

**GeneWatch UK comments on the application for the placing on the market of food, feed and other products containing or consisting of genetically modified herbicide tolerant and stearidonic acid containing soybean MON 87769 × MON 89788 and food and feed produced from this soybean**

This GM crop combines altered fatty acid content (from Monsanto's "SDA soybean" MON 87769) with tolerance to the weedkiller glyphosate (RoundUp), from MON 89788.

3. Comments

a. Assessment:

**Molecular characterisation**

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

Environment and gene-environment interactions (GxE) are known to have important effects on nutrient (including fatty acid) composition of soybeans, <sup>1</sup> leading to significant alterations in fatty acid content in different environmental conditions (e.g. temperature and rainfall) and such effects can vary at different developmental stages<sup>2</sup>. It is therefore essential that data on nutrient composition of the edible parts of the plant is obtained from a wide variety of agronomic conditions, representative of expected growing conditions.

Data on agronomic and phenotypic characteristics of soybean MON 87769, its conventional counterpart and a set of non-GM commercial varieties were collected in field trials performed in the USA over 2 years in 2006 and 2007. These field trials also supplied seed and forage material for compositional analysis of the various soybean materials. In both years, the field trial was carried out at five geographical sites representative of the soybean cultivation areas of the USA. At minimum, data from Canadian trial sites is also required to establish the nutritional composition for this soybean due to likely very different cultivation conditions (e.g. climate, soil types).

For molecular characterisation, plants with the stacked trait were also grown at five locations (three replicate blocks) under field conditions in the USA in 2007. Since the expression in immature seeds was shown to be markedly higher than in mature seeds, the PjΔ6D and NcΔ15D levels were also analysed in two-event stack immature soybean seeds. The applicant also supplied data on the composition of forage and seeds of soybean MON 87769 × MON 89788 and its comparator harvested from another set of field trials carried out at five locations in the major soybean growing regions of the USA in 2007. The comparator A3525 and the non-GM soybean varieties received only conventional herbicide treatment, while soybean MON 87769 × MON 89788 received a single application of a glyphosate-based herbicide (between growth stage V2 to R1) in addition to the conventional herbicide treatment. However, this does not reflect the likely development of long-term use of herbicides on these crops, which increases as resistant "superweeds" develop, leaving high residues of glyphosate in glyphosate tolerant soybeans.<sup>3,4</sup>

The applicant also supplied data on agronomic and phenotypic characteristics of soybean MON 87769 × MON 89788 from a set of field trials carried out at five locations in the major soybean growing regions of Argentina during the 2007/2008 season, but the treatment of the genetically modified (GM) soybean with glyphosate-based herbicides, which would have allowed the assessment of herbicide effects, was not included. Compositional analysis of soybean forage and

seeds of soybean MON 87769 × MON 89788, its comparator and the commercial non-GM varieties used only the plants harvested from the field trials carried out in the USA during the 2007 growing season. Data from a single country in a single year is insufficient to account for G-E interactions.

The field trials used are inadequate to account for (i) gene-environment interactions and (ii) likely herbicide use in real-world applications. This means that the compositional analysis cannot form a proper basis for assessment of health impacts, as nutritional content may vary in different environments and herbicide residues are likely to be higher than those studied.

The applicant should be required to supply more field data to complete the compositional analysis.

#### **b. Food Safety Assessment:**

##### **Toxicology**

The safety impact of the altered fatty acid profile has not been evaluated (see comments on “nutritional assessment”). The product should therefore not be approved.

The approval of the glyphosate tolerant trait also needs to be reviewed in the light of new evidence regarding the toxicity of glyphosate residues and the importance of testing the health impacts of the whole herbicide formulation, including surfactants.

Evidence that should have been considered includes the IARC’s designation of glyphosate as a “probable human carcinogen”<sup>5</sup> and evidence that additional ingredients, such as surfactants (e.g. POAE), in commercial formulations of glyphosate (such as RoundUp) may significantly enhance toxicity.<sup>6,7,8,9,10</sup>

This requires safety testing of the product with commercial formulations of the herbicide, applied in sufficient doses to represent real world use. In the absence of this safety testing, the application should be refused.

##### **Allergenicity**

##### **Nutritional assessment**

EFSA’s Scientific Opinion states that it could not complete a full assessment on the possible impact of MON 87769 × MON 89788 soybean oil on health and nutrition, because of the lack of data on dietary exposure to refined bleached deodorised (RBD) oil from MON 87769 × MON 89788 soybean. It states *“In conclusion, the EFSA GMO Panel could not complete the food and feed safety assessment of soybean MON 87769 × MON 89788 because of the lack of an appropriate nutritional assessment”*.

In the stacked trait, four fatty acids ( $\gamma$ -linolenic acid, SA, trans- $\alpha$ -linolenic acid (trans-ALA), trans-SA) occurred at quantifiable levels in seed of soybean MON 87769 × MON 89788, but at levels below the limit of quantitation in soybean A3525. These major alterations in the fatty acid profile of the fat portion of seeds of soybean MON 87769 × MON 89788 were accompanied by altered levels of several other fatty acids (an increase in the proportion of palmitic acid, stearic acid, linolenic acid, arachidic acid and eicosenoic acid, and a decrease in the proportion of behenic acid and linoleic acid). The statistical analysis also revealed an increase in the protein content and a reduction in the carbohydrate content of seeds and a reduction in daidzein and genistein content of about 30%.

As observed for MON 87769, the modified fatty acid composition of soybean MON 87769 × MON 89788 seeds is also reflected in the composition of the RBD oil.

The nutritional content of the soybeans, and of oil derived from them, is clearly not (and is acknowledged not to be) “substantially equivalent” to conventional soybeans. In addition, the nutritional changes are complex and not limited to a single nutrient.

For MON 87769, the applicant cites published studies in humans and animals of the four fatty acids found in higher amounts in MON 87769 than in conventional soybean: SDA, GLA, 9c,12c,15t trans-ALA (18:3) and 6c,9c,12c,15t trans-SDA (Section 5.1.2.3 of EFSA’s Scientific Opinion on MON 87769). The opinion cites intervention studies on humans with various amounts of SDA ethyl esters and/or SDA-containing plant derived oils, and with SDA-enriched soybean oil for between 14 and 84 days and at doses ranging from 0.05 to 4.2 g SDA/day, stating no adverse effects were reported. However, such studies are wholly inadequate to assess long-term effects such as cancer risk. Similarly, several studies cited in which human diets were supplemented with GLA at doses from 1 to 5 g/day for periods of one to six months shed little light on the overall, long-term safety of the product for approval.

Studies on the reduced linoleic acid (LA) levels in soybean MON 87769 are not included in this literature review and nor are studies on the intended impact of the product on omega-3 levels. SDA is a normal intermediate in the formation of the long chain omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid [(C20:5 (n-3)] (EPA) and docosahexaenoic acid [(C22:6 (n-3)] (DHA). However, in humans, the conversion of ALA to SDA is slow. Direct consumption of SDA avoids this step in the biosynthesis and EFSA’s Scientific Opinion on this product states that the rationale for developing MON 87769 is that this may result in a more efficient synthesis of the higher chain-length PUFAs (EPA and DPA). There is some evidence of this from a study conducted by Monsanto and Southern Illinois University in rats<sup>11</sup> and a subsequent clinical trial of SDA soybean oil from biotechnology-derived soybean MON 87769 in humans.<sup>12</sup> However, the scientific literature includes evidence of potential harm to health from omega-3 fatty acids (increased prostate cancer risk), which have not been assessed.<sup>13,14,15</sup> Despite many claims to the contrary, there is no conclusive evidence of health benefit from increased omega-3.<sup>16,17,18,19</sup>

Animal studies cited in the Scientific Opinion for the stacked trait assessed toasted soybean meal derived from MON 87769 × MON 89788, but not the oil destined for human consumption.

For MON 87769, the applicant used information from the United Kingdom (UK) National Diet and Nutrition Survey (adults 19–64 years old) and the US FDA information on serving sizes to calculate the intake of SDA-rich soybean oil and SDA. A twenty-eight-day repeated dose toxicity study, a sub-chronic toxicity study, and a one generation reproductive toxicity study were also conducted with soybean oil in Sprague–Dawley rats.

It is widely recognised that human studies are needed to assess bioavailability of nutrients from nutrient-altered GM crops.<sup>20,21,22,23,24,25</sup> Monsanto has conducted a clinical trial of SDA soybean oil from biotechnology-derived soybean MON 87769 in humans (Lemke et al., 2010, cited in EFSA’s Scientific Opinion) but (despite the title of the paper) this does not address the safety of the nutritional changes.

For MON87769, the applicant focuses on the intended physiological consequence of consuming the soybeans i.e. enhanced synthesis of the long chain omega-3 polyunsaturated fatty acids (PUFAs) EPA) and DHA. The EFSA Opinion relies heavily on the fact that EFSA has set an adequate intake (AI)

level of 250 mg EPA + DHA/day for adults, based on considerations of cardiovascular health. This is inadequate for a number of reasons including: (i) the EFSA report which established the AI is out of date<sup>26</sup> and more recent studies must be included (e.g. studies suggesting increased prostate cancer risk as cited above); (ii) it does not consider population subgroups who may be particularly affected by changes in the fatty acid profile of their food (discussed further below); (iii) it requires an extrapolation, based on limited data, of the impacts of the product on EPA+DHA and ignores other nutritional changes (contrary to Codex Guidance) (iii) it is not applicable to GMO foods which require a full safety assessment under Regulation (EC) No. 1829/2003.

Further, in the dietary assessment for MON 87769, only average adult intakes are considered. Bioavailability studies in vulnerable subpopulations have not been included and persons with chronic diseases have also been neglected. For example, there are a number of monogenic genetic disorders, e.g. in the category of Fatty Acid Metabolism Disorders (MCAD, LCAD and SCAD deficiencies) in which medium-chain triglycerides (MCTs) can't be broken down and linoleic acid deficiency may occur.<sup>27</sup> The implications of the low linoleic acid levels observed in soybean MON 87769 and the stacked trait should have been considered for these vulnerable groups.

EFSA's Opinion for MON 87769 (Section 5.1.2.3 (c)) states that it is assumed that trans-SDA is mainly formed by trans-isomerisation of unsaturated fatty acids during the processing of the oil: but no specific studies have looked at the effects of consuming trans-SDA. Other products for human consumption including soybean milk, protein concentrates, flour, sprouts, baked or roasted soybeans, tofu and soybean sauce are not assessed for their fatty acid content or health impacts.

For the stacked trait, the applicant was asked to provide a dietary exposure assessment based on the compositional analysis of the RBD oil from soybean MON 87769 × MON 89788, taking into account different exposure scenarios, covering low and high consumer groups. However, the applicant did not provide this data. The EFSA GMO Panel therefore could not complete the assessment on the possible impact of soybean MON 87769 × MON 89788 oil on human health and nutrition. Because of the lack of data on dietary exposure, based on the compositional analysis of RBD oil from soybean MON 87769 × MON 89788, the EFSA GMO Panel could not complete an assessment on the possible impact of MON 87769 × MON 89788 soybean oil on human health and nutrition. Therefore, the EFSA GMO Panel is not in the position to conclude on the food safety of soybean MON 87769 × MON 89788. It follows that the application should be refused.

Based on the data provided, the EFSA GMO Panel concludes that feeding of full-fat soybean MON 87769 or inclusion of the oil derived from MON 87769 could alter the lipid content of animal tissues (Section 5.1.5.2 of the relevant Scientific Opinion). However, the Panel did not consider the nutritional impact from consuming products of animal origin derived from animals fed whole fat MON 87769 or its oil on consumers. In the case of the stacked trait, this assessment has also been omitted.

In summary, the lack of Guidance for the assessment of nutritionally-altered GM crops, and the lack of data on dietary exposure noted by EFSA, has resulted in an inadequate assessment process which fails to protect human health.

In the absence of a proper nutritional assessment, the application should be refused.

### **Others**

EFSA's Scientific assessment states that the single events MON 87769 (SDA soybean) and MON 89788 (glyphosate tolerance) were assessed previously and no concerns were identified for human

and animal health or environmental safety. The EFSA evaluation therefore focuses on the stacked events and issues related to: a) stability of the inserts, b) expression of the introduced genes and their products and c) potential synergistic or antagonistic effects resulting from the combination of the events. GeneWatch UK disagrees with this approach because:

(i) The SDA soybean should not have been approved for import, as detailed in: Request for a review of the authorisations for GM crops with altered oil content, GeneWatch UK and TestBiotech, May 2015;

(ii) The approval of the glyphosate tolerant trait also needs to be reviewed in the light of new evidence regarding the toxicity of glyphosate residues and the importance of testing the health impacts of the whole herbicide formulation, including surfactants.

Specifically, the MON 87769 (SDA soybean) authorisation should not have been granted because:

1. EFSA has initiated but not completed a process of developing guidance for the assessment of GM crops with significantly altered nutritional content. As well as being incomplete, this process has not been independent or transparent. In the absence of this guidance, approvals should not have been granted for nutritionally-altered GM crops.

2. The lack of guidance has led to inconsistent and inadequate risk assessment which fails to meet the requirements of the legislation.

3. Labelling and post-marketing monitoring proposals are also inadequate and inconsistent.

Further, the Panel itself notes in its Scientific Opinion on the stacked crop that it could not complete the food and feed safety assessment of soybean MON 87769 × MON 89788 because of the lack of an appropriate nutritional assessment.

The application should therefore be refused.

### **3. Environmental risk assessment**

### **4. Conclusions and recommendations**

EFSA could not complete the food and feed safety assessment of soybean MON 87769 × MON 89788 because of the lack of an appropriate nutritional assessment.

Further, as a full assessment on the possible health and nutritional impact of MON 87769 × MON 89788 soybean oil was not made, the EFSA GMO Panel was not in the position to comment on the post-market monitoring plan and labelling provided by the applicant, in accordance with Articles 13(2)(a) and 25(2)(c) of Regulation (EC) No 1829/2003.

More data is also required for the comparative assessment and for the toxicology assessment, as described above.

The application should therefore be refused.

### **5. Others**

The EFSA Scientific Opinion states that, as a full assessment on the possible health and nutritional impact of MON 87769 × MON 89788 soybean oil was not made, the EFSA GMO Panel is not in the position to comment on the post-market monitoring plan and labelling provided by the applicant, in accordance with Articles 13(2)(a) and 25(2)(c) of Regulation (EC) No 1829/2003.

It is not possible for post-market monitoring to fulfil its role if intakes of relevant nutrient levels throughout the EU have not been established in the application and if potential adverse health effects raised in the scientific literature have not been considered (see comments above). In particular, there is no proposed collection of information to allow the detection of indications on whether any (adverse) effect on health may be related to genetically modified food or feed consumption, or to collect data from particular age groups.

The application should therefore be refused.

## 6. Labelling proposal

Since the EFSA GMO Panel was not in the position to make a full assessment on possible health and nutritional impact of soybean MON 87769 × MON 89788, the need for a specific labelling in accordance with Articles 13(2) (a) and 25(2)(c) of Regulation (EC) No 1829/2003 was not considered. Neither did the EFSA GMO Panel consider methods of detection (including sampling and the identification of the specific transformation event in the food/feed and/or food/feed produced from it), which are matters related to risk management.

The application should therefore be refused.

To meet legal requirements the label should describe the altered composition in full, including all the new fatty acids (stearidonic acid (SDA), also known as octadecatetraenoic acid; alpha-linolenic acid; and two trans-fatty acids, 9c,12c,15t trans-ALA (18:3) and 6c,9c,12c,15t trans-SDA (C18:4)) and the reduction in linoleic acid (LA). Particular attention should be paid to the labelling needs of vulnerable groups.

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