



## **Friends of the Earth Europe**

**Friends of the Earth's comments on Monsanto's applications for GM maize varieties NK603xMON810, MON863xMON810, NK603xMON863xMON810 and NK603xMON863**

**Date: April 2006**

### **General comments applying to all four applications**

The 30 day opportunity for public comment is already a major constraint on providing detailed comments on application. Releasing four applications simultaneously seriously impacts on the ability to fully engage in this process, and should not be repeated. Furthermore, there does not appear to be any notification system in place for when new applications are placed on [http://europa.eu.int/comm/food/food/biotechnology/authorisation/public\\_comments\\_en.htm](http://europa.eu.int/comm/food/food/biotechnology/authorisation/public_comments_en.htm) - at the very least the ability to sign up to an email alert system should be implemented.

Access to full applications is still only available via multiple downloads from the EFSA extranet following specific requests for permission to view individual dossiers. No information is provided on EFSA's webpage about how to obtain these dossiers, making public participation in the decision making process more difficult. Public access to these documents must be made easier, making it clear that documents are available and, at the very least, creating a single, downloadable Zip file for each dossier.

The recent EC support for improvements in scientific consistency and transparency in EFSA's decision making is very welcome, but the suggested practices need to be implemented now. Opinions released for public comment must be revisited to ensure that EFSA, for example, provides more detailed justifications for dismissing Member State objections, and explicitly addresses potential long-term effects and biodiversity issues in risk assessments. All assumptions made must be made explicit, and the reasoning behind conclusions reached must be fully detailed.

**Specific comments on individual applications**  
**(NB: because the applications are hybrids of three existing GM events some comments are repeated for each application)**

**NK603xMON810**

**Molecular characterisation**

EFSA's earlier Opinions for NK603<sup>1</sup> noted that new unintended RNA sequences were present in the genome of NK603, but speculative and largely unsupported assumptions were made about their safety. It was stated that the unpredicted transcription "*is not expected to have a regulatory function*", but no evidence was supplied to support this claim. In describing the transcription it is stated that "*This could create 2 or more mRNA species, a smaller one at 1.4 kb (predicted as the cp4 epsps L214p transcript) and a larger species at >1.4 kb (a product likely to be the result of incomplete termination at the NOS 3' genetic element due to "read through")*". 'Read through' transcription is dismissed because it is routinely observed in many plant genes, yet there is evidence that it can shut down neighbouring genes<sup>2</sup>. The new Opinion for NK603xMON810 does not consider these issues to pose a safety risk, but gives little justification for this conclusion.

**Comparative analysis**

EFSA's earlier Opinions for NK603<sup>3</sup> found a difference in the stearic acid composition of NK603 compared to non-GM maize in one year, but not the other. This is not considered to be of biological significance due to additional tests that did not find "*conclusive differences requiring further studies*". It is not stated whether further statistically significant differences were found – further detail would be useful to explain why the compositional difference was not thought relevant. The new Opinion for NK603xMON810 does not explore this issue in any more detail.

All compositional analyses for NK603xMON810 and its comparator were carried out in France, which is considered to be representative for maize growing regions within the EU. Yet maize is grown in a wide range of EU countries – grain production takes place in Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Luxembourg, Netherlands, Poland, Slovakia, Slovenia and Spain<sup>4</sup>. Maize is also grown for forage in cooler countries such as the UK. Furthermore, as the application is for import only, it would seem necessary to provide information from countries in which maize is exported, for example as in the applications for MON863xMON810, MON863xNK603 and MON863xMON810xNK603, where data from Argentina is provided.

**Toxicology**

The EFSA Opinion for NK603xMON810 states "Given the functional properties of the proteins, the GMO Panel considers that interactions between the expressed proteins are unlikely", and that "*because no relevant changes in compositional analysis were*

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<sup>1</sup> Opinions of the Scientific Panel for NK603 in relation to 258/97 and 2001/18  
[http://www.efsa.eu.int/science/gmo/gmo\\_opinions/catindex\\_en.html](http://www.efsa.eu.int/science/gmo/gmo_opinions/catindex_en.html)

<sup>2</sup> Kusaba M et al (2003) Low glutelin content1: A dominant mutation that suppresses the glutelin multigene family via RNA silencing in rice Plant Cell 15(6):1455-1467

<sup>3</sup> Op cit 1

<sup>4</sup> FAOSTAT data, 2006

*detected no further safety assessment of new constituents in NK603xMON810 is warranted*". EFSA therefore reject a Member State request for a 90-day toxicology study in rats to confirm the safety of NK603xMON810 maize.

But this is at odds with a recently released EU document produced for the WTO dispute<sup>5</sup>, which states *"it can not be excluded that unintended effects may result from hybridisation between the two parental GM events"*, and *"the intended hybrid must be subject to separate evaluation including additional data from appropriate feeding trials"*. It points out that *"information on the parent lines alone cannot provide full reassurance that the cross will be safe as well. For example, the introduced genetic material and the products that are derived from this genetic material (eg enzymes), may interact with each other within the conventional cross of GM lines"*, with examples cited for GM crosses where features distinctive from the parental lines were seen and gene silencing. Insufficient evidence has been provided by EFSA to justify dismissing calls for toxicology tests on the hybrid maize.

Additionally, evidence for the safety of the Cry1Ab protein expressed in MON810 is based upon testing of a surrogate protein produced by *E. coli*. The use of surrogate proteins has been criticised, as different proteins can be produced by plants and bacteria even when transformed with the same gene, and so tests using such surrogates may not reflect the toxicity of the plant-produced protein<sup>6</sup>.

### **Allergenicity**

Allergenicity assessment is based purely upon the proteins expected to be expressed by the inserted genes in the two separate parent lines (Cry1Ab and CP4 EPSPS). As explained above, unintended effects must be considered as a result of hybridisation between the two GM parental events, and so a consideration of allergenicity of the whole GM plant seems essential.

Furthermore, the assessments for Cry1Ab and CP4 EPSPS are themselves flawed. The assessments are based purely on indirect evidence such as analysis of sequence homology and pepsin resistance of bacterial surrogate proteins. But a recent study by Spök et al<sup>7</sup> casts doubt on the suitability of such studies to address allergenic potential, and Freese & Schubert<sup>8</sup> found industry procedures often failed to accurately simulate gastric fluid content. Additionally, for Cry1Ab, Chowdhury et al<sup>9</sup> found that the protein can pass through the digestive tract and be detected in the faeces of farm animals – so the *"rapid and extensive degradation"* observed in pepsin studies cited in the Opinion may not occur in reality. Additionally, Prescott et al<sup>10</sup>

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<sup>5</sup> Paras 546, 536, European Communities – Measures Affecting the Approval and Marketing of Biotech Products: Comments by the European Communities on the Scientific and Technical Advice to the Panel. [http://www.foeeurope.org/biteback/EC\\_case.htm](http://www.foeeurope.org/biteback/EC_case.htm)

<sup>6</sup> Freese W & Schubert D (2004). Safety testing and regulation of genetically engineered foods. In Harding SE (Ed) Biotechnology & Genetic Engineering Reviews 21.

<sup>7</sup> Spök A et al (2005). Suggestions for the assessment of the allergenic potential of genetically modified organisms. International Archives of Allergy and Immunology 137:167-80

<sup>8</sup> Op cit 6

<sup>9</sup> Chowdhury EH et al (2003). Detection of corn intrinsic and recombinant DNA fragments and Cry1Ab protein in the gastrointestinal contents of pigs fed genetically modified corn Bt11. J. Anim. Sci 81(10):2546-2551.

<sup>10</sup> Prescott VE et al (2005). Transgenic expression of bean alpha-amylase inhibitor in peas results in altered structure and immunogenicity. Journal of Agricultural and Food Chemistry 53:9023-30.

found that a genetically modified pea containing a protein not previously associated with immune reactions provoked immune responses in mice, as well as priming them to react to other foods. This is thought to be due to post-translational modification of the protein – an effect that would not be picked up by the indirect testing used for Cry1Ab and CP4 EPSPS.

Yet EFSA's opinion states that they are "*not aware of any new information on allergenicity that requires a change in this opinion*", and that they are "*not aware of any new, validated tests that produce additional relevant or accurate information on possible allergenicity of the proteins*". But the FAO/WHO Expert Consultation<sup>11</sup> that sought to establish a reliable methodology to assess the allergenicity of GM foods recommended targeted serum screening and immunogenicity testing in animal models for all GM foods, even from sources not known to be allergenic. Yet the Codex guidelines<sup>12</sup>, on which EFSA's guidance<sup>13</sup> is based, only suggest the use of such tests where the source of the introduced gene is considered allergenic, or there are consistent indications of sequence homology to known allergens, which seems remiss based on the findings of Prescott et al.

There is currently no validated and widely accepted animal model for allergenicity testing, so clearly further research is needed – a fact acknowledged by recent calls for research<sup>14</sup> from the UK's Food Standards Agency for bioinformatic and proteomic techniques to identify potential allergens in novel food, and methods to study post-translational modification of transgenic proteins compared with native equivalents. Until research in this area is completed, it seems premature to conclude a low probability of allergenicity.

This is further backed up by the EU's WTO dispute document<sup>15</sup>, which states "*Even if a given protein per se does not represent an allergen, its expression in another host organism may indirectly upregulate the expression of potential allergens. It is therefore recommended to compare the engineered plant/plant product with that of the parent/wildtype plant/plant product regarding IgE reactivity to establish whether the transgenic organism represents a more potent allergen source than the parent/wildtype organism for already sensitized patients. The potentially increased ability of the transgenic organism versus the parent/wildtype organism to induce de novo IgE responses (i.e. allergic sensitization) needs to be compared by immunization experiments.*"

Concerns that the allergenicity of the whole crop could have been altered are dismissed in the Opinion, stating that the issue "*does not appear relevant to the Panel since maize is not considered a common allergenic food*". Yet this ignores the potential for unintended effects that could occur as a result of hybridisation between the GM parental lines, as discussed above. Additionally, as maize consumption increases, particularly in processed foods, consumers could be widely exposed to the GM maize, so even uncommon allergic reactions could become an issue due to wide exposure.

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<sup>11</sup> [www.fao.org/es/ESN/food/pdf/allergygm.pdf](http://www.fao.org/es/ESN/food/pdf/allergygm.pdf)

<sup>12</sup> [www.codexalimentarius.net/download/standards/10021/CXG\\_045e.pdf](http://www.codexalimentarius.net/download/standards/10021/CXG_045e.pdf)

<sup>13</sup> [www.efsa.eu.int/science/gmo/gmo\\_guidance/660\\_en.html](http://www.efsa.eu.int/science/gmo/gmo_guidance/660_en.html)

<sup>14</sup> <http://food.gov.uk/multimedia/pdfs/rrd20.pdf> and <http://food.gov.uk/multimedia/pdfs/rrd21>

<sup>15</sup> Para 717, European Communities – Measures Affecting the Approval and Marketing of Biotech Products: Comments by the European Communities on the Scientific and Technical Advice to the Panel. [http://www.foeeurope.org/biteback/EC\\_case.htm](http://www.foeeurope.org/biteback/EC_case.htm)

Finally, the EFSA Opinion dismisses the fact that the Cry1Ab protein has been shown to act as an adjuvant, yet gives little evidence or reasoning to justify this. It is simply stated that *“the adjuvant effect of Cry proteins, observed after high dosage intragastric or intranasal administration will not raise any concerns regarding allergenicity caused by maize consumption or contact. Furthermore, maize is not a common allergenic food, and only a rare cause of occupational allergy may occur”*.

Bearing in mind the lack of allergenicity testing carried out, the decision that no post-market monitoring of the GM food/feed is regarded as necessary seems unwise.

### **Long-term effects**

Article 14(4) of Regulation 178/2002 explicitly states that regard must be given to not only short-term effects, but effects on subsequent generations, cumulative toxic effects and the effects on health sensitive consumers. But there is no mention of long-term effects in EFSA’s Opinion. Yet compounds in maize have been linked with both carcinogenic and endocrine disrupting effects. For example, maize products have been shown to disrupt the oestrous cycle of rats, either by consumption or through exposure in bedding<sup>16</sup>, extracts of fresh maize and maize cob products have been shown to stimulate breast and prostate cancer cell proliferation in vitro, with sensitivity occurring at  $\mu$ Molar concentrations<sup>17</sup> and research identified a mixture of THF-diols in maize that produce endocrine disrupting effects at concentrations 200 times lower than those of classical plant estrogens<sup>18</sup>. A thorough assessment must be carried out to determine whether the production of these newly identified carcinogenic and endocrine disrupting compounds has been increased as a consequence of genetic modification.

### **Environmental risk assessment**

Minimal assessment is made of the potential for dissemination and accidental release of NK603xMON810 because the application is for import only. But this ignores the experience of Mexico, where despite the fact that only food and feed imports of GM maize were allowed, local landraces of maize were found to be contaminated with GM constructs. It is suggested that GM maize grains sold as food or feed were inadvertently planted, and no evidence is given to show that this will not occur in Europe. Maize seed saving is still practised in Europe, and maize landraces are still cultivated that represent a valuable source of genetic variation and an important cultural heritage. Cultivation of traditional landraces has been documented in Italy, Spain, Portugal, France and Romania<sup>19</sup>. Although the EFSA Opinion *“advises that appropriate management systems should be in place to restrict seeds... entering cultivation”*, this does not appear to be an absolute requirement, and no further detail is given as to how this will be achieved in practice.

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<sup>16</sup> Markaverich BM et al (2002) Identification of an endocrine disrupting agent from corn with mitogenic activity Biochemical and Biophysical Research Communications 291: 692-700

<sup>17</sup> Markaverich BM et al. (2002) A novel endocrine-disrupting agent in corn with mitogenic activity in human breast cancer and prostatic cancer cells. Environmental Health Perspectives 110: 169-177

<sup>18</sup> Ibid

<sup>19</sup> Papa R. Maize landraces in Europe: a special case for co-existence. [http://europa.eu.int/comm/research/biosociety/pdf/rt\\_papa\\_abstract.pdf](http://europa.eu.int/comm/research/biosociety/pdf/rt_papa_abstract.pdf)

## **MON863xMON810**

### **Molecular characterisation**

Expression levels of the Cry proteins are of concern. Cry3Bb1 expression in MON863xMON810 is much higher than that of Cry proteins in other GM maize varieties, such as MON810, Bt11, Bt176 (producing Cry1Ab) and even Starlink (producing Cry9C). Expression levels in the hybrid are also higher than those of the parental GM lines - the applicant notes that *“Average levels of the Cry3Bb1 protein in tissues of Mon 863xMon 810 were estimated to be 1 -2 fold higher than in Mon 863”*. Similarly the average level of Cry1Ab was 83% higher in the hybrid (0.84 µg/g fw) than in MON810 parent grains (0.46 µg/g fw). In the case of NPTII, the protein was expressed at a very low level in both hybrid and parent grains (<0.076 µg/g fw) although it was expressed at a higher level in both leaves and forage<sup>20</sup>. EFSA's Opinion concludes that these data do not raise safety concerns, but no evidence is given to support this.

### **Comparative analysis (for compositional analysis and agronomic traits and GM phenotype)**

Compositional analysis is based on forage and grain obtained from field trials in Argentina, which is considered “representative of major countries exporting maize to the EU”. However, maize is imported into the EU from a variety of countries, including Brazil, the USA and South Africa<sup>21</sup>, each of which will have markedly different climatic conditions to Argentina.

### **Allergenicity**

Allergenicity assessment is based purely upon the proteins expected to be expressed by the inserted genes in the two separate parent lines (Cry1Ab and Cry3Bb1). Yet a recently released EU document<sup>22</sup>, states *“it can not be excluded that unintended effects may result from hybridisation between the two parental GM events”*, and *“information on the parent lines alone cannot provide full reassurance that the cross will be safe as well.”* A consideration of allergenicity of the whole GM plant seems essential.

Furthermore, the assessments for Cry1Ab and Cry3Bb1 are themselves flawed. The assessments are based purely on indirect evidence such as analysis of sequence homology and pepsin resistance of bacterial surrogate proteins. But a recent study by Spök et al<sup>23</sup> casts doubt on the suitability of such studies to address allergenic potential, and Freese & Schubert<sup>24</sup> found industry procedures often failed to accurately simulate gastric fluid content. Additionally, for Cry1Ab, Chowdhury et al<sup>25</sup> found that the protein can pass through the digestive tract and be detected in the faeces of farm animals – so the *“rapid and extensive degradation”* observed in pepsin

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<sup>20</sup> Monsanto. Application for authorisation of MON863xMON810 maize in the European Union according to Regulation EC No 1829/2003 on genetically modified food and feed. Part I – Technical Dossier.

<sup>21</sup> Op cit 4

<sup>22</sup> Op cit 5

<sup>23</sup> Op cit 7

<sup>24</sup> Op cit 6

<sup>25</sup> Op cit 9

studies cited in the Opinion may not occur in reality. Additionally, Prescott et al<sup>26</sup> found that a genetically modified pea containing a protein not previously associated with immune reactions provoked immune responses in mice, as well as priming them to react to other foods. This is thought to be due to post-translational modification of the protein – an effect that would not be picked up by the indirect testing used for Cry1Ab and Cry3Bb1.

Yet EFSA's opinion states that they are “*not aware of any new information on allergenicity that requires a change in this opinion*”, and that they are “*not aware of any new, validated tests that produce additional relevant or accurate information on possible allergenicity of the proteins*”. But the FAO/WHO Expert Consultation<sup>27</sup> that sought to establish a reliable methodology to assess the allergenicity of GM foods recommended targeted serum screening and immunogenicity testing in animal models for all GM foods, even from sources not known to be allergenic. Yet the Codex guidelines<sup>28</sup>, on which EFSA's guidance<sup>29</sup> is based, only suggest the use of such tests where the source of the introduced gene is considered allergenic, or there are consistent indications of sequence homology to known allergens, which seems remiss based on the findings of Prescott et al.

There is currently no validated and widely accepted animal model for allergenicity testing, so clearly further research is needed – a fact acknowledged by recent calls for research<sup>30</sup> from the UK's Food Standards Agency for bioinformatic and proteomic techniques to identify potential allergens in novel food, and methods to study post-translational modification of transgenic proteins compared with native equivalents. Until research in this area is completed, it seems premature to conclude a low probability of allergenicity.

This is further backed up by the EU's WTO dispute document<sup>31</sup>, which states “*Even if a given protein per se does not represent an allergen, its expression in another host organism may indirectly upregulate the expression of potential allergens. It is therefore recommended to compare the engineered plant/plant product with that of the parent/wildtype plant/plant product regarding IgE reactivity to establish whether the transgenic organism represents a more potent allergen source than the parent/wildtype organism for already sensitized patients. The potentially increased ability of the transgenic organism versus the parent/wildtype organism to induce de novo IgE responses (i.e. allergic sensitization) needs to be compared by immunization experiments.*”

Concerns that the allergenicity of the whole crop could have been altered are dismissed in the Opinion, stating that the issue “*does not appear relevant to the Panel since maize is not considered a common allergenic food*”. Yet this ignores the potential for unintended effects that could occur as a result of hybridisation between the GM parental lines, as discussed above. Additionally, as maize consumption increases, particularly in processed foods, consumers could be widely exposed to the GM maize, so even uncommon allergic reactions could become an issue due to wide exposure.

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<sup>26</sup> Op cit 10

<sup>27</sup> Op cit 11

<sup>28</sup> Op cit 12

<sup>29</sup> Op cit 13

<sup>30</sup> Op cit 14

<sup>31</sup> Op cit 15

Finally, the EFSA Opinion dismisses the fact that the Cry1Ab protein has been shown to act as an adjuvant, yet gives little evidence or reasoning to justify this. It is simply stated that *“the adjuvant effect of Cry proteins, observed after high dosage intragastric or intranasal administration will not raise any concerns regarding allergenicity caused by maize consumption or contact. Furthermore, maize is not a common allergenic food, and only a rare cause of occupational allergy may occur”*.

Bearing in mind the lack of allergenicity testing carried out, the decision that no post-market monitoring of the GM food/feed is regarded as necessary seems unwise.

### **Long-term effects**

Article 14(4) of Regulation 178/2002 explicitly states that regard must be given to not only short-term effects, but effects on subsequent generations, cumulative toxic effects and the effects on health sensitive consumers. But there is no mention of long-term effects in EFSA’s Opinion. Yet compounds in maize have been linked with both carcinogenic and endocrine disrupting effects. For example, maize products have been shown to disrupt the oestrous cycle of rats, either by consumption or through exposure in bedding<sup>32</sup>, extracts of fresh maize and maize cob products have been shown to stimulate breast and prostate cancer cell proliferation in vitro, with sensitivity occurring at  $\mu$ Molar concentrations<sup>33</sup> and research identified a mixture of THF-diols in maize that produce endocrine disrupting effects at concentrations 200 times lower than those of classical plant estrogens<sup>34</sup>. A thorough assessment must be carried out to determine whether the production of these newly identified carcinogenic and endocrine disrupting compounds has been increased as a consequence of genetic modification.

### **Environmental risk assessment**

Minimal assessment is made of the potential for dissemination and accidental release of MON863xMON810 because the application is for import only. But this ignores the experience of Mexico, where despite the fact that only food and feed imports of GM maize were allowed, local landraces of maize were found to be contaminated with GM constructs. It is suggested that GM maize grains sold as food or feed were inadvertently planted, and no evidence is given to show that this will not occur in Europe. Maize seed saving is still practised in Europe, and maize landraces are still cultivated that represent a valuable source of genetic variation and an important cultural heritage. Cultivation of traditional landraces has been documented in Italy, Spain, Portugal, France and Romania<sup>35</sup>. Although the EFSA Opinion *“advises that appropriate management systems should be in place to restrict seeds... entering cultivation”*, this does not appear to be an absolute requirement, and no further detail is given as to how this will be achieved in practice.

EFSA also conclude that the antibiotic resistance gene nptII does not pose a risk to the environment or to human and animal health due to limited use of kanamycin and neomycin in medicine, widespread presence in bacterial populations and low risk of gene transfer from plants to bacteria. But these drugs are still important for specific purposes, such as bowel sterilisation prior to surgery and treatment of neonatal infections.

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<sup>32</sup> Op cit 16

<sup>33</sup> Op cit 17

<sup>34</sup> Op cit 17

<sup>35</sup> Op cit 19

## MON863xMON810xNK603

### **Molecular characterisation**

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<sup>36</sup> Op cit 1

<sup>37</sup> Op cit 2

<sup>38</sup> Op cit 4

<sup>39</sup> Op cit 5

<sup>40</sup> Op cit 7

<sup>41</sup> Op cit 6

<sup>42</sup> Op cit 9

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<sup>43</sup> Op cit 10

<sup>44</sup> Op cit 11

<sup>45</sup> Op cit 12

<sup>46</sup> Op cit 13

<sup>47</sup> Op cit 14

<sup>48</sup> Op cit 15

Finally, the EFSA Opinion dismisses the fact that the Cry1Ab protein has been shown to act as an adjuvant, yet gives little evidence or reasoning to justify this. It is simply stated that *“the adjuvant effect of Cry proteins, observed after high dosage intragastric or intranasal administration will not raise any concerns regarding allergenicity caused by maize consumption or contact. Furthermore, maize is not a common allergenic food, and only a rare cause of occupational allergy may occur”*.

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<sup>49</sup> Op cit 16

<sup>50</sup> Op cit 17

<sup>51</sup> Op cit 18

<sup>52</sup> Op cit 19

## MON863xNK603

### **Molecular characterisation**

EFSA's earlier Opinions for NK603<sup>53</sup> noted that new unintended RNA sequences were present in the genome of NK603, but speculative and largely unsupported assumptions were made about their safety. It was stated that the unpredicted transcription "*is **not expected** to have a regulatory function*", but no evidence was supplied to support this claim. In describing the transcription it is stated that "*This **could** create 2 or more mRNA species, a smaller one at 1.4 kb (predicted as the cp4 epsps L214p transcript) and a larger species at >1.4 kb (a product **likely** to be the result of incomplete termination at the NOS 3' genetic element due to "read through")*". 'Read through' transcription is dismissed because it is routinely observed in many plant genes, yet there is evidence that it can shut down neighbouring genes<sup>54</sup>. The new Opinion for MON863xNK603 does not consider these issues to pose a safety risk, but gives little justification for this conclusion.

### **Comparative analysis (for compositional analysis and agronomic traits and GM phenotype)**

Compositional analysis is based on forage and grain obtained from field trials in Argentina, which is considered "representative of major countries exporting maize to the EU". However, maize is imported into the EU from a variety of countries, including Brazil, the USA and South Africa<sup>55</sup>, each of which will have markedly different climatic conditions to Argentina.

### **Allergenicity**

Allergenicity assessment is based purely upon the proteins expected to be expressed by the inserted genes in the two separate parent lines (Cry3Bb1 and CP4 EPSPS). Yet a recently released EU document<sup>56</sup>, states "*it can not be excluded that unintended effects may result from hybridisation between the two parental GM events*", and "*information on the parent lines alone cannot provide full reassurance that the cross will be safe as well.*" A consideration of allergenicity of the whole GM plant seems essential.

Furthermore, the assessments for Cry3Bb1 and CP4 EPSPS are themselves flawed. The assessments are based purely on indirect evidence such as analysis of sequence homology and pepsin resistance of bacterial surrogate proteins. But a recent study by Spök et al<sup>57</sup> casts doubt on the suitability of such studies to address allergenic potential, and Freese & Schubert<sup>58</sup> found industry procedures often failed to accurately simulate gastric fluid content. Additionally, Prescott et al<sup>59</sup> found that a genetically modified pea containing a protein not previously associated with immune reactions provoked immune responses in mice, as well as priming them to react to other foods. This is thought to be due to post-translational modification of the protein

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<sup>53</sup> Op cit 1

<sup>54</sup> Op cit 2

<sup>55</sup> Op cit 4

<sup>56</sup> Op cit 5

<sup>57</sup> Op cit 7

<sup>58</sup> Op cit 6

<sup>59</sup> Op cit 10

– an effect that would not be picked up by the indirect testing used for Cry3Bb1 and CP4 EPSPS.

Yet EFSA’s opinion states that they are “*not aware of any new information on allergenicity that requires a change in this opinion*”, and that they are “*not aware of any new, validated tests that produce additional relevant or accurate information on possible allergenicity of the proteins*”. But the FAO/WHO Expert Consultation<sup>60</sup> that sought to establish a reliable methodology to assess the allergenicity of GM foods recommended targeted serum screening and immunogenicity testing in animal models for all GM foods, even from sources not known to be allergenic. Yet the Codex guidelines<sup>61</sup>, on which EFSA’s guidance<sup>62</sup> is based, only suggest the use of such tests where the source of the introduced gene is considered allergenic, or there are consistent indications of sequence homology to known allergens, which seems remiss based on the findings of Prescott et al.

There is currently no validated and widely accepted animal model for allergenicity testing, so clearly further research is needed – a fact acknowledged by recent calls for research<sup>63</sup> from the UK’s Food Standards Agency for bioinformatic and proteomic techniques to identify potential allergens in novel food, and methods to study post-translational modification of transgenic proteins compared with native equivalents. Until research in this area is completed, it seems premature to conclude a low probability of allergenicity.

This is further backed up by the EU’s WTO dispute document<sup>64</sup>, which states “*Even if a given protein per se does not represent an allergen, its expression in another host organism may indirectly upregulate the expression of potential allergens. It is therefore recommended to compare the engineered plant/plant product with that of the parent/wildtype plant/plant product regarding IgE reactivity to establish whether the transgenic organism represents a more potent allergen source than the parent/wildtype organism for already sensitized patients. The potentially increased ability of the transgenic organism versus the parent/wildtype organism to induce de novo IgE responses (i.e. allergic sensitization) needs to be compared by immunization experiments.*”

Concerns that the allergenicity of the whole crop could have been altered are dismissed in the Opinion, stating that the issue “*does not appear relevant to the Panel since maize is not considered a common allergenic food*”. Yet this ignores the potential for unintended effects that could occur as a result of hybridisation between the GM parental lines, as discussed above. Additionally, as maize consumption increases, particularly in processed foods, consumers could be widely exposed to the GM maize, so even uncommon allergic reactions could become an issue due to wide exposure.

Bearing in mind the lack of allergenicity testing carried out, the decision that no post-market monitoring of the GM food/feed is regarded as necessary seems unwise.

### **Long-term effects**

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<sup>60</sup> Op cit 11

<sup>61</sup> Op cit 12

<sup>62</sup> Op cit 13

<sup>63</sup> Op cit 14

<sup>64</sup> Op cit 15

