this protein is rapidly degraded under simulated gastric conditions. Furthermore, the Cry1Ab protein has been extensively assessed in previous opinions of the EFSA GMO Panel. No concerns for humans and animals were identified regarding the safety of the Cry1Ab protein.

In a 90-day feeding study in rats, no indications of adverse effects were observed. In addition, a 42-day broiler feeding study provided evidence of nutritional equivalence of maize MON810 kernels to kernels of conventional maize. The toxicological and nutritional data on maize MON810 and appropriate non-GM maize control published during the last 10 years confirm that these maize varieties have comparable influence on the test systems. Therefore, the EFSA GMO Panel is of the opinion that maize MON810 is as safe as its non-GM counterparts and that the overall allergenicity of the whole plant is not changed through the genetic modification.

The Spanish Competent Authority and its Biosafety Commission provided to EFSA its report on the environmental risk assessment in line with Articles 6.3(e) and 18.3(e) of Regulation (EC) No 1829/2003. The Spanish Competent Authority and its Biosafety Commission conclude that “according to the current state of scientific knowledge and after examining the existing information and the data provided by the Monsanto Company, the Spanish Commission on Biosafety could give a favourable opinion to the renewal of commercialization in the EU of maize MON810 if the proposals and conditions defined in this environmental risk assessment report are implemented”.

Since maize MON810 has no altered survival, multiplication or dissemination characteristics, the EFSA GMO Panel agrees with the assessment that the likelihood of unintended environmental effects due to the establishment and spread of maize MON810 will be no different from that of conventional maize varieties.

On the basis of the data provided by the applicant and obtained from a literature survey and a modelling exercise on the effect of the cultivation of maize MON810 on non-target lepidopteran species in representative maize cultivation regions in the European Union (EU), the EFSA GMO Panel concludes that the likelihood of adverse effects on non-target organisms or on ecological functions is very low, especially if appropriate mitigation measures are adopted. In agreement with the environmental risk assessment by the applicant and the assessment conducted by the Spanish Competent Authority and its Biosafety Commission, the EFSA GMO Panel identifies the possible evolution of resistance in target species, as a potential risk linked to the cultivation of

maize MON810.

In conclusion, the EFSA GMO Panel considers that the information available for maize MON810 addresses the scientific comments raised by Member States and that maize MON810 is as safe as its conventional counterpart with respect to potential effects on human and animal health. The EFSA GMO Panel also concludes that maize MON810 is unlikely to have any adverse effect on the environment in the context of its intended uses, especially if appropriate management measures are put in place in order to mitigate possible exposure of non-target Lepidoptera. Moreover, the EFSA GMO Panel advises that pest resistance management strategies continue to be employed.

9. Answer of Greenpeace with a major factual mistake: mixing up literature citations in a fatal way

It is interesting to note, that the answer of Greenpeace does not give any factual new experimental data for their reason to contradict this EFSA confirmation (Cotter & Mueller, 2009).

But it is worthwhile to uncover a major mistake, because the report builds on this major argument, namely that EFSA has mixed up in a report of Hammond 2006, which allegedly dealt with a totally different maize trait MON863, and EFSA was erroneously applying these results to the scientific safety assessment to MON810, thus making the whole scientific assessment invalid.

This is totally wrong: Actually, there are *two reports* published in the same volume of the journal Food and Chemical Toxicology of the same year, one published 2006 in Vol. 44, 2, p. 147-160 on Yield Gard MON863, the other one actually on MON810 in the same Vol. 44, 7, p. 1092-1099. So, one wonders whether the Greenpeace authors are just doing a shoddy work (incidentally with highly biased citation selection) or whether this has been done with perfidy on purpose. If you are not documented with some precision, you would probably have a hard time to notice this grave error.

Have a look at the original text of the Greenpeace report:

EFSA makes us believe that it has assessed a 90 days feeding study for MON810 as the following citation shows (EFSA 2009, page 19, Section 5.1.3.3. Toxicological assessment of the whole GM food/feed): "The applicant provided a 90-day feeding study in Sprague-Dawley rats with grains of maize MON810 as a component of the diet. This study is available in the scientific literature (Hammond et al., 2006)"

In the reference list "Hammond et al., 2006" is cited as: Hammond, B.G., Lemen, J., Dudek, R., Ward, D., Jiang, C., Nemeth, M., Burns, J., 2006. Results of a 90-day safety assurance study with rats fed grain from corn rootworm protected corn. Food and Chemical Toxicology, 44: 147-160."

This study deals with MON863 maize and does not cover 90 days feeding test with MON810.

You could read this as a factual statement, but if you go to the EFSA report, you will find the correct citation with the MON810 maize in Vol. 44, 7, p. 1092ff.

The two papers are given here with their summaries:

Paper on MON863: (Hammond et al., 2006a)

Abstract:

"The results of a 90-day rat feeding study with YieldGard® (YieldGard Rootworm Corn is a registered trademark of Monsanto Technology, LLC.) Rootworm corn (MON 863) grain that is protected against feeding damage caused by corn rootworm larvae are presented. Corn rootworm-protection was accomplished through the introduction of a cry3Bb1 coding sequence into the corn genome for in planta production of a modified Cry3Bb1 protein from Bacillus thuringiensis. Grain from MON 863 and its near isogenic control were separately formulated into rodent diets at levels of 11% and 33% (w/w) by Purina Mills, Inc. Additionally,

six groups of rats were fed diets containing grain from different conventional (non-biotechnology-derived) reference varieties. The responses of rats fed diets containing MON 863 were compared to those of rats fed grain from conventional corn varieties. All diets were nutritionally balanced and conformed to Purina Mills, Inc. specifications for Certified LabDiet 5002. There were a total of 400 rats in the study divided into 10 groups of 20 rats/sex/group. Overall health, body weight gain, food consumption, clinical pathology parameters (hematology, blood chemistry, urinalysis), organ weights, gross and microscopic appearance of tissues were comparable between groups fed diets containing MON 863 and conventional corn varieties. This study complements extensive agronomic, compositional and farm animal feeding studies with MON 863 grain, confirming that it is as safe and nutritious as existing conventional corn varieties.” (Hammond et al., 2006a)

Paper on MON810: (Hammond et al., 2006b)

Abstract:

“The results of a 90-day rat feeding study with grain from MON 810 corn (YieldGard (R) Cornborer - YieldGard Cornborer is a registered trademark of Monsanto Technology, LLC) that is protected against feeding damage from corn and stalk boring lepidopteran insects are presented. Corn borer protection was accomplished through the introduction of cry1Ab coding sequences into the corn genome for in planta production of a bioactive form of Cry I Ab protein. Grain from MON 810 and its near-isogenic control was separately formulated into rodent diets at levels of 11% and 33% (w/w) by Purina Mills, Inc. (PMI). All diets were nutritionally balanced and conformed to PMI specifications for Certified LabDiet (R) (PMI Certified LabDiet 5002 is a registered trademark of Purina Mills, Inc.) 5002. There were a total of 400 rats in the study divided into 10 groups of 20 rats/sex/group. The responses of rats fed diets containing MON 810 were compared to those of rats fed grain from conventional corn varieties. Overall health, body weight, food consumption, clinical pathology parameters (hematology, blood chemistry, urinalysis), organ weights, and gross and microscopic appearance of tissues were comparable between groups fed diets containing MON 810 and conventional corn varieties. **This study complements extensive agronomic, compositional and farm animal feeding studies with MON 810 grain, confirming that it is as safe and nutritious as grain from existing commercial corn varieties”** (Hammond et al., 2006b)

Typically, there is no mention in the report, downloaded on August 29, 2009 on apologies for such a grave error, which renders the whole report invalid.

10. General EFSA statement on food safety experiments 2007

A more basic statement of EFSA on food safety experiments has been published in a peer reviewed journal (EFSA, 2007). It is an extensive analysis of all aspects of food safety assessment, including an impressive literature list. Here the conclusions in extenso (there is nothing to add to those paragraphs)

“7. Conclusions and recommendations

7.1. The comparative approach to safety and nutritional testing of food and feed derived from GM plants

1. The risk assessment of GM plants and derived food and feed follows a comparative approach, i.e. the derived food and feed are compared with their non-GM near isogenic counterparts in order to identify differences which subsequently are assessed with respect to their potential impact on the environment, safety for humans and animals, and nutritional quality (Concept of Substantial Equivalence or Comparative Safety Assessment). This approach has been developed and accepted by international organisations like the EC, the FAO/WHO, Codex Alimentarius and OECD.

2. The comparative risk assessment approach for GM plant derived food and feed, is a stepwise procedure and considers two main categories of potential safety issues, i.e. those related to the intrinsic properties and function of the introduced trait(s), and those resulting from insertion and expression of the introduced gene(s) into the plant genome that might cause unintended effects. Key elements of this assessment procedure are the molecular, compositional, phenotypic, agronomic and other analyses (e.g. metabolic pathway considerations) that identify the similarities and differences between the GM plant and its non-GM near isogenic counterpart needing further evaluation.

(i) The GMO Panel considers that the comparative approach to safety and nutritional testing of food and feed derived from GM plants, using molecular, compositional, phenotypic, agronomic and other analyses, remains appropriate as the basis for deciding whether animal feeding studies are needed for the safety and nutritional assessment of GM food and feed.

7.2. Experience from testing of non-GM and GM whole foods

3. Extensive experience with the risk assessment of whole foods has been built up in recent decades from the safety and nutritional testing in animals of irradiated foods, novel foods and fruit and vegetables. Investigations including subacute, chronic, reproductive, multigeneration and carcinogenicity studies have confirmed the safety and wholesomeness of irradiated foods and several novel foods and in many cases a preventive effect of fruits and vegetables on tumor development was observed.

4. Many subchronic feeding studies in rodents have been conducted over the past 15 years on food and feed derived from GM plants developed so far. Those studies which were well designed and followed internationally accepted protocols did not reveal indications of adverse effects. The results obtained from the testing of GM food and feed in rodents indicate that large safety margins can be established between the levels of animal exposure and the estimated human daily intakes without adverse effects.

5. Numerous livestock feeding studies have also been performed in food-producing animals with feed derived from GM plants, modified for agronomic input traits. Results indicate that animals fed with feed derived from GM plants do not differ with respect to uptake of nutrients, health and performance, hatchability, milk yield, milk quality, etc., compared to animals fed with conventional comparable feed.

7.3. In silico and in vitro tools available for safety and nutritional testing of GM plant derived food and feed

6. The scientific tools available for studies on the safety and nutritional aspects of GM food and feed include in silico, in vitro and in vivo methods. However, few in vitro tests have so far met the necessary criteria of validation and reproducibility required to gain regulatory acceptance, and little progress has been made in reducing or replacing the use of animals in repeated dose studies, such as 28-day or 90-day studies. At present, in vitro tests should be considered as complementary to current in vivo testing methods and as early warning systems which may provide a quick and inexpensive way for gaining additional insights into potential toxicity endpoints.

7. A number of in silico and in vitro tests can be applied during the initial phase of the safety assessment, in particular to characterise the properties of newly expressed proteins and/or metabolites in GM plant derived food and feed. Among them are structure-activity relationship studies, sequence homology and/or structural similarity searches for known toxins and allergens, and biodegradation studies under simulated gastro-intestinal conditions. Results of these studies will further guide the risk assessment and possibly refine, reduce or replace the need for animal studies.

(ii) It is recommended that any programme for the risk assessment of GM food and feed should first consider what safety and nutritional aspects need to be investigated and whether initial studies using in silico and in vitro approaches may answer some of the safety questions and enable subsequent in vivo studies, and hence the use of animals, to be better focused and possibly reduced.

(iii) More efforts should be invested in the development of in vitro tests suitable for safety and nutritional evaluation of whole (GM) food and feed and derived ingredients.

7.4. Testing of defined single substances from GM plant derived food and feed in in vivo studies

8. A comprehensive range of in vivo laboratory animal tests are available to evaluate the toxicity of defined single substances, in cases where such substances present in GM food and feed need to be tested ([EFSA, 2006a](#)). Methods for such studies are described in OECD Test Guidelines or in European Commission Directives concerning the testing of chemicals. Guidelines are available for a range of repeated-dose toxicity tests, reproductive and developmental toxicity tests, while models for allergenicity testing are in development.

9. These methods may be applied, on a case-by-case basis, in order to characterise the safety of newly expressed proteins and metabolites in GM plant derived food and feed. Acute toxicity testing adds very little to the risk assessment of dietary exposure to defined single substances present in foods, but may be of some value for proteins. Subchronic toxicity studies in general reveal

most major toxic effects of defined substances and are often sufficient in themselves to allow safety assessment to proceed to a conclusion.

10. In some instances, effects on particular tissues or target organs may need to be investigated further in specially designed studies, like reproductive and developmental toxicity testing, immunotoxicity testing and/or allergenicity testing. Long-term studies, extending over most of the lifetime of the test species, can be used, if needed, to assess the potential of defined single substances for chronic toxicity and/or carcinogenicity.

(iv) It is recommended that, where needed, laboratory animal feeding studies on defined single substances should follow OECD Test Guidelines and should be carried out according to the principles of Good Laboratory Practice (GLP).

(v) Further development and validation of test models, including animal models, for the detection and evaluation of allergenicity of proteins expressed in GM plant derived foods (and of the whole modified food), is recommended, since so far no validated animal tests to detect potential allergenicity of foods for humans are available.

7.5. Testing of whole GM plant derived food and feed in animal feeding studies

11. In cases where testing of the safety and nutritional value of whole GM plant derived food and feed is indicated, either because the composition of the GM plant is modified substantially, or there are indications for the potential occurrence of unintended effects, the testing program should include at least a subchronic, 90-day toxicity test in rodents ([EFSA, 2006a](#)).

(vi) A subchronic, 90-day rodent feeding study on whole GM plant derived food and feed is considered to have sufficient specificity, sensitivity and predictivity to act as a sentinel study in order to detect in a comparative manner toxicologically relevant differences as well as nutritional deficiencies/improvements that may be due to the expression of new substances, alterations in levels of natural compounds or unintended effects.

12. The current generation of GM plants cultivated for commercial purposes, has been modified through the introduction of one or a few genes coding for herbicide tolerance, insect resistance or a combination of these traits. In these plants the genetic insert leads to the production of a gene product, which does not interfere with the overall metabolism of the plant cell, and does not alter the composition of the GM plant except for the introduced trait

(vii) In cases where molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence between the GM plant derived food and feed and their conventional counterpart, except for the inserted trait(s), and results of these analyses do not indicate the occurrence of unintended effects, the performance of animal feeding trials with rodents or with target animal species adds little if anything to the overall safety assessment, and is not recommended.

13. More extensive genetic modifications of plants are targeted at specific alterations of the plant's metabolism, for example leading to improved responses to environmental stress conditions, like salt or metal tolerance, or drought resistance. Moreover GM plants are under development with quality or output traits with the purpose to improve human or animal nutrition and/or health. In these cases relatively complex genetic modifications are applied, through for instance the insertion of gene cassettes, leading to substantial changes in the metabolism and composition of the GM plants and derived food and feed.

(viii) In cases where molecular, compositional, phenotypic, agronomic and other analyses have demonstrated differences between the GM plant derived food and feed and their conventional counterpart, apart from the inserted trait(s), or if there are any indications or remaining uncertainties for the potential occurrence of unintended effects, animal feeding studies with rodents should be considered.

14. Livestock feeding studies with target animal species should be considered, on a case-by-case basis and be hypothesis driven. The focus should be on the safety of expressed products, on the identification and characterisation of unintended effects, and on the nutritional impact of any intentional, substantial, compositional modifications of the GM plant. In the case of GM plant derived feed with claimed nutritional/health benefits, their purpose is to establish the growth, performance and potential nutritional benefits that might be expected.

(ix) Where livestock feeding studies with target animal species are indicated for a GM plant derived feed, possible effects of the new feed resource on animal performance, animal health, efficacy, and acceptability of the new feed ingredient should be investigated. Time spans for each study should be determined on a case-by-case basis. Further development of test protocols at an international level for livestock feeding studies is recommended.

15. Ninety-day studies with rodents are normally of sufficient duration for the identification of general toxicological effects of

compounds that would also be seen after chronic exposure. In general, long term, chronic toxicity testing of whole GM food and feed is not expected to generate information additional to what is already known from *in silico/in vitro* testing and from subchronic testing. However, the subchronic, 90-day rodent feeding study is not designed to detect effects on reproduction or development, other than effects on adult reproductive organ weights and histopathology. Thus, in some cases, testing of the whole food and feed beyond a 90-day rodent feeding study may be needed.

(x) In cases where structural alerts, indications from the subchronic study or other information on the whole GM plant derived food and feed are available that suggest the potential for reproductive, developmental or chronic toxicity, the performance of such testing should be considered.

16. There is a need for a more uniform approach to the design and analysis of animal feeding trials, and in particular for appropriate statistical analysis of data. The process of data interpretation requires extensive professional experience of the field, together with a thorough understanding of the concept of causality. One of the pivotal requirements is to distinguish those effects which are potentially treatment related from spurious occurrences or those that result from normal individual biological variation.

(xi) The suitability and possible application of bioequivalence and difference testing approaches for the comparative safety assessment of GM plants and derived food and feed should be further explored.

17. It can be anticipated that in the future the predictive value of a 90-day rodent feeding studies used for the safety assessment of whole food and feed will be enhanced by the integration of new technologies like transcriptomics, proteomics and metabolomics into the experimental risk assessment approach. Moreover, the use of 'profiling' technologies may also facilitate a non-targeted approach in compositional analysis in order to aid the detection of unintended effects in GM plant derived food and feed due to the genetic modification.

(xii) Further validation of these technologies and experience with their interpretation of data will be needed and standardisation of experimental procedures etc is recommended, before they can be utilised in routine safety assessment of food and feed derived from GM plants.

18. Ninety-day studies are not suited for identification of potential allergenicity. An integrated, stepwise approach for the assessment of potential allergenicity of newly expressed proteins has been put forward by the [Codex Alimentarius \(2003\)](#).

19. OECD methods for subchronic, reproductive, developmental and chronic toxicity testing can be adapted for the testing of whole GM plant derived food and feed.

(xiii) It is recommended that OECD should develop supplementary guidelines for safety and nutritional testing of whole food and feeds (e.g. type of control and test diets, spiking regimes, type of test groups and number of animals per test group, dosage regimes, toxicological and nutritional endpoints to be measured).

7.6. Importance of a structured approach for development of data for the pre-market safety and nutritional testing of GM plant derived food and feed

20. Each GM plant is unique and therefore each study necessary for the pre-market assessment of the safety and nutritional properties of the derived food and feed need to be designed on a case-by-case basis using knowledge already available or generated. The strategic scheme in Section 6 proposes the sequence of questions to be raised and answered by the appropriate scientific studies discussed in this report.

(xiv) The structured approach in testing is important in order to improve the outcome and save resources in the assessment process. In accordance with this, each study to be performed in the overall sequence of studies should be based upon a thorough examination of already generated data, leading to well designed studies with clear objective(s), precise study designs, protocols, dose level selection, sensitivity, statistical validity, data analysis and science based interpretation of the results.

7.7. Role of post-market monitoring

21. Post-market monitoring (PMM) is not a substitute for thorough pre-marketing risk assessment, neither should it be considered as a routine need. It is a later step which may additionally inform risk management. Knowledge gained through PMM might at best describe only broad patterns of human nutritional exposure. It may not always have the sensitivity to estimate individual intakes, or intakes of particular age groups. Thus in general it cannot be relied upon as a technique for monitoring

adverse events or other health outcomes related to the consumption of GM plant derived foods. Specific hypothesis driven studies may be required to relate adverse events to the consumption of these foods.

(xv) Models for prospective nutritional monitoring in humans should be further developed, utilising market-research food consumption databases combined with comprehensive food composition data, in order to describe patterns of food/food ingredient exposure at household level. The possibilities for linkages of exposure information to health data should be further explored.” From (EFSA, 2007).

11. Comments in Nature Biotechnology

Instead of giving further comments, it is better to cite from an article from Nature Biotechnology, where a science journalist tries her best to paint the complex picture on opinionated science writing, on honest defense of biosafety and on an outcome, which is far from clear today (Sinha, 2009): After a detailed description of the Austrian mice study:

The study, funded by the Austrian Ministry for Health, Family and Youth, wasn’t published, nor was it peer reviewed. Rather, the results were announced at a press conference last fall (Velimirov et al., 2008). Greenpeace issued a press release touting the study: “Forget condoms—eat GM maize,” read the headline. Other anti-GM groups also jumped on the news, and the internet was awash with stories touting the new study and its frightening findings. In its release, Greenpeace demanded a worldwide recall of all GM foods and crops, stating: “GM food appears to be acting as a birth control agent, potentially leading to infertility.”

[Monsanto’s].....criticism focused specifically on two major flaws. First, the authors did not use historical controls or reference groups throughout the study when comparing groups of mice. Without a proper control group of mice to assess natural variability in fertility, it’s difficult to say how much of the fertility decline was caused by diet alone. In addition, the authors used inconsistent calculation methods, did not use standard units in some calculations and also miscalculated some data. And even when the calculations were corrected, the lack of a control group made the results impossible to interpret, Monsanto argued. Monsanto’s criticisms have been confirmed and elaborated upon by several scientists. At Monsanto’s request, James Lamb, executive vice president of the Weinberg Group, a multinational regulatory consulting firm, wrote a review in which he concluded: “When properly analyzed, these data do not appear to support an effect on fertility or reproduction from consumption of GM corn”⁴.

Lamb was the researcher who had originally developed the continuous breeding study design, at the Research Triangle Park, North Carolina-based U.S. National Toxicology Program during the 1980s.

But the authors aren’t to blame, says Klaus Ammann, emeritus professor at the University of Bern in Switzerland. They are merely the latest victims of what has become the political gerrymandering of science to bolster and support anti-GM sentiment in Europe.

“The Austrian government had exhausted all legal avenues to ban cultivation of GM crops,” Ammann says. “The Ministry of Health decided to avoid the peer-review process and announce study results at a conference, hide the data from scientists, and let the activists run amok with the help of uncritical media.”

Indeed, in the ensuing months the Austrian government has backpedaled. The Ministry of Health responded to a request to interview Zentek or other authors with the following:

“We asked the scientists to reevaluate their statistical analysis. Additionally the external evaluation will soon be started. I kindly ask you to wait with your proposal until the reevaluation is completed.”

12. Austrian Government has officially withdrawn the study on March 26, 2010

Comments from GMCompass:

Austria withdraws study on the long-term consequences of GM maize

<http://www.gmo-compass.org/eng/news/499.docu.html>

(26 March 2010) Austria has withdrawn a study on long-term feeding trials with mice that was published in November 2008. The study had caused quite a public stir since some of the mice that were fed with genetically modified maize gave birth to fewer offspring. The media and gene technology critics had interpreted the result as evidence of a reduced fertility caused by GM maize.

The Austrian government had announced in a meeting of the 'Standing Committee for the Food Chain and Animal Health' at the EU commission in October 2009 that the scientists commissioned to do the study failed to deliver a satisfactory report on this study, especially with respect to the statistical analysis of the data. In addition, the Austrian Ministries that had commissioned the study no longer expected to receive such an evaluation.

Almost a year before, the committee had discussed the then newly published study and had come to the conclusion that the data did not allow any inferences to be drawn concerning the investigated GM maize - a cross between the maize lines NK603 and MON810. At that time, Austria had agreed to reappraise the statistical evaluation of the data.

The study, carried out by a working group of the University of Vienna under the leadership of Prof. Jürgen Zentek (now at the TU Berlin), was presented at a meeting in Vienna in November 2008. At the same time the first press releases appeared:

"Consumption of GM maize reduces fertility" wrote Greenpeace and demanded that the European Food Safety Authority (EFSA) should be closed because of incompetence and that all approved genetically modified plants should be removed from the market. The news service Glocialist going a step further wrote "GM maize causes impotence". Austrian politicians of all parties regarded their 'enormous concern' about gene technology in agriculture as confirmed.

Zentek and his coworkers had fed their experimental mice a diet that comprised of one third GM maize from the NK603×MON810 cross. A control group had received conventional maize. In another experiment mice were fed over four generations with both diets. In the evaluation of the long-term study published at that time, the number of offspring in the third and fourth litters were less than for the control group fed with conventional feed. Although Zentek warned about hasty generalisations, since then the study has been consistently cited by gene technology critical groups as evidence for health risks through genetically modified food plants.

Subsequently, Austria introduced the study into the consultation at the EU level. It was, according to a government representative speaking to the Standing Committee on 16 December 2008, "Part of comprehensive efforts of the Austrian Government regarding the safety of GM plants". After the discussion, it was observed in the protocol of the "Consensus between Member States" meeting that "the study did not answer the question of safety of the GM maize NK603×MON810. The Austrian authorities should consider whether they could provide EFSA and the Member States with the raw data."

Previously both EFSA and some national authorities had examined the results of the feeding study and had come to the conclusion that no inferences could be drawn from the report since the data were incomplete and contradictory. In addition, important information necessary for a scientific evaluation of the study was missing.

Despite their acceptance at that time, the Austrian government was apparently not able to provide either these data or a statistically correct evaluation.

Here the original text inserted into an EFSA report by the Austrian Government:

http://ec.europa.eu/food/committees/regulatory/scfcah/modif_genet/sum_19102009_en.pdf

"Miscellaneous

Long-term reproduction studies on mice

The delegation of Austria informed the Committee about the last developments regarding a study entitled "Biological effects of transgenic maize NK603×MON810 fed in long term reproduction studies on mice" that was financed by the Austrian Federal Ministry of Health, Family and Youth and the Ministry of Agriculture, Forestry, Environment and Water Management with a view to examine effects of the stacked GM crop NK603×MON810 in different models (MGS, RACB) of long-term feeding studies. This study was already discussed in the Committee on 16 December 2008 and it was considered that it did not allow to draw conclusions on the investigated GM maize.

The delegation of Austria indicated that the contracted researchers still failed to deliver a satisfactory report on this study, especially with respect to the statistical analysis of the data, and that the Austrian Ministries do not expect anymore to receive such a report. For the sake of transparency, raw data that were provided by the researchers were made available to EFSA and Member States. Despite the difficulties encountered with this specific research project, the Austrian delegation reiterated its interest in establishing an adequate model for long-term feeding studies.”

It is interesting to note that at the time of the insertion of this note above the leading scientist of the study has reiterated a new version of the study to the Austrian government, despite of the declaration of the Austrian government above. In this new version they did not draw anymore any conclusions from the mice experiments related to reduced fertility.

See also further comments on statistics in feeding experiments by Marianne Schauzu
<http://www.gmo-safety.eu/en/news/558.docu.html>

The publication has also been removed from the Organic Repository <http://orgprints.org/19253/>



The screenshot shows the Organic eprints website interface. At the top, the logo 'Organic eprints' is displayed in green and red. Below the logo is a navigation menu with links: 'home', 'about', 'browse', 'search', 'latest', and 'help'. Underneath the menu are links for 'Login | Create Account'. The main content area displays the message 'Item Removed' and a sub-message: 'You seem to be attempting to access an item that has been removed from the repository.' At the bottom of the page, there are logos for 'contact us supporters', 'ICROFS', 'FiBL', 'BÖLN' (with the text 'Bundesprogramm Ökologischer Landbau und andere Formen nachhaltiger Landwirtschaft' below it), and 'auf deutsch'.

13. Comments on the use and abuse of scientific arguments in politics

It is obvious, that politics play into the scientific debate on GM crops – especially in Europe. It is also obvious, that scientists should try to abstain from writing in a way which could hamper their own reputation as so called neutral impairs in disputes. Unfortunately, the battle fields are full of smoke and the situation is rarely clear. In this sense the Austrian maize study is a good learning piece. Scientists should stick to internationally agreed protocols when conducting feeding experiments with mice, a rule which has *not been obeyed* in the case of the Austrian study. The study is still in revision and not published properly in a peer reviewed journal. It has been officially withdrawn by the Austrian Government for good reasons on March 26, 2010, see chapter 12 above.

It will also be interesting to see who is going to author the final publications. In a thoughtful paper, the case of new experts is discussed: (Durodie, 2003):

“CONCLUSION

As the aspiration for real social change has receded, so science has been inflated in terms of import and impact, out of all proportion. This has been both by those who see science as a danger as well as by those who see it as the solution to everything.

Brian Wynne argues that the 'increasing dependence on the scientific has given science a new role'. In fact, it is the failure of politics that has done so.

We should not include 'lay values' or 'local knowledge' into science, peer review or anywhere else, as there is no such thing. These are in fact mere opinions that need to be interrogated just as much as the scientific evidence itself. Labelling them 'values', as many now seem prone to do, is in fact a conscious attempt to set this debate off-limits by suggesting that we should not offend people's values.

But science is not about making us feel good about ourselves. It can reveal some quite disconcerting truths. Indeed, we owe a debt to those who, in the past, were prepared to put their heads above the parapet of perception, prejudice and power, in order to expose the real workings of the world. This was not done by accommodating to majority, or even minority, views.

THE CHANGING ROLE OF THE PUBLIC INTELLECTUAL

Having said that, mavericks do have a role to play within science. But this is by ruthlessly revealing assumed values and eliminating them, rather than by importing a few more of their own into the debate. Above all else, mavericks need to corroborate their evidence and convince their peers.

We should move away from our growing obsession with the impact of science upon society and begin to examine a bit more critically the impact of society upon science. This is especially so in a society that faces no greater difficulties, or complexities, than in the past, but that despite this, has lost its sense of ambition, of the need to develop a broader vision and of the paramount importance of the will to explore and experiment, a society that appears so riddled by self-doubt and cynicism that it has become afraid of taking risks and hence unable to establish trust. Sadly, unlike in the past, when change largely coincided with periods of social optimism or mass political engagement, what we have today is a fear of change that stems from social pessimism and mass political disengagement. It is this that will need to be addressed if we are to restore the primacy of science. Thus, irrespective of whether we benefit or not from a scientifically more literate public, the more important process of reengaging the public cannot be forced and will need to derive from advocating a broader social vision.

There has never really been what one could call 'Science Wars', fought through to a conclusion. There may be no better time to start them than now.

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