



## **The European Food Safety Authority (EFSA): Failing Consumers and the Environment**

### **Summary**

**The GMO panel of the European Food Safety Authority (EFSA) was set up to contribute to an improved risk assessment of genetically engineered (GE) crops in the EU. However, analysis of the two assessments made so far by the EFSA (maize NK603 and oilseedrape GT73) show that the EFSA has not contributed to a higher level of consumer and environmental protection from GE crops and foodstuffs. The criticisms made of the old regulatory framework, of poor quality data and lack of investigation of irregularities and departures from substantial equivalence are still valid.**

### **Introduction**

Since the first application for import of genetically engineered (GE) foodstuffs in 1996, the regulation of GE crops for cultivation, food and feed in the EU has been severely criticised as wholly inadequate to ensure food, feed and environmental safety. Against this background, the EU introduced new legislation and a new body, the European Food Safety Authority<sup>1</sup>, which became operational in 2003. But, has the assessment of GE crops in the EU really changed? Or are the regulators merely just paying lip service to those who demand a rigorous assessment of GE crops for food safety?

### **Old Legislation and Old Criticisms**

The environmental aspects of GE crops were regulated by Directive 90/220/EC until Directive 2001/18/EC on the deliberate release of GMOs into the environment entered into force on October 17<sup>th</sup>, 2002. The food aspects were then regulated by Regulation EC 258/97 on “Novel Food”, which entered into force in January 1997. Regulation 258/97 relies heavily on the concept of “substantial equivalence”. Substantial equivalence has been severely criticised ever since its inception (see, e.g. Millstone et al.<sup>2</sup>) as an excuse by the biotechnology sector to perform only minimal analysis of GE foodstuffs.

### **Criticism 1 : Report commissioned by the Dutch Consumentbond and Bureau Européen des Unions de Consommateurs.**

In June 2001, Schenkelaars Biotechnology Consultancy published a highly detailed critique of the regulation of GE food crops and the application of substantial equivalence in the EU<sup>3</sup>.

The report found that :

- 1) data submitted were often of poor statistical quality, including pooled data from different trial sites and lacking in consistency of analyses and
- 2) where statistical differences in composition were noted (e.g. Bt11, T25 and MON810), these were not acted upon any further.

The report concluded that :

- 1) the concept of substantial equivalence urgently needed an operational definition, with prescribed analysis and protocols and

- 2) that significant differences in compositional data and/or from toxicological studies (including animal feeding trails) should be subject to further assessment.

### **Criticism 2 : The Royal Society of Canada**

The Royal Society of Canada<sup>4</sup> suggested that a GE organism could only be regarded as substantially equivalent after a rigorous scientific analysis. Any departures from the simple “precise” GE engineering model should be entry points for follow-up studies. They discussed that current regulatory use of substantial equivalence uses a “*decision threshold*” interpretation where it is assumed that no changes occur in the plant other than those directly attributable to the inserted gene. The Royal Society of Canada suggested a “*safety standard*” interpretation which would require rigorous scientific analysis to assess (and possibly attribute) all and each the effects created by genetic engineering.

### **Criticism 3 : FAO/WHO Codex Alimentarius guidelines**

The recent FAO/WHO Codex Alimentarius guidelines<sup>5</sup> state: “*The concept of substantial equivalence is a key step in the safety assessment process. However, it is not a safety assessment in itself; rather it represents the starting point which is used to structure the safety assessment of a new food relative to its conventional counterpart. This concept is used to identify similarities and differences between the new food and its conventional counterpart. It aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy to date for safety assessment of foods derived from recombinant-DNA plants.*”

### **Criticism 4 : Federal Environment Agency – Austria**

A report by Umweltbundesamt, the Austrian Federal Environment Agency<sup>6</sup> commented that “*Studies on how the concept is applied in the course of risk assessment procedures reveal both lacking validity and conclusiveness in the line of reasoning and criticise also the limited range of compounds analysed. Furthermore, a lack of consistency in the range of testing and methods applied as well as in statistical evaluation could be shown. This points to the wide margins of interpretation of the requirements.*”

**These criticisms have two principal points :**

- 1) **Data submitted in applications to import or cultivate GE crops are often not of sufficient quality to allow valid statistical comparisons to be made.**
- 2) **The concept of substantial equivalence should be a starting point. Where differences or irregularities are noted, these should be examined further.**

### **The new European legislation on the authorisation of GMOs**

The new EU legislation tries to address part of those criticisms. Recital 6 of Regulation 1829/2003 on GM Food and Feed states that : “*Whilst substantial equivalence is a key step in the procedure for assessment of the safety of genetically modified food, it is not a safety assessment in itself.*” Article 14.4 of Regulation (EC) 178/2002, which sets up the EFSA, writes that :”*In determining whether any food is injurious to health, regard shall be had: (a) not only to the probable immediate and/or short-term and/or long-term effects of that food on the health of a person consuming it, but also on subsequent generations ; (b) to the probable cumulative toxic effects*”. In the case of environmental risk assessment, for which the EFSA has not delivered an opinion yet, Annex II of Directive 2001/18/EC lists a number of requirements which include taking into account indirect and delayed effects as well as cumulative long-term effects. The new legislation therefore sets up more stringent requirements but those only make sense if they are put into practice in the actual evaluation procedures.

## **The situation now – EFSA’s assessments**

The new European body, the European Food Safety Authority, has a remit to “*contribute to a high level of consumer health protection in the area of food safety, through which consumer confidence can be restored and maintained.*”<sup>7</sup> For GE crops, this includes environmental considerations.

Under Directive 2001/18/EC, dossiers containing information on GE crops are submitted to an EU Member State. If that member state gives a positive opinion, the dossier is then forwarded to all member states for examination. Member states may make objections at this point and the objections are arbitrated by EFSA.

Has this new body taken into account the criticisms made in the past of the regulation of GE crops and foodstuffs in the EU? Do their scientific assessments live up to the requirements laid down in the European legislation? Is there now a rigorous scientific consideration of high quality data where any departures from substantial equivalence are investigated thoroughly? Does the EFSA contribute to a high level of consumer and environmental protection for GE crops and foodstuffs?

The following examination of the two GE crops that have been evaluated by EFSA, namely NK603 and GT73, reveals that that is not the case and that the regulation of GE crops and foodstuffs in the EU is as poor as it was before.

### **Assessment 1: EFSA Opinion of Monsanto’s Roundup Ready Maize, NK603.**

Two documents have been produced by the EFSA on this GE Roundup Ready maize that are virtually identical<sup>8</sup>. The references in this document refer to the import and processing document.

#### **Unintended extra fragments**

In the EFSA documents, the section on the molecular characterisation of NK603 (Section 1.2) states “*The insert also includes an inversely linked 217 bp DNA fragment of the enhancer region of the rice actin promoter (at the 3’ end). This fragment does not contain sequences needed for promoter activity. Next to this 217 bp fragment is a 305 bp region with homology to chloroplast DNA.*”

This means that, not only is an unintended back-to-front fragment of the promoter incorporated into the plant’s genome, but it also appears that an additional fragment of DNA from elsewhere in the plant cell has accidentally been inserted during the genetic engineering process.

#### **The unintended fragments are functional!**

The EFSA documents state that these unintended extra fragments are functional: these fragments are transcribed into RNA. In gene expression, DNA is read (transcribed) first to RNA (an intermediary product) and then to a protein. **Hence, this is one step away from creating an unintended novel protein.**

The documents state that the analytical technique used: “*did detect a transcription product which initiates within the NK603 insert (in the actin or 35S CaMV promoter regions) and which is processed through the NOS 3’ terminator into the maize genome flanking 3’ region.*” This means that the fragments inbetween the genetic insert in NK603 and the normal maize DNA, comprising the back-to-front promoter and chloroplast fragment, are actually functional. Indeed, one RNA species was actually detected by further analysis, but no further action was taken.

#### **But EFSA said integration of functional DNA sequences from chloroplast is rare!**

When discussing the possible significance of the presence of chloroplast DNA in the nucleus, EFSA states “*functional gene establishment of organellar DNA in the nucleus is rare*”.

### **What did the EFSA do next? Nothing!**

When considering whether these functional fragments pose a hazard to environmental or human health, EFSA did not reject NK603 on these grounds, as they should have done. Indeed, EFSA did not even demand further studies. They simply decided that because they didn't know what function the RNA produced from these fragments performed, they assumed it wasn't important.

*“The RNA fragment ...is not expected to have a regulatory function as described for micro RNAs which are short RNAs between 21 and 23 nt long derived from the processing of longer RNAs of around 70 nt. This is much shorter than the RNA fragments amplified from NK603.”*

The assumption of no regulatory function is based on current scientific opinion of a poorly understood subject. For example, microRNAs have only been discovered in the last few years. Indeed, the discovery of one type of micro RNA, interference RNA (RNAi) was reported as a scientific highlight of the year 2002 in the leading scientific journal, *Nature*<sup>9</sup>. The different roles of RNA are poorly understood – how can this GE food crop be regarded as safe for the environment and human/animal health when it produces molecules that we don't know the possible effects of? This is not a rigorous scientific investigation.

The documents state that *“Data provided demonstrate that in the unlikely event that junction polypeptides were translated they would not share a sufficient degree of sequence similarity or identity to known allergens or toxins.”* However, no rationale is presented as to why translation into protein or polypeptides would be unlikely. If transcription to RNA occurs, the next logical step is for translation to occur to produce proteins or polypeptides. Most allergens are proteins. It is quite possible that, should translation occur, there could be sequence similarity with *unknown* allergens or toxins. Or indeed, an unintended protein could interfere with a normal plant function. It simply isn't known what the consequences of producing an unintended protein are.

The EFSA concludes that *“Specifically for NK603, and concerning the chloroplast fragment inserted, the Panel considers that data provided from bioinformatic analysis and other safety studies address the issue of potential unintended effects caused by insertion of the fragment.”* But this conclusion is based on assumptions, not rigorous scientific study. Shouldn't the real significance of these fragments be studied in depth?

### **Rearrangements caused by GE different to those that occur during conventional breeding**

Rearrangements of DNA do occur in conventional breeding. Indeed, they are thought to be an important process in evolution, giving rise to new species or subspecies. However, these rearrangements occur on an evolutionary timescale, possibly occurring more frequently over periods of stress, e.g. environmental stress. Whilst not fully understood, it is thought that there is a limit to the amount of rearrangement that can occur. The rearrangements are thought to be constrained by a pre-established rearrangement potential. In addition, it is thought that there is channelling (i.e. control) of rearrangements, with most designed to “switch off” genes<sup>10</sup>.

In GE, rearrangements occur whether *Agrobacterium* or biolistics is used. Both can give rise to rearrangements or scrambling of the host DNA. Although there are very few studies on the rearrangements caused by GE, they appear to involve the formation of secondary structures of the introduced DNA and also involve break-repair mechanisms<sup>11</sup>. Thus, they are a response to the disruption of the genome caused by the insertion of DNA and wholly different to rearrangements that occur during conventional plant breeding.

### **The “stop” signal doesn't work!**

In addition, these unintended fragments should not be transcribed because it reads through a “stop” codon. This undermines one of the GE paradigms, that the “stop” codon ends transcription, i.e. it

stops the DNA being read into RNA and then a protein. It clearly does not work. However, once again, instead of investigating further, the EFSA simply stated “*Read through transcription is routinely observed in many plant genes.*” This is true, but the important difference here is that the “stop” is important because of the presence of strong promoters (“go” signals to make the genes functional) at the beginning of the inserted gene.

**Significant differences have not been investigated.** A number of significant differences are noted in Section 2.2 (Field Trials and Compositional Analysis) and Section 4.1 (Toxicology). For example, a difference in the stearic acid composition was noted in one year but not another. A significant difference between fat pad weights of broilers was noted. However, these are “*not considered to be of biological significance*”. The use of the term “biological significance” is not applicable here. There is no rigorous definition or methodology of calculation and, since biological and ecological systems are incompletely understood, it is not possible to state what is and what is not of biological significance. This is why rigorously defined statistical analyses are used. These differences must be thoroughly investigated. Else, any significant difference can be described as “*not considered to be of biological significance*” and thus ignored.

### **Conclusions on NK603**

- **Unintended fragments in NK603 appear to be functional. By itself, this should render this GE product unsafe. The EFSA have not evaluated the full significance of these fragments, including the ineffectiveness of the “stop” codon.**
- **Significant differences have been noted between NK603 and its conventional counterpart. The significant differences have not been further investigated, but regarded simply as “not of biological significance”.**

### **Assessment 2: EFSA Opinion of Monsanto’s Roundup Ready Oilseed Rape, GT73<sup>12</sup>**

When describing the GE constructs in GT73, (Section 2.2.2) EFSA states “*The sequencing of 3’ and 5’ flanking regions revealed that 40 base pairs (bp) of parental (Westar) DNA is absent from GT73, and that GT73 contains 22 bp of DNA adjacent to the 5’ insert/plant junction which is not present in Westar*”. This means that there has been a small deletion of plant DNA in the GE plant and small extra fragment of DNA (it is not clear where this extra fragment originates from). The significance of these irregularities has not been examined in depth. EFSA should have initiated further studies, but instead it simply states that there are no similarities between these sequences and known toxins and allergens. But these are not the only concerns from molecular irregularities. Are these fragments functional? What has been deleted from the plant, was a gene or regulatory sequence? These questions remain unanswered.

### **Compositional analysis – pooled data and significant differences**

The EFSA detail (Section 3.2.2) the analysis performed “*Kernels from oilseed rape (GT73, Westar and other commercial varieties) were obtained from field trials in Canada (1992 [7 sites], 1993 [5 sites]), 1997 [4-19 sites per variety]) and Europe (1994 [3 sites], 1995 [3 sites]).*” But, in the dossier and further information, these data are pooled from the different locations. This is exactly one of the major criticisms of poor quality data that was made prior to the initiation of the EFSA. Pooling of data can mask any variations present. Therefore, such data cannot be submitted in support of compositional sameness.

Even though the data was pooled significant differences were noted: the level of linolenic acid was lower and, importantly, glucosinolate levels were higher in the GE oilseed rape. Why these levels are different has not been investigated further, the EFSA has simply accepted two possible

explanations for the difference in glucosinolate levels from Monsanto as “*reasonable explanations*”. These explanations include variation within the original cultivar and variation induced by tissue cultivation. This is not scientifically rigorous, the EFSA should have rejected the GE crop at this point, or at least asked for further studies to determine exactly why these differences exist. It is certainly not in keeping with the philosophy of substantial equivalence as a starting point, i.e. where significances are noted they should be investigated.

### **The differences in glucosinolate levels could be important**

The glucosinolate levels are important because they are known antinutrients. As the EFSA states, the EC maximum allowable for this type of oilseed rape is 25 µmol/g seeds (9 % moisture content). But Monsanto haven’t even given the concentration of glucosinolate in seeds, they have only estimated that they are below the threshold by converting this maximum into alkyl glucosinolates/g of defatted meal, which have been measured. However, no indication of moisture content is given and the estimates are just rough calculations. Much of the analysis on these glucosinolate levels is from samples pooled from different locations and most of the data are from GE oilseed rape that hasn’t even been sprayed with Roundup (the herbicide that would be used with the GE oilseed rape). Analysing for glucosinolate levels in seeds is routine analysis – if would be easy for EFSA to ask for further studies on the glucosinolate levels but instead, they simply conclude “*The glucosinolate levels reported are thus clearly below the maximum content set by the European Commission*”.

### **Why are there no environmental considerations of oilseed rape imports?**

It is not clear why EFSA do not consider the environmental implications of imports of oilseed rape, as environmental considerations are supposed to be part of their remit. Whilst the application is import for food/feed purposes only, seeds may escape to the environment, e.g. during processing and transport. As feral populations of oilseed rape are widespread in Europe, it is highly possible that any escaped seed could germinate, flower and either cross-pollinate with oilseed rape crops, feral populations or wild relatives in Europe, raising serious biosafety issues and coexistence concerns.

### **Conclusions on GT73**

- **Irregularities in the molecular characterisation have not been studied further.**
- **Compositional analysis has been performed on samples pooled from different sites.**
- **Significant differences in composition have been found, but have not been investigated further.**
- **There is no environmental consideration of oilseed rape imports.**

### **Overall Conclusions**

**The initiation of the EFSA has not improved the regulation of GE crops. The criticisms made of the old legislation, before the EFSA were set up, are still valid. The data is often of poor quality and where differences and irregularities have been found, these have not been followed up sufficiently. There is no rigorous scientific consideration of high quality data where any departures from substantial equivalence are investigated thoroughly. The European Commission and Member States have the duty to take action in order to make sure that the requirements and standards for risk assessment in the European legislation are met by the EFSA and by national competent authorities. For now, the EFSA most certainly has not contributed to a high level of consumer and environmental protection from GE crops and foodstuffs.**

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<sup>1</sup> EFSA website: <http://www.efsa.eu.int>

<sup>2</sup> Millstone, E., Brunner, E. & Mayer, S. (1999) Beyond ‘substantial equivalence’ *Nature* 401, 525 – 526.

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- <sup>3</sup> Schenkelaars Biotechnology Consultancy (June 2001) GM food crops and application of substantial equivalence in the European Union. Available at: <http://www.sbcbiotech.nl/> and Schenkelaars, P. (2002) Rethinking substantial equivalence. *Nature Biotechnology*, 20, 119.
- <sup>4</sup> Royal Society of Canada. Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada (2001).
- <sup>5</sup> Codex Alimentarius (2003) Joint FAO/WHO Food Standard Programme Codex Alimentarius Commission, Report of the twenty-fifth session, Rome, Italy 30 June - 5 July 2003 ALINORM 03/34 [ftp://ftp.fao.org/codex/alinorm03/A103\\_34e.pdf](ftp://ftp.fao.org/codex/alinorm03/A103_34e.pdf)
- <sup>6</sup> Spök, A., Karner, S., Stirn, S & Gaugitsch, H. (2003) Toxikologie und allergologie von GVO-produkten – Teil 2b. Untersuchung von regelungen zur sicherheitsbewertung von gentechnisch veränderten lebensmitteln in der EU und den USA. Monographien Band 164B <http://www.ubavie.gv.at> (Executive summary in Austrian and English).
- <sup>7</sup> [http://www.efsa.eu.int/about\\_efsa/catindex\\_en.html](http://www.efsa.eu.int/about_efsa/catindex_en.html)
- <sup>8</sup> EFSA (2003a) Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to the Notification (Reference CE/ES/00/01) for the placing on the market of herbicide-tolerant genetically modified maize NK603, for import and processing, under Part C of Directive 2001/18/EC from Monsanto, *The EFSA Journal* (2003) 10, 1-13. <http://www.efsa.eu.int>
- EFSA (2003b) Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to the safety of foods and food ingredients derived from herbicide-tolerant genetically modified maize NK603, for which a request for placing on the market was submitted under Article 4 of the Novel Food Regulation (EC) No 258/97 by Monsanto, *The EFSA Journal* (2003) 9, 1-14. <http://www.efsa.eu.int>
- <sup>9</sup> Dennis C (2002) 2002 in context: the genome's guiding hand? *Nature*, 420, 732.
- <sup>10</sup> Lönnig, W-E., & Saedler, H. (2002) Chromosome rearrangements and transposable elements. *Annual Review of Genetics*, 36, 389-410.
- <sup>11</sup> Svitashv, S.K., Pawlowsk, W.P., Makarevitch, I., Plank, D.W. & Somer, D.A. (2002) Complex transgene locus structures implicate multiple mechanisms for plant transgene rearrangement *Plant Journal*, 32, 433–445.
- <sup>12</sup> EFSA (2004) Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to the Notification (Reference C/NL/98/11) for the placing on the market of glyphosate-tolerant oilseed rape event GT73, for import and processing, under Part C of Directive 2001/18/EC from Monsanto, *The EFSA Journal* (2004) 29, 1-19.