

## **Statement of the Scientific Panel on Genetically Modified Organisms on the analysis of data from a 90-day rat feeding study with MON 863 maize**

**adopted on 25 June 2007**

### **1. BACKGROUND**

In 2004 the Panel on Genetically Modified Organisms (GMO Panel) of the European Food Safety Authority (EFSA) gave its opinion on the safety of MON 863 maize for import and processing, food and feed uses (EFSA, 2004a,b) and released a statement on the same topic shortly after (EFSA, 2004c). In these documents it was concluded that the MON 863 maize would not have an adverse effect on human and animal health or the environment in the context of its proposed use. One of the studies assessed by the Panel was a 90-day (subchronic) feeding study in rats using kernels of MON 863 maize (Monsanto, 2002). Since then, two scientific papers dealing with this study have been published (Hammond *et al.*, 2006; Séralini *et al.*, 2007). Hammond *et al.* (2006) described the study and its outcomes, but in less detail than the original report provided by Monsanto (2002). Séralini *et al.* (2007) published a statistical re-analysis of the original data from Monsanto and concluded that ‘with the present data it cannot be concluded that GM corn MON 863 is a safe product’. The European Commission asked EFSA on 15 March 2007 to consider, in cooperation with the Member States, what impact the re-analysis might have on the earlier opinions and statement of the GMO Panel (EFSA, 2004a,b,c).

In response to the question from the European Commission, EFSA set up a Task Force to assess the statistical methodology applied by Séralini *et al.* (2007), and to perform an additional statistical analysis. The outcome of the Task Force’ analysis is reported in a document entitled: “EFSA review of statistical analyses conducted for the assessment of the MON863 90-day rat feeding study” (EFSA, 2007). In addition EFSA asked Member States whether there were any further relevant data or views on the Monsanto study and its statistical approach. EFSA also convened a technical meeting with the authors of the paper (Séralini *et al.* 2007) in order to have a full understanding of their statistical considerations and approaches.

### **2. ASSESSMENT**

In their study Séralini *et al.* (2007) applied certain statistical methods in the analysis of growth curves, and concluded that rats fed kernels from MON 863 maize showed slight but dose-related significant variations in growth for both genders. Moreover biochemical measurements of hematological, clinical-chemistry, urinalysis and histopathological parameters and of organ weights revealed a large number of statistically significant differences. Some of these differences, according to the authors, are indicative for hepato and/or renal toxicity.

## **2.1. Analysis of body weight data**

Weight gain data, as analysed by S eralini *et al.* (2007), showed differences between the groups fed GM maize and those fed the near-isogenic non-GM control maize. The authors reported a slight, but statistically significant, decrease (3.3%) in weight of male rats receiving 11% MON 863 maize in their diet, and an increase (3.7%) in weight of female rats receiving 33% MON 863 maize in their diet. Two independent statistical analyses, employing sophisticated statistical methodologies capable of detecting small differences in growth rate parameters, have been applied to the experimental data submitted by Monsanto. One study (Monod, 2007) was performed upon request of the French CGB (Commission du G enie Mol culaire) and the other by EFSA (2007).

The Monod study did not show significant differences in weight gain between GM maize fed animals and controls, except for a marginal statistically significant difference in the rate of growth of female rats at the highest dose applied (33%), during part of the study period, while the final total weight was not affected. Transient changes in food intake were the most likely source of this difference.

The statistical analysis performed by EFSA did not show significant differences in total weight gain over the test period between GM maize fed animals and controls, when data were averaged over gender and doses, and there was no significant effect of the doses applied (11% versus 33%). In all cases but one, males at 12 weeks, differences between GMO and control were consistent with random variation. Also, growth rates of the animals fed GM maize and control maize were within the variations found in the additional study groups fed a range of non-GM maize commercial varieties.

The EFSA (2007) statistical assessment concluded that the assumptions underlying the statistical methodology employed by S eralini *et al.* (2007) did not hold and therefore would lead to an excess of spurious significant results; the Monod and EFSA analyses confirmed this.

## **2.2. Analysis of biological parameters**

The analysis of haematological, clinical-chemistry, urinalysis and histopathological parameters and of organ weights indicated a number of significant differences, as already reported in the opinions of the GMO Panel (2004 a,b).

The results of the statistical analysis on the above mentioned parameters as reported by S eralini *et al.* (2007) are largely consistent with the findings previously reported by Monsanto and by EFSA (2004 a,b). S eralini *et al.* reported 40 significant differences out of 494 tested endpoints, whereas only 25 would be expected by chance alone. However, the EFSA (2007) analysis shows that, since correlation exists between various parameters, and since there might be a slight systematic difference between the GMO and control, the probability of 40 significant differences occurring by chance alone is substantial.

EFSA (2007) investigated in detail the variability in the data. For the majority of endpoints the variability in values of test parameters obtained from GM maize-fed rats and from animals fed the near-isogenic control was considerably smaller than that shown between animals fed the commercial (reference) maize varieties. Furthermore, the statistically significant differences did not show consistency patterns over endpoint variables, dose and gender.

### 3. CONSIDERATIONS OF THE EFSA GMO PANEL

In its previous assessment of MON 863 maize (EFSA, 2004 a,b), the GMO Panel has evaluated comprehensively an extensive data set on (i) the genetic modification process, (ii) agronomic traits and composition of the GM maize and its near-isogenic line, (iii) the safety of introduced proteins including the potential for allergenicity, and (iv) the safety and nutritional properties of the whole food/feed.

With respect to the results from the 90-days feeding trial, the GMO Panel has examined the behaviour of numerous haematological, clinical-chemistry, urinalysis and histopathological parameters, and of organ weights measured on animals fed diets containing GM maize, near-isogenic maize and maize from commercial varieties. The Panel has considered all Student t-test results for the various contrasts provided by Monsanto, including the direct comparison of the GM maize exposed groups with the respective non-GM near-isogenic control groups, and evaluated all statistically significant differences in the test parameters. These differences have been evaluated with respect to (i) type and severity, (ii) extent and frequency of occurrence, and (iii) potential dose and sex relationship.

Observed differences in test parameters of exposed male and female rats were in most cases neither dose-related nor sex-dependent. In some cases there was an increase and in some cases a decrease in value and these were considered as isolated phenomena occurring by chance. Changes observed in certain serum or urine analysis parameters were not indicative of damage in, for instance, liver, spleen or kidney, since histopathological analysis did not show statistically significant effects.

Séralini *et al.* (2007), suggested in their paper that the observed significant changes in weight gain of both females and males, as became evident from their statistical analysis, could be an indication of endocrine disruption and/or effects on hormonal metabolism. This hypothesis is not substantiated by experimental data. No effects have been observed in macroscopic appearance, weight, and histopathology of reproductive and endocrine organs tested such as the pituitary, thyroid, testis, prostate, ovary, and uterus (Monsanto, 2002).

In contrast to Séralini *et al.* (2007), the GMO Panel has considered the biological relevance of all statistically significant differences in test parameters identified between the GM fed animals and their respective non-GM near-isogenic controls, which is a crucial element in risk assessment. To this end, natural variability in test parameters have been taken into account, as estimated from data obtained from animals fed several commercial maize varieties. Given the fact that deviations in test parameters were relatively small and for the greatest part within natural variation ranges, the GMO Panel did not consider these effects as biologically relevant.

### 4. RESPONSES FROM MEMBER STATES

EFSA received responses from several Member States: Austria, The Czech Republic, Eire, France, Germany, Hungary, Italy, The Netherlands, Romania, Sweden and the UK. Of those that provided data or views, seven agreed that no new evidence was provided that would cast doubt on the previous opinion of the GMO Panel, two provided no further evidence, whereas two believed that before an assessment can be made further investigation is necessary. Detailed responses from Member States with respect to the Séralini *et al.* study (2007) are published as annexes to the EFSA report (EFSA, 2007).

## 5. CONCLUSIONS

The GMO Panel has carefully considered the results of the statistical re-analysis of the 90-day rat feeding study with MON 863 maize in relation to the previous evaluation (EFSA, 2004a,b,c).

The GMO Panel has considered the biological relevance of all statistically significant differences in test parameters. Observed differences in test parameters of exposed male and female rats were in general neither dose-related nor sex-dependent and were therefore considered as isolated phenomena occurring by chance. Furthermore the GMO Panel has taken the natural variability of the test parameters into account. Given the fact that deviations in test parameters were relatively small and for the greatest part within natural variation ranges, the GMO Panel did not consider these effects as biologically relevant.

In the absence of any indications that the observed differences in test parameters are indicative of adverse effects, the GMO Panel does not consider that the publication by Séralini *et al.* (2007) raises new issues which are toxicologically relevant. Therefore, the GMO Panel sees no reason to revise its previous opinion that the MON 863 maize would not have an adverse effect on human and animal health or the environment in the context of its proposed use.

The GMO Panel is aware of the fact that different approaches are applied in the statistical analysis of data obtained from animal experiments and has signalled the need for a harmonised approach in this area. A working group of the Panel is currently addressing this issue.

## DOCUMENTATION PROVIDED TO EFSA

1. Letter from DG SANCO, dated 15 March 2007, concerning a new analysis of the 90-day rat feeding study with MON 863 maize (ref. SANCO/E1/Da/cc (2007)D/510172).
2. Contributions from Member States, included as Appendix 1 to the EFSA statistical report (EFSA, 2007).

## REFERENCES

EFSA, 2004a. Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to the Notification (Reference C/DE/02/9) for the placing on the market of insect-protected genetically modified maize MON 863 and MON 863 x MON 810, for import and processing, under Part C of Directive 2001/18/EC from Monsanto. The EFSA Journal, 49, 1-25.

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[http://www.ogm.gouv.fr/experimentations/evaluation\\_scientifique/cgb/autres\\_avis/Avis\\_CGB\\_MON\\_863\\_15juin2007.pdf](http://www.ogm.gouv.fr/experimentations/evaluation_scientifique/cgb/autres_avis/Avis_CGB_MON_863_15juin2007.pdf)

Monsanto, 2002. 13-Week Dietary Subchronic Comparison Study with MON 863 Corn in Rats Preceded by a 1-Week Baseline Food Consumption Determination with PMI Certified Rodent Diet #5002

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