

Brief No. 07/50

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Minister for Food Safety

REVIEW OF REPORT BY SÉRALINI ET AL RE MON863 CORN 90-DAY RAT FEEDING STUDY

Purpose

1. *The purpose of this briefing is to advise you on the outcome of reviews conducted by the European Food Safety Authority (EFSA), Food Standards Australia New Zealand (FSANZ) and the New Zealand Institute of Environmental Science and Research (ESR) on a report by Séralini et al entitled "New analysis of a rat feeding study with a genetically modified maize reveals signs of hepatorenal toxicity". This briefing also provides an explanation of the role of animal feeding studies in safety assessments of genetically modified (GM) foods.*

Background

2. In December 2002 Monsanto applied to FSANZ to update the Australia New Zealand Food Standards Code to provide approval for the use in food of MON863 corn. Following a comprehensive assessment conducted in accordance with internationally agreed guidelines, FSANZ recommended the approval of MON863 to the Australia and New Zealand Food Regulation Ministerial Council (the Ministerial Council). The Ministerial Council accepted the approval in December 2003. The approval was subsequently given effect in New Zealand by gazette notice in April 2004.
3. MON863 corn is marketed as "Yieldgard Rootworm Corn Seed" and has been modified for resistance to corn rootworm pest. This resistance is achieved through the insertion of the *cry3Bb1* gene from soil bacterium *Bacillus thuringiensis*. The *cry3Bb1* gene encodes a crystal protein which is toxic to Coleopteran insects and has specific activity against corn rootworm larvae.
4. Cry proteins are a highly specific group of toxins. They bind only to specific receptors in the gut of target organisms. Without such receptor binding, no toxic effect can be exerted. For this reason, Cry proteins are not toxic to other species. No receptors for Cry proteins have been identified in the gut of mammalian species.
5. As well as being approved for use in food in New Zealand and Australia, MON863 corn is also approved for use in a number of other countries, including the United States (US), Canada, Japan, China, the European Union, Korea, Mexico, the Philippines and Taiwan.

6. During its assessment of MON863 corn, FSANZ completed a comprehensive safety assessment and evaluated all of the available safety data including an acute oral toxicity study using mice and a feeding study using chickens. No potential public health and safety concerns were identified and no further data was deemed necessary or requested.
7. In late 2003 the French Commission for Genetic Engineering raised safety concerns in relation to the results of a MON863 90-day rat feeding study commissioned by Monsanto. This study was performed by Covance Laboratories, in compliance with internationally agreed Good Laboratory Practice principles. These principles set out, amongst other things, the requirements for data recording and reporting when toxicity testing is being carried out. The study was provided by Monsanto to EFSA following a request by an EU member state.
8. FSANZ does not require animal feeding studies to be submitted as part of an application for approval of a GM food; therefore FSANZ did not receive or request this information from Monsanto. However, if studies are available, FSANZ includes them in the safety assessment of a GM food. Where GM varieties have been shown to be compositionally equivalent to conventional varieties (as is the case with MON863), animal feeding studies add little to a safety assessment and are generally not warranted.
9. In the case of MON863 corn, FSANZ was of the opinion that the compositional data, molecular characterisation and toxicity/allergenicity data that was provided by Monsanto was sufficient to establish the nutritional adequacy of MON863 corn.
10. Despite establishing this adequacy, FSANZ requested and received a copy of the unpublished 90-day feeding study and came to the conclusion that the study did not reveal any treatment-related adverse effects. This conclusion was consistent with the findings of other regulatory authorities including EFSA, the US Food and Drug Administration, Canadian Food Inspection Agency, Food Directorate Health Canada and the Japanese Ministry of Health, Labour and Welfare.
11. In 2007 Greenpeace announced the publication of a study on MON863 it had commissioned by Séralini *et al*. The study involved a re-analysis of data from the Monsanto 90-day rat feeding study in which the authors claimed to find statistically significant differences indicating liver and kidney toxicity in rats fed MON863 corn. Séralini *et al* therefore stated that it cannot be concluded that MON863 corn is a safe product.

NZFSA's Response

12. The Séralini *et al* study did not present new raw data, but involved a statistical re-analysis of data from the original Monsanto 90-day rat feeding study. The differing conclusions were the result of the use of different statistical tests.
13. NZFSA's resident toxicologist reviewed the Séralini *et al* study. NZFSA's toxicologist was of the opinion that the re-analysis confirmed the original findings of FSANZ and other regulatory authorities: that MON863 corn poses no greater risk to consumers than non-genetically modified corn. The following conclusions were drawn by NZFSA's toxicologist:
 - the Séralini *et al* study claimed to have found differences indicating liver and kidney toxicity in rats fed MON863 genetically modified corn. However the differences found were all small and within the normal physiological ranges for rats;
 - changes in physiology can occur randomly and without any toxicity. For the parameters measured to have any value in assessing possible risk, there would have to have been changes seen in the pathology of the organs identified as affected. These were not seen; and

- despite claims by the authors to the contrary, there was no dose response seen in the re-analysis. Rats fed 11% modified corn showed a claimed effect, while rats fed 33% modified corn showed no effects.
14. As the Séralini *et al* study was published in a peer reviewed journal, NZFSA commissioned the Institute of Environmental Science and Research (ESR) to evaluate the statistical methods used by the authors and to provide NZFSA with an independent expert opinion on both the study and its significance in relation to the FSANZ approval of MON863 corn.
 15. Separate to the NZFSA commissioned research, FSANZ and EFSA also undertook analyses of the Séralini *et al* study. These reports were made publicly available in June and July 2007 respectively.

The Role of Animal Feeding Studies in the Safety Assessment of GM Foods

16. When assessing the safety of a GM food, FSANZ requires a wide range of information from an applicant. This includes, among other things, data on the nature of the genetic modification, the presence of any antibiotic resistance genes, a characterization of the novel protein, characterization of any other novel substances, compositional analyses, information on the nutritional impact, and information on overseas approvals (or refusals to approve). A statutory declaration is also required to submit with all applications.
17. Toxicity testing in animals in accordance with international protocols is routinely used in the safety assessment of discrete chemicals (e.g. food additives and pesticides). The chemicals being tested are usually well-characterised, of known purity, have no particular nutritional value, and human exposure levels tend to be relatively low. Therefore, such substances can be fed to animals at a range of doses, sometimes many thousands of times greater than the expected human exposure levels. This allows the testing to identify and characterise any potential adverse health effects.
18. In contrast, several international bodies have noted the difficulties in applying such toxicity testing to whole foods, and the likelihood that such testing methods can provide misleading results or fail to identify hazardous properties.
19. Foods are complex mixtures of many different chemical substances. Due to their bulk and effect on satiety, they can usually only be fed to animals at low levels relative to amounts that might be present in the human diet. This means that, even if hazardous chemicals were present in the foods, such studies may be inadequate for detecting adverse effects.
20. Additionally, where the substance being tested (a whole food) makes up a significant proportion of the test animals' total diet, the nutritional value and balance of the animal diets are easily disrupted. The resulting nutritional imbalances can induce a range of adverse effects not related directly to the food itself. Conclusively tying the observed adverse effects to an individual characteristic of the food can be extremely difficult in practice and prone to misinterpretation.
21. FSANZ recently convened an expert panel to consider the use of whole food animal feeding studies to ensure its consistency with the most up-to-date thinking on the subject. The expert panel's particular focus was on the use of whole food animal feeding studies in the safety assessment of GM foods. Two important statements arising from the work of the expert panel were:
 - that whole food animal feeding studies may be informative in some limited circumstances, but these studies need further refinement in relation to experimental design; and

- where the results of relevant animal feeding studies are available, evaluate them with critical attention to the methodology and potential limitations in interpretation of these types of studies.
22. Where GM varieties have been shown to be compositionally equivalent to conventional varieties, animal feeding studies add little to a safety assessment and are generally not warranted. As discussed above, the interpretation of these studies in relation to the safety of food is limited. Animal feeding studies may be provided as confirmation that a GM food is nutritionally adequate and that it will support typical growth and well being. However, they cannot be relied upon to give information about the potential toxicity of a food.
 23. In contrast, oral toxicity testing is designed to assess the potential for any adverse effects of a novel protein by studying effects at a wide range of concentrations and toxicological endpoints. Acute oral toxicity testing involves the purification of the novel protein and the administration of it to animals at very high doses. Such testing can provide additional reassurance that the novel proteins will have no adverse effects in humans when consumed as part of a food. Such testing also provides more meaningful information about potential toxicological effects than animal feeding studies using whole foods.
 24. When Monsanto applied to FSANZ for approval of MON863 corn, it provided the full data from an acute oral toxicity study in mice of the novel protein in MON863. No potential public health and safety concerns were identified from this study.

EFSA Review of the Séralini *et al* Study

25. In April 2004 the EFSA Panel on Genetically Modified Organisms (GMO Panel) gave its opinion on the safety of MON863 corn. The GMO Panel concluded that the placing on the market of MON863 corn is unlikely to have an adverse effect on humans and animals. One of the studies assessed by the panel was the Monsanto 90-day rat feeding study.
26. Following the publication of the Séralini *et al* study, the European Commission asked EFSA to consider what impact the study might have on the earlier opinion of the GMO Panel. EFSA established a Task Force to assess the statistical methodology applied by Séralini *et al* and to perform additional statistical analyses. In addition, a French institute was commissioned to carry out another statistical analysis of the original data. 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*", which is available from www.efsa.europa.eu (the EFSA Statement summarising the review is attached as Appendix 1).
27. EFSA also convened a technical meeting with the authors of the Séralini *et al*. study in order to have a full understanding of their statistical considerations and approaches. (EFSA, 28/06/2007).
28. The conclusions of the EFSA review were:
 - that there were problems with the statistical methodology used by Séralini *et al*;
 - that, generally, there was a lack of statistical significance in the differences between animals fed the MON863 corn and those fed conventional corn when more robust statistical analyses were used; and
 - those differences that were observed were consistent in the two (Monsanto and Séralini *et al*) studies and were most likely not caused by toxicity of MON863 corn. The differences were no more significant than would be expected by chance alone and were not biologically relevant to the health of the animals.

29. The GMO Panel concluded that the results reported by Séralini *et al* on the biochemical parameters, clinical pathology and organ weights of the animals were largely consistent with the findings previously assessed by the GMO Panel and reported in the Monsanto application. Therefore there was no evidence presented in the Séralini *et al.* study that would warrant a change to the conclusions already reached by the GMO Panel on the safety of MON863 corn.

FSANZ Review of the Séralini *et al* Study

30. The FSANZ review of the Séralini *et al* study considered the scientific basis for the findings and the implications in relation to the safety of food derived from MON863 corn. The review, entitled "*FSANZ reaffirms its risk assessment of genetically modified corn MON863*" is publicly available at www.foodstandards.gov.au (attached as Appendix 2).
31. FSANZ pointed out that no new data were generated or analysed by the authors of the Séralini *et al* study. The study is a statistical re-analysis of the same data, which had already been reviewed by FSANZ and other regulatory agencies around the world.
32. FSANZ concluded that while the alternative statistical methods utilised by Séralini *et al* identified a number of statistically significant differences between rats fed diets containing MON863 corn and rats fed control diets, the authors did not apply conventional toxicological interpretation strategies to investigate the biological relevance of those differences.
33. FSANZ concluded that in the absence of this important step, the approach used is scientifically flawed. Therefore there are no grounds to revise FSANZ's previous conclusions on the safety of MON863 corn as a food.

ESR Review of the Séralini *et al* Study

34. The aim of the ESR review was to evaluate the statistics used in the Séralini *et al* study and provide expert advice to NZFSA on the significance of the study to the FSANZ approval of MON863 corn.
35. In June 2007, ESR submitted the review report. In a cover letter to the report, the author qualified the conclusion with the following:

"No conclusions can be drawn as to the safety or otherwise of MON863 for human consumption based on the two papers alone"

This qualification is important in so far as the conclusion of the report was as follows:

*"Toxicological concerns were raised by Séralini *et al* that cannot be refuted without further study".*

36. Following receipt of the ESR report in June, several changes within the NZFSA office (and absence of key staff) resulted in no consideration immediately being given to the ESR report. By the time NZFSA staff were in a position to consider the report, the EFSA and FSANZ reports had been published. In light of these substantial independent international developments (which were not available to ESR at the time of presenting the report in June), NZFSA went back to ESR to ask if the report could be updated to reflect the most recent information available.
37. In the course of that discussion, NZFSA was advised that the report sent in June had not been subject to usual ESR internal review processes and that ESR wished to withdraw the report and submit a revised and updated final. However, as the withdrawn report could be relevant to your overall consideration of this issue it has been provided along with the revised final which was submitted in October 2007 (both reports are attached as Appendix 3).

38. The final report (as per the cover letter to the withdrawn report) states that ESR was unable to properly evaluate the *Séralini et al* study without access to the data set on which the study was based.
39. However ESR did make the following comments in relation to the *Séralini et al* study and a related study by Hammond *et al* (2006), which presented the results of the original Monsanto rat feeding study:
 - Hammond *et al* may have assumed a normal distribution of data, that may have led to a skewing of results that would have led to concurrent skewing of the conclusions drawn; and
 - *Séralini et al* have apparently not correlated their observations for individuals over time, which could lead to inappropriate conclusions being made.
40. ESR also stated that neither the Hammond *et al* nor *Séralini et al* studies “provide an indication of the variation in body weight within groups, or the change in body weight they consider to be significant. Thus it is not possible to ascertain if the differences are within the natural variation that could be expected”.
41. ESR found no reason to disagree with the conclusions of the EFSA and FSANZ reviews. ESR stated that while it did not analyse the raw dataset, it saw no reason to do so and commented that substantially more funding would be required from NZFSA for such an investigation.
42. ESR further pointed out that animal feeding studies are not typically required by FSANZ for safety assessments and that they are only required by EFSA if specifically requested by a member state.
43. ESR concluded by stating that with the sole exception of *Séralini et al* the bulk of independent scientific opinions consider that there is no scientific evidence to suggest that consumption of MON863 corn is not safe for humans.

Conclusions

44. NZFSA considers that on the basis of the extensive pre-market safety assessments carried out on MON863 corn and the recent reviews of the *Séralini et al* study by FSANZ, ESFA, ESR and NZFSA, that there is no evidence presented in the *Séralini et al* study that would justify revising the previous conclusions of regulatory authorities on the safety of food derived from MON863 corn.

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