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Assessment of genetically modified soybean MON 87705 × MON 87708 × MON 89788, for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2015-126)

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Abstract

Soybean MON 87705 × MON 87708 × MON 89788 (three-event stack soybean) was produced by conventional crossing to combine three single soybean events: MON 87705, MON 87708 and MON 89788. This combination is intended to alter the fatty acid profile in the seed (in particular increasing the levels of oleic acid) and tolerance to glyphosate-based and dicamba herbicides. The Genetically Modified Organisms Panel previously assessed the three single soybean events and did not identify safety concerns. No new data on the single soybean events, leading to modification of the original conclusions on their safety have been identified. The molecular characterisation, comparative analysis (agronomic, phenotypic and compositional characteristics) and the outcome of the toxicological, allergenicity and nutritional assessment indicate that the combination of the single soybean events and of the newly expressed proteins in the three-event stack soybean does not give rise to food and feed safety and nutritional concerns. In the case of accidental release of viable three-event stack soybean seeds into the environment, this would not raise environmental safety concerns. The post-market environmental monitoring plan and the reporting intervals are in line with the intended uses of soybean MON 87705 × MON 87708 × MON 89788. Considering the altered fatty acid profile of the three-event stack soybean, a proposal for post-market monitoring needs to be provided by the applicant. The GMO Panel notes that in the context of this application EFSA-GMO-NL-2015-126 the applicant did not provide a 90-day study on MON 87705 soybean in line with the applicable legal requirements. Therefore, the GMO Panel is not in the position to finalise the risk assessment of soybean MON 87705 × MON 87708 × MON 89788 under the current regulatory frame.

Keywords: GMO, soybean (*Glycine max*), MON 87705 × MON 87708 × MON 89788, herbicide tolerant and altered fatty acid profile, stack

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Summary

Following the submission under Regulation (EC) No 1829/2003 of application EFSA-GMO-NL-2015-126 from Monsanto Company (hereafter referred to as 'the applicant'), the Panel on Genetically Modified Organisms of the European Food Safety Authority (hereafter referred to as the 'GMO Panel') was asked to deliver a scientific opinion on genetically modified (GM) soybean MON 87705 × MON 87708 × MON 89788 (hereafter referred to as 'the three-event stack soybean'). The scope of application EFSA-GMO-NL-2015-126 is for the placing on the market of the three-event stack soybean for food and feed uses, import and processing.

The three-event stack soybean was produced by conventional crossing to combine three single soybean events: MON 87705 (producing dsRNAs downregulating endogenous FAD2 and FATB enzymes, and expressing the CP4 EPSPS protein); MON 87708 (expressing DMO) and MON 89788 (expressing CP4 EPSPS). This combination is intended to confer an altered fatty acid profile (increased oleic acid content), and tolerance to dicamba and to glyphosate containing herbicides.

The GMO Panel evaluated the three-event stack soybean with reference to the scope and appropriate principles described in its guidelines for the risk assessment of GM plants and derived food and feed, the environmental risk assessment of GM plants and the post-market environmental monitoring (PMEM) of GM plants. The GMO Panel considered the information available on the single soybean events, the three-event stack soybean, the scientific comments submitted by the Member States and the relevant scientific literature.

The single soybean events MON 87705, MON 87708 and MON 89788 were previously assessed by the European Food Safety Authority (EFSA) and no concerns on their safety were identified. No new safety issue was identified by updated bioinformatic analyses, nor reported by the applicant concerning the three single soybean events, since the publication of the respective scientific opinions. Consequently, the GMO Panel considers that its previous conclusions on the safety of the single soybean events remain valid.

For the three-event stack soybean, the risk assessment included the molecular characterisation of the inserted DNA and analysis of protein expression. An evaluation of the comparative analysis of agronomic/phenotypic and compositional characteristics was undertaken, and the safety of the newly expressed proteins, of the dsRNAs and the whole food and feed were assessed with respect to potential toxicity, allergenicity and nutritional characteristics. An evaluation of environmental impacts and the PMEM plan was also undertaken.

The molecular characterisation data establish that the events stacked in soybean MON 87705 × MON 87708 × MON 89788 have retained their integrity. Protein expression analysis showed that the levels of DMO in the different plant tissues are similar in the three-event stack soybean and the single event soybean MON 87708. As regards CP4 EPSPS, the results showed in general the expected higher levels in the three-event stack soybean. In addition, the provided data indicate that there is no impact of the FAD2-1A and FATB1-A dsRNAs on the expression levels of the newly expressed proteins. No indications of interactions that may affect the integrity of the events and the levels of the newly expressed proteins or dsRNAs in this three-event stack soybean were identified.

The GMO Panel considered the compositional, phenotypic and agronomic data supplied and the observed statistically significant differences between soybean MON 87705 × MON 87708 × MON 89788 and its comparator, taking into account the natural variability. No differences were identified that required further assessment for food/feed safety or environmental impact, except for changes in the fatty acid profile in seeds (palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), arachidic acid (C20:0), eicosenoic acid (C20:1), behenic acid (C22:0)) that are consistent with the intended trait, and changes in Gly m 3 and total fat levels.

The newly expressed proteins CP4 EPSPS and DMO and the dsRNAs and their deriving siRNAs present in soybean MON 87705 x MON 87708 × MON 89788 do not raise safety concerns for human and animal health. Interactions between the newly expressed proteins CP4 EPSPS and DMO raising food and feed safety concerns (in terms of toxicology, allergenicity and adjuvanticity) are not expected. There is no evidence that the genetic modification might change the overall allergenicity of the three-event stack soybean. Based on the outcome of the animal and human nutritional assessments, the consumption of soybean MON 87705 × MON 87708 × MON 89788 does not represent any nutritional concern, in the context of the scope of this application.

Considering the altered fatty acid profile of MON 87705 × MON 87708 × MON 89788 soybean, in accordance with Regulation (EC) No 1829/2003 and Regulation (EU) No 503/2013 a proposal for post-market monitoring (PMM) needs to be provided by the applicant. EFSA recommends a PMM plan

initially focused on the collection of import data to Europe of MON 87705 × MON 87708 × MON 89788 soybean and/or its products, in particular refined bleached deodorised (RBD) oil. Following the identification of imports, an updated nutritional assessment should be conducted in the case the available information on consumption (e.g. new dietary surveys, data from FAOSTAT database on amounts and type of vegetable oils consumed) differs from that used during the risk assessment. Likewise, the applicant should collect and provide any scientific information that might change the conclusions of the pre-market nutritional assessment.

For specific labelling, in accordance with Articles 13(2)(a) and 25(2)(c) of Regulation (EC) No 1829/2003, the applicant proposed that operators shall be required to label food and feed products containing, consisting of or produced from MON 87705 × MON 87708 × MON 89788 soybean with the words 'produced from genetically modified soybean with increased monounsaturated fat and reduced polyunsaturated fat'. The GMO Panel considers that this proposal is consistent with the composition of this three-event stack soybean.

Considering the combined soybean events and their potential interactions, the outcome of the agronomic and phenotypic analysis, the routes of exposure and limited exposure levels, the GMO Panel concludes that soybean MON 87705 × MON 87708 × MON 89788 would not raise safety concerns in the case of accidental release of viable GM soybean seeds into the environment.

Based on the relevant publications identified through the literature searches, the GMO Panel did not identify any safety issues pertaining to the uses of soybean MON 87705 × MON 87708 × MON 89788. In the context of PMEM, the applicant could further fine-tune future literature searches according to the GMO Panel recommendations.

The GMO Panel notes that in the context of this application EFSA-GMO-NL-2015-126 the applicant did not provide a 90-day study on MON 87705 soybean in line with the applicable legal requirements (i.e. no treatment with the intended herbicide was applied to MON 87705 soybean used to produce the test material). Therefore, the GMO Panel is not in the position to finalise the risk assessment soybean MON 87705 × MON 87708 × MON 89788 under the current regulatory frame.

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1. Introduction

The scope of application EFSA-GMO-NL-2015-126 is for food and feed uses, import and processing in the European Union (EU) of the genetically modified (GM) herbicide tolerant and altered fatty acid profile (increased oleic acid) soybean MON 87705 × MON 87708 × MON 89788 for food and feed uses, import and processing.

1.1. Background

On 16 September 2015, the European Food Safety Authority (EFSA) received from the Competent Authority of the Netherlands the application EFSA-GMO-NL-2015-126 for authorisation of soybean MON 87705 × MON 87708 × MON 89788 (Unique Identifiers MON-877Ø5-6 × MON-877Ø8-9 × MON-89788-1), submitted by Monsanto Company (hereafter referred to as 'the applicant') according to Regulation (EC) No 1829/2003[1].

Following receipt of application EFSA-GMO-NL-2015-126, EFSA informed the EU Member States (MS) and the European Commission (EC), and made the summary of the application available to the public on the EFSA website.[2]

EFSA checked the application for compliance with the relevant requirements of Regulation (EC) No 1829/2003 and Regulation (EU) No 503/2013[3], and, when needed, asked the applicant to supplement the initial application. On 12 February 2016, EFSA declared the application valid, and made the valid application available to the EU MS and EC.

From the validity date, EFSA and its scientific Panel on Genetically Modified Organisms (hereafter referred to as the 'GMO Panel') endeavoured to respect a time limit of six months to issue a scientific opinion on application EFSA-GMO-NL-2015-126. Such time limit was extended whenever EFSA and/or its GMO Panel requested supplementary information to the applicant. According to Regulation (EC) No 1829/2003, any supplementary information provided by the applicant during the risk assessment was made available to the EU MS and EC (for further details, see the section 'Documentation', below).

In accordance with Regulation (EC) No 1829/2003, EFSA consulted the nominated risk assessment bodies of EU MS, including national Competent Authorities within the meaning of Directive 2001/18/EC[4]. The EU MS had three months to make their opinion known on the application EFSA-GMO-NL-2015-126 as of date of validity.

1.2. Terms of Reference as provided by the requestor

According to Articles 6 and 18 of Regulation (EC) No 1829/2003, EFSA and its GMO Panel were requested to carry out a scientific risk assessment of soybean MON 87705 × MON 87708 × MON 89788 in the context of its scope as defined in application EFSA-GMO-NL-2015-126.

According to Regulation (EC) No 1829/2003, this scientific opinion is to be seen as the report requested under Articles 6(6) and 18(6) of that Regulation including the opinions of the nominated risk assessment bodies of EU MS.[5]

In addition to the present scientific opinion, EFSA was also asked to report on the particulars listed under Articles 6(5) and 18(5) of Regulation (EC) No 1829/2003.

The relevant information is made available in the EFSA Register of Questions including the information required under Annex II to the Cartagena Protocol; a labelling proposal; a Post-Market Environmental Monitoring (PMEM) plan as provided by the applicant; the method(s), validated by the Community reference laboratory, for detection, including sampling, identification of the transformation event in the food-feed and/or foods-feeds produced from it and the appropriate reference materials.[6]

[1] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. OJ L 268, 18.10.2003, p. 1–23.

[2] Available at the EFSA Register of Questions: http://registerofquestions.efsa.europa.eu/roqFrontend/login?0) querying the assigned Question number.

[3] Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L157, 8.6.2013, p. 1–48.

[4] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 12.3.2001, p. 1–38.

[5] Opinions of the nominated risk assessment bodies of EU MS can be found at the EFSA Register of Questions (http://registerofquestions.efsa.europa.eu/roqFrontend/login?0) querying the assigned Question number.

[6] http://registerofquestions.efsa.europa.eu/roqFrontend/login?0 querying the assigned Question number.

2. Data and methodologies

2.1. Data

The GMO Panel based its scientific risk assessment of soybean MON 87705 × MON 87708 × MON 89788 on the valid application EFSA-GMO-NL-2015-126, additional information provided by the applicant during the risk assessment, relevant scientific comments submitted by EU MS and relevant peer-reviewed scientific publications. In addition to this comprehensive information package, the GMO Panel also received unpublished studies submitted by the applicant in order to comply with the specific provisions of Regulation (EU) No 503/2013. A list of these additional unpublished studies is provided in Appendix B.

2.2. Methodologies

The GMO Panel conducted its assessment in line with the principles described in Regulation (EU) No 503/2013, its applicable guidelines (i.e. EFSA GMO Panel, 2010a,b, 2011a,b, 2015a), explanatory notes and statements (i.e. EFSA, 2017a, 2017b, 2019a) for the risk assessment of GM plants. During its risk assessment, the GMO Panel considered all additional unpublished studies as listed in Appendix B for potential effects on human and animal health and the environment.

For the assessment of 90-day animal feeding studies, the GMO Panel took into account the criteria included in the EFSA guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed (EFSA Scientific Committee, 2011) and the explanatory statement for its applicability (EFSA, 2014).

The GMO Panel also assessed the applicant's literature searches, which include a scoping review, in accordance with the recommendations on literature searching outlined in EFSA (2010, 2017a).

In the frame of the contracts OC/EFSA/GMO/2013/01 and OC/EFSA/GMO/2014/01, contractors performed preparatory work and delivered reports on the methods applied by the applicant in performing bioinformatic and statistical analyses, respectively.

3. Assessment

3.1. Introduction

Application EFSA-GMO-NL-2015-126 covers soybean MON 87705 × MON 87708 × MON 89788. This three-event stack soybean was produced by conventional crossing to combine the single soybean events MON 87705 (containing the soybean FAD2-1A/FATB1-A gene fragments downregulating endogenous FAD2 and FATB enzymes in seeds by RNA interference (RNAi), and expressing the 5-enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS protein)), MON 87708 (expressing dicamba mono-oxygenase (DMO protein)) and MON 89788 (expressing CP4 EPSPS protein). This combination is intended to confer an altered fatty acid profile (increased oleic acid content) and tolerance to glyphosate-based and dicamba herbicides.

The three single soybean events MON 87705, MON 87708 and MON 89788 have been previously assessed by the GMO Panel and no concerns for human or animal health or environmental safety were identified. In addition, the two-event stack soybean MON 87705 × MON 89788 and MON 87708 × MON 89788 have also already been assessed by the GMO Panel, and no concerns for human or animal health or environmental safety were identified (Table 1).

Table 1: Single event and two-event stack soybean already assessed by the GMO Panel

Event	Application or mandate	EFSA Scientific Opinion
MON 87705	EFSA-GMO-NL-2010-78 EFSA-Q-2013-00423	EFSA GMO Panel (2012) EFSA GMO Panel (2013a)
MON 87708	EFSA-GMO-NL-2011-93	EFSA GMO Panel (2013b)
MON 89788	EFSA-GMO-NL-2006-36	EFSA (2008)
MON 89788	EFSA-GMO-RX-011	EFSA GMO Panel (2018a)
MON 87705 × MON 89788	EFSA-GMO-NL-2011-100	EFSA GMO Panel (2015b)
MON 87708 × MON89788	EFSA-GMO-NL-2012-108	EFSA GMO Panel (2015c)

3.2. Updated information on the events

Since the publication of the respective GMO Panel Scientific Opinions (Table 1), no safety issues concerning the three single soybean events have been reported by the applicant.

Updated bioinformatic analyses for soybean events MON 87705, MON 87708 and MON 89788 confirm that no known endogenous genes were disrupted by any of the inserts.

Updated bioinformatic analyses of the amino acid sequence of the newly expressed proteins CP4 EPSPS and DMO confirm previous results indicating no significant similarities to toxins and allergens.[7] In addition, updated bioinformatics analyses of the newly created Open Reading Frames (ORFs) within the inserts or spanning the junctions between the insert and the flanking regions for events MON87705, MON 87708 and MON 89788 confirm previous results that do not indicate significant similarities to toxins or allergens for any of the events in soybean MON 87705 × MON 87708 × MON 89788 (Table 1).[7]

According to Regulation (EU) No 503/2013, when silencing approaches by RNAi have been used in GM plant applications, a bioinformatic analysis to identify potential 'off target' genes is required. The applicant has followed the recommendations by the GMO Panel for an RNAi off-target search in the three-stack soybean expressing the FAD2-1A and FATB1-A dsRNAs.[8]

Out of the few soybean transcript sequences that had regions matching to those siRNAs produced by the two dsRNAs only one had a perfect match for FATB1-A dsRNA. The remaining hits had matching regions with one to four mismatches. Some of these sequences presented matches for more than one potential siRNA. The applicant discussed these results, taking into account the predicted function of the proteins encoded by the mRNAs matching the siRNAs. The GMO Panel assessed this information and based on the number of hits, gene function and implications as regards the compositional and agronomic-phenotypic endpoints, concludes that there is no indication for an off-target effect of the dsRNA expression that would need further assessment.

In order to assess the possibility for horizontal gene transfer (HGT) by homologous recombination (HR), the applicant performed a sequence identity analysis for events MON 87705, MON 87708 and MON 89788 to microbial DNA. The likelihood and potential consequences of plant-to-bacteria gene transfer are described in Section 3.7.2.1.

Based on the above information, the GMO Panel considers that its previous conclusions on the safety of the single soybean events remain valid.

3.3. Systematic literature review[9]

The GMO Panel assessed the applicant's literature searches on soybean MON 87705 × MON 87708 × MON 89788, which include a scoping review, according to the guidelines given in EFSA (2010, 2017a).

A systematic review as referred to in Regulation (EU) No 503/2013 has not been provided in support to the risk assessment of the application EFSA-GMO-NL-2015-126. Based on the outcome of the scoping review, the GMO Panel agrees that there is limited value of undertaking a systematic review for soybean MON 87705 × MON 87708 × MON 89788 at present.

Although the overall quality of the performed literature searches is acceptable, the GMO Panel considers that future searches on soybean MON 87705 × MON 87708 × MON 89788 could be improved. The GMO Panel, therefore, recommends the applicant to:

- ensure that enough search term variation is used (covering possible synonyms, related terms, acronyms, spelling variants, old and new terminology, brand and generic names, lay and scientific terminology, common typos, translation issues);
- ensure that enough truncation is used and used consistently.

None of the relevant publications identified through the literature searches reported information pointing to safety issues associated with soybean MON 87705 × MON 87708 × MON 89788 relevant to the scope of this application.

[7] Additional information: 6/10/2017, 4/7/2019.
[8] Annex II of the Minutes of the 118th GMO Panel plenary meeting (2017).
[9] Dossier: Part II – Section 7; Additional information: 23/3/2016, 6/10/2017, 22/1/2018, 6/4/2018, 24/4/2018, 4/7/2019, 24/1/2020 and 18/3/2020.

3.4. Molecular characterisation

In line with the requirements laid down by Regulation (EU) No 503/2013, the possible impact of the combination of the events on the integrity of the events, the expression levels of the newly expressed proteins or the biological functions conferred by the individual inserts are considered below.

3.4.1. Genetic elements and their biological function[10]

The three-event stack soybean was obtained by conventional crossing of soybean events MON 87705, MON 87708 and MON 89788. The structure of the inserts introduced into soybean events MON 87705, MON 87708 and MON 89788 is described in detail in the respective GMO Panel Scientific Opinions (Table 1), and no new genetic modifications were involved. Genetic elements in the expression cassettes of the single soybean events are summarised in Table 2. Intended effects of the inserts in the three-event stack soybean are summarised in Table 3.

Based on the known biological function (Table 3) of the newly expressed proteins or dsRNAs, no foreseen interactions at the biological level are expected.

Table 2: Genetic elements in the expression cassettes of the events stacked in the three-event stack soybean MON 87705 × MON 87708 × MON 89788

Event	Promoter	5′ UTR	Transit peptide	Coding region	Terminator
MON 87705	7Sα′ from the *SphasI* gene (*Glycine max*)* *FMV (Figwort Mosaic Virus)/ Tsf1* (*Arabidopsis thaliana*)	*7Sα′* from the *SphasI* gene (*G. max*) *Tsf1* (*A. thaliana*)	– CTP2 (*A. thaliana*)	*FAD2-1A, FATB1-A* (*G. max*) CP4 epsps (*Agrobacterium tumefaciens sp.* strain CP4)	3′ UTR of the H6 gene from *Gossypium barbadense* E9 (*Pisum sativum*)
MON 87708	Full-length transcript promoter from *Peanut chlorotic streak virus*	5′ UTR from Tobacco etch virus	*RbcS* (*Pisum sativum*)	*dmo* (*S. maltophilia*)	3′ UTR of *RbcS2* (*P. sativum*)
MON 89788	35S promoter from *Figwort mosaic virus* and promoter from the Tsf1 gene of *Arabidopsis thaliana*	5′ UTR and intron from *Tsf1* gene of *A. thaliana*	*ShkG* (*A. thaliana*)	CP4 *epsps* (*A. tumefaciens* strain CP4)	3′ UTR of *RbcS2* (*P. sativum*)

*: Source of genetic information.
(–): When no element was specifically introduced to optimise expression.

Table 3: Characteristics and intended effects of the events stacked in the three-event stack soybean MON 87705 × MON 87708 × MON 89788

Event	Protein/ dsRNA	Donor organism and biological function	Intended effects in GM plant
MON 87705	CP4 EPSPS	Based on a gene from *Agrobacterium* sp. strain CP4. 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) is an enzyme involved in the shikimic acid pathway for aromatic amino acid biosynthesis in plants and microorganisms (Herrmann, 1995)	Event MON 87705 expresses the bacterial CP4 EPSPS protein which confers tolerance to glyphosate-containing herbicides as it has lower affinity towards glyphosate than the plant endogenous enzyme

[10] Dossier: Part II – Section 1.2.2.2.

Event	Protein/ dsRNA	Donor organism and biological function	Intended effects in GM plant
	FAD2-1A/ FATB1-A	Based on genes from *Glycine max* FAD2-1A Δ-12 desaturase FATB1-A palmitoyl acyl carrier protein thioesterase. Both proteins function in fatty acid biosynthesis (Fillatti et al., 2003)	The sense and antisense segments of the FAD2-1A and FATB1-A single suppression cassette express RNA with inverted repeats of the endogenous soybean gene segments under a seed-specific promoter. This transcript produces double-stranded RNA giving rise to deriving small silencing RNAs (siRNAs) responsible of inhibiting the expression of the endogenous constitutive soybean FAD2-1A and FATB1-A transcripts, by RNAi. The intended trait achieved by RNAi is demonstrated by the altered fatty acid profile of the GM soybean seeds
MON 87708	DMO	Based on a gene from *Stenotrophomonas maltophilia* strain DI-6 Dicamba mono-oxygenase (DMO) is an enzyme that catalyses the demethylation of dicamba to the non-herbicidal compound 3,6-dichlorosalicylic acid and formaldehyde (Herman et al., 2005)	Event MON 87708 expresses DMO protein which degrades the herbicide dicamba and thus confers tolerance to this herbicide
MON 89788	CP4 EPSPS	Based on a gene from *Agrobacterium* sp. strain CP4. 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) is an enzyme involved in the shikimic acid pathway for aromatic amino acid biosynthesis in plants and microorganisms (Herrmann, 1995)	Event MON 89788 expresses the bacterial CP4 EPSPS protein which confers tolerance to glyphosate-containing herbicides as it has lower affinity towards glyphosate than the plant endogenous enzyme

3.4.2. Integrity of the events in the three-event stack soybean[11]

The genetic stability of the inserted DNA over multiple generations in the single soybean events MON 87705, MON 87708 and MON 89788 was demonstrated previously (see Table 1). Integrity of these events in soybean MON 87705 × MON 87708 × MON 89788 was demonstrated by polymerase chain reaction (PCR) and sequence analysis that showed that the sequences of the events (inserts and their flanking regions) in the three-event stack soybean are identical to the sequences originally reported for the three single events, thus confirming that the integrity of these events was maintained in the three-event stack soybean.

3.4.3. Information on the expression of the inserts[12]

CP4 EPSPS and DMO protein levels were analysed by enzyme-linked immunosorbent assay (ELISA) in material harvested from field trials at five locations in Argentina in 2013–2014. Samples analysed included leaves (V3-V4, V6-V7, R2-R3, R6), roots (R6), forage (R6-R7) and seeds (R8) treated with dicamba and glyphosate. In order to assess the changes in protein expression levels which may result from potential interactions between the events, protein levels were determined for the three-event stack and the corresponding single events in different parts of the plant.

The levels of the DMO protein in the three-event stack soybean and the corresponding single soybean event MON 87708 were similar in all tissues. Differences in CP4 EPSPS protein levels were expected because of the combination of soybean events MON 87705 and MON 89788 both producing CP4 EPSPS in the three-event stack soybean (Appendix A). Therefore, based on all the molecular elements present in the three-event stack soybean, there is no indication of an interaction that may affect the levels of the newly expressed proteins or dsRNAs in this stack.

3.4.4. Conclusions of the molecular characterisation

The molecular data establish that the events stacked in soybean MON 87705 × MON 87708 × MON 89788 have retained their integrity. Protein expression analysis showed that the levels

[11] Dossier: Part II – Section 1.2.2.4.
[12] Dossier: Part II – Section 1.2.2.3.

of DMO are similar in the three-event stack and the single event soybean MON 87708. As regards CP4 EPSPS, the results showed in general the expected higher levels in the three-event stack soybean compared to the single soybean events MON 87705 and MON 89788. Therefore, there is no indication of interaction that may affect the integrity of the events or the levels of the newly expressed proteins or dsRNAs in this three-event stack soybean.

Based on the known biological function of the newly expressed proteins and dsRNA, no foreseen interactions at the biological level are expected.

3.5. Comparative analysis[13]

3.5.1. Overview of studies conducted for the comparative analysis

Application EFSA-GMO-NL-2015-126 presents data on agronomic and phenotypic characteristics as well as on forage and seed composition of soybean MON 87705 × MON 87708 × MON 89788 (Table 4). The comparative analysis was assessed using the methodology recommended by the EFSA GMO Panel (2011a) and the applicable sections of the guidance on agronomic and phenotypic characterisation of the GM plants (EFSA GMO Panel, 2015a).

Table 4: Overview of the comparative analysis studies to characterise the three-event stack soybean provided in application EFSA-GMO-NL-2015-126

Study focus	Study details	Comparator	Commercial non-GM soybean reference varieties
Agronomic and phenotypic analysis	Field study, Argentina, 2013/2014, eight sites[(a)]	A3525	18[(b)]
Compositional analysis			

GM: Genetically modified.

(a): The field trials were located in Berdier (Buenos Aires), Chacabuco (Buenos Aires), Galvez (Santa Fe), Ines Indart (Buenos Aires), Los Indios (Buenos Aires), San Pedro (Buenos Aires), Tacuari (Buenos Aires), Urquiza (Buenos Aires).

(b): The commercial non–GM soybean reference varieties used in the field trials, with their corresponding maturity group indicated in brackets, were Crows C2804 (2.8), Stine 3300-0 (3.3), Lewis 372 (3.7), DWIGHT (2.9), Stewart SB3454 (3.4), Hoffman HS387 (3.8), Wilken 3316 (3.1), eMerge 348TC (3.4), Maverick (3.8), C3211N (3.2), FS 3591 (3.5), Williams 82 (3.9), A3244 (3.2), Garst 3585N (3.5), Hoffman H419 (4.1), NE3202 (3.2), Midland 363 (3.6), Gateway 427 (4.2).

3.5.2. Experimental field trial design and statistical analysis

At each field trial site, the following materials were grown: soybean MON 87705 × MON 87708 × MON 89788, a non-GM comparator (soybean A3525) and four non-GM soybean reference varieties (hereafter 'non–GM reference varieties'), all treated with conventional herbicides management regimes; and soybean MON 87705 × MON 87708 × MON 89788 exposed to the intended glyphosate- and dicamba-containing herbicides in addition to the conventional herbicides.

The agronomic/phenotypic and compositional data were analysed as specified by the EFSA GMO Panel (2010b, 2011a,b). This includes, for each of the two treatments of the three-event stack soybean, the application of a difference test (between the GM soybean and the comparator) and an equivalence test (between the GM soybean and the set of non-GM soybean reference varieties).[14] The results of the equivalence test are categorised into four possible outcomes (I–IV, ranging from equivalence to non-equivalence).[15]

3.5.3. Suitability of selected test materials

3.5.3.1. Selection of the GM soybean line and comparator

To obtain the three-event stack GM soybean, the single events MON 87708 and MON 89788 were combined by conventional crossing in the non-GM soybean variety A3525. Soybean

[13] Dossier: Part II – Section 1.3; additional information: 3/6/2016 and 8/8/2016.

[14] The purpose of the test of equivalence is to evaluate the estimated mean values for the stack GM crop taking into account natural variability as defined by a set of commercial non-GM soybean reference varieties with a history of safe use for consumption as food or feed.

[15] In detail, the four outcomes are: category I (indicating full equivalence to the non-GM reference varieties); category II (equivalence is more likely than non-equivalence); category III (non-equivalence is more likely than equivalence); and category IV (indicating non-equivalence).

MON 87708 × MON 89788 was then crossed with GM soybean MON 87705 before being stabilised in soybean variety A3525.

The comparator used in the field trials is the non-GM soybean variety A3525, which has a genetic background similar to that of soybean MON 87705 × MON 87708 × MON 89788 (as documented by the pedigree), and is therefore considered a suitable non-GM comparator.

Both the three-event stack soybean and its non-GM comparator belong to maturity group 3.5, which is considered appropriate for growing in environments across Argentina, where the comparative field trials were conducted.

3.5.3.2. Selection of commercial non-GM reference varieties

Eighteen non-GM soybean reference varieties with maturity groups ranging from 2.8 to 4.2 were selected by the applicant and at each field trial site four of them were tested (Table 4). On the basis of the information provided and on relative maturity classes, the GMO Panel considers the selected non-GM reference varieties appropriate for the comparative analysis.

3.5.3.3. Seed production and quality

Seeds of the three-event stack soybean and of the non-GM comparator were produced, harvested and stored under similar conditions, before being sown in the field trials. The seed lots were verified for their purity via event specific quantitative PCR analysis. The GMO Panel considers that the starting seed used as test material in the agronomic, phenotypic and compositional studies was of acceptable quality.

3.5.3.4. Conclusion on suitability

The GMO Panel is of the opinion that the three-event stack soybean, the non–GM comparator and the non-GM reference varieties were properly selected and of adequate quality. Therefore, the test materials are considered suitable for the comparative analysis.

3.5.4. Representativeness of the receiving environments

The GMO Panel required further information on the representativeness of the selected field trial sites (EFSA GMO Panel, 2015a) due to the potential that they do not capture the variability that may exist across potential receiving environments for the commercial cultivation of this GM soybean.

3.5.4.1. Selection of field trial sites

The selected field trial sites were located in the major commercial soybean-growing regions of Argentina, covering a limited geographical range. The soil characteristics of the selected fields correspond to optimal and near-optimal conditions[16] for soybean cultivation (Sys et al., 1993).

3.5.4.2. Meteorological conditions

Maximum and minimum mean temperatures and sum of precipitations were provided on a monthly basis. No exceptional weather conditions were reported at any of the selected field trial sites. The GMO Panel considers that the meteorological data set falls within the range of climatic conditions normally occurring at these sites.

3.5.4.3. Management practices

The field trials included plots containing the three-event stack soybean, plots with the non-GM comparator and plots with non-GM reference varieties, mostly managed according to local agricultural practices. In addition, the field trials included plots containing the three-event stack soybean managed following the same agricultural practices, plus exposed to the intended herbicides. A glyphosate-containing herbicide was applied at V2-R1 stage and a dicamba-containing herbicide was applied at V6–R2. At some field trial sites, planting was done later than usual, resulting in a shorter growing cycle. However, the GMO Panel considers that the management practices including sowing, harvesting and application of plant protection products were acceptable for the field trials.

[16] Soil types of the field trials were clay loam, silty clay loam, loam and silt loam; soil organic matter ranged from 2.6% to 4.3%; soil pH ranged from 6.0 to 6.5.

3.5.4.4. Conclusion on representativeness

On the basis of the additional information provided by the applicant, the GMO Panel concludes that the geographical locations, soil characteristics, meteorological conditions of the field trial sites and the management practices applied are typical for receiving environments where the test materials could be grown.

3.5.5. Agronomic and phenotypic analysis

Nine agronomic/phenotypic endpoints[17] as well as information on abiotic stressors, disease incidence and arthropod damage were evaluated in the field trials (see Table 4). The statistical analysis was applied to the nine endpoints, with the following results:

- For the three-event stack soybean treated with conventional herbicides, statistically significant differences with the non-GM comparator were identified for four endpoints (days to 50% flowering, seed moisture, 100 seed weight and yield), which fell under equivalence category I.
- For the three-event stack soybean treated with the intended herbicides, statistically significant differences with the non-GM comparator were identified for six endpoints (early stand count, days to 50% flowering, pod shattering, final stand count, seed moisture and 100 seed weight), which fell under equivalence category I.

3.5.6. Compositional analysis

Soybean forage and seeds harvested from the field trials located in Argentina in 2013/2014 (Table 4) were analysed for 74 constituents (7 in forage and 67 in seeds), including the key constituents recommended by the OECD (OECD, 2012). For 14 fatty acids in seeds, more than half of the observations were below the limit of quantification and were excluded from the statistical analysis.[18] The fatty acid profile was not analysed in forage since the FAD2-1A/ FATB1-A single suppression cassette leading to the altered fatty acid profile is under the regulation of a seed-specific promoter (Section 3.1).

The statistical analysis was applied to a total of 60 constituents (7 in forage[19] and 53 in seed,[20] of which eight fatty acids). A summary of the outcome of the test of difference and the test of equivalence is presented in Table 5.

- For the three-event stack soybean not treated with the intended herbicides, statistically significant differences with the non-GM comparator were identified for 35 endpoints (five in forage and 30 in seeds). Among them, a total of eight endpoints in seeds fell under equivalence category III/IV: arachidic acid (C20:0), behenic acid (C22:0), eicosenoic acid (C21:0), linoleic acid (C18:2), oleic acid (C18:1), palmitic acid (C16:0), stearic acid (C18:0) and total fat.
- For soybean treated with the intended herbicides, the test of difference identified statistically significant differences with the non-GM comparator for 33 endpoints (five in forage and 28 in seeds). Same seed endpoints as above were identified as equivalence category III/IV together with Gly m 3 (cat III).

[17] Early stand count, days to 50% flowering, plant lodging, pod shattering, plant height, final stand count, seed moisture, 100 seed weight and yield.

[18] Caprylic acid (8:0), capric acid (10:0), lauric acid (12:0), myristic acid (14:0), myristoleic acid (14:1), pentadecanoic acid (15:0), pentadecenoic acid (15:1), palmitoleic acid (16:1), heptadecanoic acid (17:0), heptadecenoic acid (17:1), γ-linolenic acid (18:3), eicosadienoic acid (20:2), eicosatrienoic acid (20:3) and arachidonic acid (20:4).

[19] Ash, moisture, total fat, carbohydrates by calculation, protein, acid detergent fibre (ADF) and neutral detergent fibre (NDF).

[20] Ash, moisture, carbohydrates by calculation, total fat, protein, ADF, NDF, palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), linolenic acid (C18:3), arachidic acid (C20:0), eicosenoic acid (C21:0), behenic acid (C22:0), calcium, phosphorus, α-tocopherol, phylloquinone, alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine valine, phytic acid, lectin, raffinose, stachyose, genistein, glycitein, daidzein, trypsin inhibitor, Gly m 1, Gly m 3, Gly m 4, Gly m 5 (β-conglycinin), Gly m 6 (glycinin), Gly m Bd 28k, Gly m Bd 30k, 2S albumin.

Table 5: Outcome of the comparative compositional analysis in forage and seeds of soybean MON 87705 × MON 87708 × MON 89788. The table shows the number of endpoints in each category

		Test of difference[a]			
		Not treated[c]		Treated[c]	
		Not different	Significantly different	Not different	Significantly different
Test of equivalence[b]	Category I/II	25	27[d]	27	24[d]
	Category III/IV	–	8[e]	–	9[e]
	Total endpoints	60		60	

(a): Comparison between soybean MON 87705 × MON 87708 × MON 89788 and the non-GM comparator.
(b): Four different outcomes: category I (indicating full equivalence to the non-GM reference varieties); category II (equivalence is more likely than non-equivalence); category III (non-equivalence is more likely than equivalence); and category IV (indicating non-equivalence).
(c): Not treated/treated with the intended glyphosate and dicamba containing herbicides.
(d): Endpoints with significant differences between the three-event stack soybean and the non-GM comparator and falling in equivalence category I-II. In forage, not treated only: ash. Treated only: moisture. Both treated and not treated: ADF, carbohydrates, NDF, protein. In seeds, not treated only: Gly m 1, Gly m 3, Gly m 4, methionine, tyrosine and glycitein. Treated only: Gly m Bd28k and phenylalanine, NDF. Both treated and not treated: calcium, phosphorus, 2S albumin, cystine, lysine, threonine, raffinose, lectin, stachyose, trypsin inhibitor, linolenic acid (C18:3), ADF, daidzein, genistein, phylloquinone and α-tocopherol.
(e): Endpoints with significant differences between the three-event stack soybean and the non-GM comparator and falling in equivalence category III-IV. In seeds, treated only: Gly m 3. Both treated and not treated: palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), arachidic acid (C20:0), eicosenoic acid (C21:0), behenic acid (C22:0) and total fat. Quantitative results for these endpoints are reported in Table 6.

The GMO Panel assessed all the significant differences between the three-event stack soybean and the non-GM comparator, taking into account the potential impact on plant metabolism and the natural variability observed for the set of non-GM reference varieties. Quantitative results for the endpoints showing significant differences between the three-event stack soybean and the non-GM comparator and falling under equivalence category III/IV are given in Table 6.

Table 6: Quantitative results (estimated means and equivalence limits) for endpoints in seed with significant differences between soybean MON 87705 × MON 87708 × MON 89788 and the non-GM comparator and falling under equivalence category III/IV (see Table 5)

	Soybean MON 87705 × MON 87708 × MON 89788		Non-GM Comparator	Non-GM reference varieties	
	Not treated[a]	Treated[a]		Mean	Equivalence limits
Saturated fatty acids (% FA)					
Palmitic acid (C16:0)	2.66*	2.65*	11.60	10.8	(9.60, 11.94)
Stearic acid (18:0)	3.35*	3.37*	4.52	4.62	(3.79, 5.44)
Arachidic acid (C20:0)	0.27*	0.28*	0.33	0.34	(0.28, 0.40)
Behenic acid (C22:0)	0.26*	0.26*	0.28	0.325	(0.29, 0.36)
Mono-unsaturated fatty acids (% FA)					
Oleic acid (C18:1)	67.36*	67.73*	18.98	20.1	(17.63, 22.64)
Eicosenoic acid (C20:1)	0.27*	0.28*	0.13	0.16	(0.13, 0.19)
n-6 poly-unsaturated fatty acids (% FA)					
Linoleic acid (C18:2)	16.79*	16.46*	54.57	54.7	(52.50, 56.83)
Compound other than fatty acids					
Total fat (% DM)	16.60*	16.51*	16.89[b]	19.2	(17.58, 20.89)
Gly m 3 (μg/g FW)	1.52*	1.46*	2.15	3.24	(1.51, 4.96)

For the GM soybean, significantly different values are marked with an asterisk, while the outcomes of the test of equivalence are differentiated by greyscale backgrounds. Light and dark grey backgrounds correspond to equivalence category III and IV, respectively. A white background is used for equivalence category I/II.
DM = dry matter; FW = fresh weight; % FA = percentage total fatty acids.
(a): Not treated: treated only with conventional herbicides. Treated: treated with glyphosate- and dicamba-containing herbicides.
(b): Mean value for total fat in the non-GM comparator was out of the equivalence limits.

3.5.7. Conclusions of the comparative analysis

Taking into account the natural variability observed for the set of non-GM reference varieties, the GMO Panel concludes the following:

- None of the differences identified in the agronomic and phenotypic characteristics tested between soybean MON 87705 × MON 87708 × MON 89788 and the non-GM comparator needs further assessment regarding their potential environmental impact.
- The changes in the fatty acid profile in seeds (palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), arachidic acid (C20:0), eicosenoic acid (C20:1), behenic acid (C22:0)) are consistent with the intended trait and assessed in Section 3.6.6. In addition, compositional differences between soybean MON 87705 × MON 87708 × MON 89788 and the non-GM comparator were also identified for Gly m 3 and total fat and are further assessed in Sections 3.6.4 and 3.6.6, respectively.

3.6. Food and feed safety assessment

3.6.1. Effects of processing[21]

Soybean MON 87705 × MON 87708 × MON 89788 will undergo existing production processes used for conventional soybean. Based on this, the characteristic of the intended trait and the outcome of the comparative assessment, processing of the three-event stack soybean into food and feed products is not expected to result in products being different from those of conventional non-GM soybean varieties, except for the intended changes in fatty acid composition and the newly expressed proteins DMO and CP4 EPSPS.

Among the processed commodities produced from the three-event stack soybean, additional information was provided on the fatty acid composition of refined bleached deodorised (RBD) oil. As observed for MON 87705 and MON 87705 × MON 89788, the altered fatty acid composition of the three-event stack soybean seeds is also reflected in the composition of the RBD oil.

The relatively high content in oleic acid and the relatively low content in linoleic acid in the RBD oil extracted from the seeds of the three-event stack soybean is expected to result in an oil with higher oxidative stability than the conventional soybean oil. This allows the use of this RBD oil in many different food product applications (shortenings, bakery, deep frying) without the need of undergoing partial hydrogenation, a process used to increase hardness and to stabilise fats but that can give rise to trans-fatty acids which are linked to an increase in the risk of coronary heart disease (EFSA NDA Panel, 2010). RBD oil from the three-event stack soybean possesses a particular fatty acid profile that is more similar to other types of vegetable oil (e.g. olive oil) than conventional soybean. Therefore, the production of this specialty RBD oil (as described for the single and the double stack, Table 1) is expected to be kept separated from production of oil from conventional soybean varieties.

3.6.1.1. Influence of Temperature and pH on newly expressed proteins[22]

The effects of temperature and pH on proteins CP4 EPSPS and DMO newly expressed in this three-event stack soybean have been previously evaluated by the GMO Panel (Table 1).

3.6.2. Toxicology[23]

3.6.2.1. Testing of newly expressed proteins

Two proteins (CP4 EPSPS and DMO) are newly expressed in soybean MON 87705 × MON 87708 × MON 89788 (Section 3.4.1). The GMO Panel has previously assessed these proteins in the context of the single soybean events and of the two-event stack soybean MON 87705 × MON 89788 and MON 87708 × MON 89788 (Table 1), and no safety concerns were identified for humans and animals. The GMO Panel is not aware of any other new information that would change its previous conclusions on the safety of these proteins.

The potential for a functional interaction between the proteins newly expressed in the three-event stack soybean was previously assessed by the GMO Panel (EFSA GMO Panel, 2015b,c) with regard to human and animal health. The CP4 EPSPS and DMO proteins are enzymes that catalyse distinct

[21] Dossier: Part II – Section 1.3.6 and additional information: 16/12/2019.
[22] Dossier: Part II – Section 1.4.1.3.
[23] Dossier: Part II – Section 1.4.

biochemical reactions and act on unrelated substrates in the plant with high substrate specificity. On the basis of the known biological function of the individual newly expressed proteins (Table 3), there is currently no expectation for their possible interactions relevant to the food and feed safety of the three-event stack soybean.

In vitro protein degradation studies on CP4 EPSPS and DMO proteins have been previously evaluated by the GMO Panel (Table 1) and no indications of safety concerns were identified.

The GMO Panel concludes that there are no safety concerns to human and animal health related to the proteins CP4 EPSPS and DMO newly expressed in soybean MON 87705 × MON 87708 × MON 89788.

3.6.2.2. Testing of new constituents other than proteins

The dsRNAs produced by the FAD2-1A/FATB1-A suppression cassette and its deriving siRNAs present in soybean MON 87705 × MON 87708 × MON 89788 are designed to suppress endogenous soybean *FATB* and *FAD2* genes (Section 3.1 and Table 3). The same construct was assessed by the GMO Panel in the context of the single soybean event MON 87705 and of the two-event stack soybean MON 87705 × MON 89788 (Table 1) and no safety concerns were identified. The GMO Panel considered the potential of dsRNAs and deriving siRNAs to exert any biological effects once ingested by humans and animals taking into account recent information (EFSA GMO Panel, 2018b; Dávalos et al., 2019). The GMO Panel confirms its previous conclusions on dsRNAs and its deriving siRNAs present in soybean MON 87705 × MON 87708 × MON 89788 and considers that no toxicological studies are necessary on these constituents.

3.6.2.3. Information on altered levels of food and feed constituents

The compositional analysis showed that the levels of fatty acids (palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), arachidic acid (C20:0), eicosenoic acid (C20:1), behenic acid (C22:0)), total fat and Gly m 3 were significantly different in seeds of MON 87705 × MON 87708 × MON 89788 soybean as compared to its conventional counterpart, and showed a lack of equivalence with the set of non-GM reference varieties (see Section 3.5.6).

The GMO Panel took into account the biological characteristics and functions of these compounds, and the available literature. The GMO Panel considers that at the current status of knowledge, the information available is not raising toxicological concerns. Further information on the safety of these soybean constituents is provided in Sections 3.6.4 and 3.6.5.

3.6.2.4. Testing of the whole genetically modified food and feed

Based on the outcome of the molecular characterisation assessment, comparative analysis and toxicological assessment, no indication of findings relevant to food/feed safety related to the stability and expression of the inserts or to interaction between the transformation events, and no modifications of toxicological concern in the composition of the soybean have been identified (see Sections 3.4.4, 3.5.7 and 3.6.2). Therefore, animal studies on food/feed derived from the three-event stack soybean are not necessary (EFSA GMO Panel, 2011a).

In accordance to Regulation (EU) No 503/2013, the applicant provided a 90-day oral repeated-dose toxicity study in rats on whole food and feed from each of the single soybean event MON 87705, MON 87708 and MON 89788. The three studies had already been provided in the context of the single-event applications and assessed by the GMO Panel; no adverse effects related to the administration of the respective GM diets had been identified (Table 1).

In order to fulfil the requirements of Regulation (EU) No 503/2013 for the three-event stack soybean, the GMO Panel asked the applicant to provide additional information for each of the studies on single event soybean.[24] The additional information provided by the applicant on MON 87708 and MON 89788 had been previously assessed by the GMO Panel in the context of another application under Regulation (EU) 503/2013, and allowed to conclude that these are in line with the legal requirements and that there are no indications of adverse effects related to the 90-day administration to rats of diets including defatted toasted meal from soybean MON 87708 and MON 89788 (EFSA GMO Panel, 2019a, 2019b). As regards the study on MON 87705, the applicant confirmed that the study was conducted using a test material not treated with the intended herbicide (glyphosate), claiming that the *cp4epsps* gene introduced in the single soybean event MON 87705 was intended to be used

[24] The following clarifications were requested: treatment of the test material with the intended herbicide glyphosate and missing histopathology (MON 87705); diet homogeneity and missing histopathology (MON 87708) and selection of the dose level (MON 89788).

as a selectable marker only. The applicant did not provide a new study with intended herbicide-treated test material. The GMO Panel highlights that the risk assessment of the single event soybean MON 87705 was conducted taking into account glyphosate tolerance (EFSA GMO Panel, 2012). Therefore, the GMO Panel notes that the study on MON 87705 in the context of the assessment of MON 87705 × MON 87708 × MON 89788 is not in line with Regulation (EU) No 503/2013[25].

3.6.3. Allergenicity

For the allergenicity assessment, a weight-of-evidence approach was followed, taking into account all the information obtained on the newly expressed proteins, as no single piece of information or experimental method yields sufficient evidence to predict allergenicity (Codex Alimentarius, 2009; EFSA GMO Panel, 2011a; Commission Regulation (EU) No 503/2013). In addition, when known functional aspects of the newly expressed protein or structural similarity to known adjuvants may indicate an adjuvant activity, the possible role of these proteins as adjuvants is considered. When newly expressed proteins with a potential adjuvant activity are expressed together, possible interactions increasing adjuvanticity and impacting the allergenicity of the GM crop are assessed. Furthermore, an assessment of specific newly expressed proteins in relation to their potential to cause coeliac disease was also performed (EFSA GMO Panel, 2017).

3.6.3.1. Assessment of allergenicity of the newly expressed proteins[26]

The GMO Panel has previously evaluated the safety of CP4 EPSPS and DMO proteins individually, and no concerns on allergenicity were identified in the context of the applications assessed (Table 1). No new information on allergenicity of these proteins that might change the previous conclusions of the GMO Panel has become available. Based on the current knowledge, and as none of the newly expressed proteins showed allergenicity, no reasons for concerns regarding the simultaneous presence of these newly expressed proteins in the three-event stack soybean affecting their allergenicity are expected.

In addition, no information available on the structure or function of the newly expressed CP4 EPSPS and/or DMO proteins would suggest an adjuvant effect of these proteins in the three-event stack soybean, resulting in or increasing an eventual immunoglobulin E (IgE) response to a bystander protein.

The applicant provided spontaneous information on the safety of the CP4 EPSPS and DMO proteins regarding their potential to cause a coeliac disease response.[27,28] For such assessment, the applicant followed the principles described in the EFSA GMO Panel guidance document (EFSA GMO Panel, 2017). The assessment of the CP4 EPSPS and DMO proteins identified no perfect or relevant partial matches with known coeliac disease peptide sequences. Therefore, no indications of safety concerns were identified by the GMO Panel.

3.6.3.2. Assessment of allergenicity of GM plant products[29]

Soybean is considered a common allergenic food[30] (OECD, 2012). Therefore, any potential change in the endogenous allergenicity of the GM plant should be assessed (Regulation (EU) No 503/2013). For such assessment, the applicant included in the comparative analysis specific allergens relevant for soybean (Section 3.5.3) measured by specific ELISA methods, which have been previously considered acceptable (EFSA GMO Panel, 2010c; Fernandez et al., 2013; Selb et al., 2017). The applicant also referred to the Kunitz trypsin inhibitor as a potential soybean allergen, which is an anti-nutrient and as such it is already assessed in the compositional analysis (Section 3.5.3). These allergens were selected

[25] Reg. (EU) 503/2013 requires that in 90-day studies 'the genetically modified food and feed analysed should be relevant to the product to be consumed' and indicates that 'in the case of herbicide tolerant genetically modified plants, the tested material should come from the genetically modified plant exposed to the intended herbicide' (Annex II, II 1.4.4.1).

[26] Dossier: Part II - Section 1.5.1, 1.5.3 and additional information 4/7/2019.

[27] It is pointed out that the requirements laid down in the recent EFSA guidance on allergenicity (EFSA GMO Panel, 2017) are not applicable to this dossier, as described in Section 1.5 'Transition period' of the guidance document.

[28] Additional information: 4/7/2019.

[29] Dossier: Part II - Section 1.5.2 and additional information 11/8/2017.

[30] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.

based on the list of potential soybean allergens described in the pertinent OECD document (OECD, 2012) and a scientific rational supporting their selection was provided by the applicant and considered acceptable by the GMO Panel.

Allergen Gly m 3 levels in soybean MON 87705 × MON 87708 × MON 89788 (treated) were significantly different from those of the non-GM comparator and fell under equivalence category III (Section 3.5.3). For the assessment, the GMO Panel took into account the fact that the difference reported for this allergen consists in a decrease and that no relevant differences in the content of other allergens were observed. Based on these considerations, no changes in the levels of endogenous allergens raising concern are identified by the GMO Panel.

In the context of this application, the GMO Panel considers that there is no evidence that the genetic modification might substantially change the overall allergenicity of the three-event stack soybean when compared with that of the non-GM comparator and the non-GM reference varieties tested.

3.6.4. Dietary exposure assessment to new constituents

In line with Regulation (EU) No 503/2013, the applicant provided dietary exposure estimates to CP4 EPSPS and DMO proteins newly expressed in soybean MON 7705 x MON 87708 x MON 89788. Dietary exposure was estimated based on protein expression levels reported in this application for the three-event stack soybean treated with the intended herbicides, the current available consumption data and feed practices, the foods and feeds currently available in the market and the described processing conditions.

Table 7 describes the protein expression levels derived from replicated field trials in Argentina during 2013–2014 (five locations) and used to estimate both human and animal dietary exposure to DMO and CP4 EPSPS proteins.

Table 7: Mean values (n = 20, μg/g dry weight and μg/g fresh weight) for newly expressed proteins in seeds and forage from soybean MON 87705 × MON 87708 × MON 89788 treated with a combination of the intended herbicides[(a)]

Protein	Tissue/developmental stage	
	Seeds/R8 (μg/g dry weight[(b)] and μg/g fresh weight)	Forage/R6 (μg/g dry weight[(b)])
DMO	13/11	17
CP4 EPSPS	140/120	230

(a): Intended herbicides: dicamba and glyphosate.
(b): Dry weight values used to estimate animal dietary exposure were calculated by dividing the values on a fresh weight basis by the dry weight conversion factor obtained from moisture analysis data.

Human and animal dietary exposure assessment to the dsRNAs and the deriving siRNAs was not conducted because dsRNAs and deriving siRNAs are considered generally not to exert any biological effects once ingested by humans and animals (Section 3.6.3.2).

3.6.4.1. Human dietary exposure[31]

Human dietary exposure was estimated across different European countries on different population groups: young population (infants, toddlers, 'other children'), adolescents, adult population (adults, elderly and very elderly) and special populations (pregnant and lactating women).

MON 87705 × MON 87708 × MON 89788 mean concentration values (fresh weight basis) are considered as the most adequate to estimate human dietary exposure to newly expressed proteins (Table 7). Since no specific consumption data were available on commodities containing, consisting of or produced from MON 87705 × MON 87708 × MON 89788 soybean, a scenario with 100% replacement of conventional soybean by the three-event stack soybean was considered. In this particular application, this scenario can be considered particularly conservative since the main commodity expected to be derived from this three-event stack soybean for human consumption is oil. Consumption figures for the relevant commodities (soya bean flour, soya bread, textured soy protein, soya drink, soya-based infant formula, soya-based follow-on formula, tofu etc.) were retrieved from

[31] Dossier: Part II – Section 2.4.

the EFSA Comprehensive European Food Consumption Database (EFSA consumption database).[32] Soybean oil was excluded from the assessment since proteins are not expected to be present in the oil.

For the acute dietary exposure estimations, the applicant calculated how much of each of the newly expressed proteins is present per gram of soybean protein and multiplied this value by the amount of soybean protein consumed from soybean processed foods. The protein content of the relevant processed foods was derived from the USDA National Nutrient Database,[33] and the consumption data were retrieved from the summary statistics of the EFSA consumption database.[34] This is a conservative approach as neither recipes nor the effect of processing on the final concentration of newly expressed proteins are considered. Acute dietary exposure in high consumers within each dietary survey and age class was estimated by using the food commodity with the highest acute consumption among consumers only (95th or 97.5th percentile depending on the number of consumers). Table 8 shows the highest acute dietary exposure for the different newly expressed proteins; dietary exposure estimates were highest for CP4 EPSPS protein with 353 μg/kg body weight (bw) per day and 1,024 μg/kg bw per day in 'other children' and adults, respectively. Most relevant food commodities in terms of contribution to the exposure were soya drink and meat imitates (textured soy protein).

Table 8: Highest acute dietary exposure to CP4 EPSPS and DMO proteins (μg/kg bw per day) estimated across European dietary surveys and different age classes

	Acute dietary exposure (μg/kg bw per day)	
	DMO	**CP4 EPSPS**
Other children	33	353
Adults	94	1,024

bw: body weight.

The GMO Panel estimated chronic dietary exposure to CP4 EPSPS and DMO proteins. Individual consumption data of the relevant food commodities were retrieved from the EFSA Consumption Database, using dietary surveys with at least 2 days consumption and covering a total of 22 European countries.[35] Different recipes and factors were considered to estimate the amount of soybean in the consumed commodities before assigning CP4 EPSPS and DMO protein levels to the relevant commodities.[36] No losses in the newly expressed proteins during processing were considered. The 95th percentile chronic exposure (highly exposed population) was derived from the distribution of the individual dietary exposure estimates within each dietary survey and age class.

Table 9 shows the highest chronic dietary exposure to each of the two newly expressed proteins across European dietary surveys; highest dietary exposure ranged between 0.03 μg/kg bw per day for DMO in infants (< 1 year old) and 95.3 μg/kg bw per day for CP4 EPSPS protein in adolescents (≥ 10-year to < 18-year old). Main average contributors to the exposure in the dietary surveys with the highest estimates were soybean flour in adolescents, and soya drink and soya yoghurt in toddlers. In a scenario where 'consumers only' are considered, the highest dietary exposure estimates in high consumers were 524.4 μg/kg bw per day and 48.1 μg/kg bw per day, for CP4 EPSPS and DMO, respectively.

[32] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database
[33] USDA, 2013. U.S. Department of Agriculture, Agricultural Research Service. 2013. USDA National Nutrient Database for Standard Reference, Release 25. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/ba/bhnrc/ndl.
[34] Summary statistics from the EFSA Comprehensive European Food Consumption Database accessed in July 2015.
[35] Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Finland, France, United Kingdom, Greece, Croatia, Hungary, Ireland, Italy, Latvia, Netherlands, Portugal, Spain, Romania, and Sweden.
[36] Example: 100 g of Tofu are made with approximately 26 g of soybeans; this would result in 31.2 μg of CP4 EPSPS per gram of tofu as compared to 120 μg/g in the soybeans.

Table 9: Highest chronic dietary exposure estimates (95th percentile, highly exposed population) to CP4 EPSPS and DMO proteins (μg/kg bw per day) across European dietary surveys and different age classes

	N	Chronic dietary exposure (μg/kg bw per day)	
		DMO	CP4 EPSPS
Infants	11	0.03	0.3
Toddlers	14	5.5	60.2
Other children	19	3.8	40.9
Adolescents	18	8.7	95.3
Adults	19	1.4	15.8
Elderly	18	1.8	20.0
Very elderly	14	0.4	3.9
Pregnant women	2	1.4	14.8
Lactating women	2	0.4	4.2

bw: body weight; N: number of dietary surveys.

An ad hoc dietary exposure scenario was carried out considering the consumption of protein-based supplements ('Protein and amino acids supplements' and 'Protein and protein components for sports people'), under the assumption that these supplements are prepared from the three-event stack soybean. Consumption data on protein-based supplements were available for a total of 14 European countries.[2] The highest average acute dietary exposures (consuming days only) were 1,307 μg/kg bw per day for CP4 EPSPS in adults and 119.8 μg/kg bw per day for DMO. For high consumers (95th percentile exposure), the highest acute exposures were 1,951 μg/kg bw per day for CP4 EPSPS and 178.8 μg/kg bw per day for DMO, also in adults. Similarly, for chronic dietary exposure (consumers only), the highest average estimates were 831.7 μg/kg bw per day for CP4 EPSPS and 76.2 μg/kg bw per day for DMO in adults. Only in one dietary survey among those reporting consumption of protein-based supplements the number of consumers was higher than 60 to allow deriving a statistically robust 95th percentile exposure representative of high consumers.[37] The estimated exposure was 41.1 μg/kg bw per day for CP4 EPSPS and 3.8 μg/kg bw per day for DMO in 'Other children'.

Furthermore, the available consumption data on 'Pollen supplements' reported in the EFSA Consumption Database[33] indicates that additional dietary exposure to the newly expressed proteins might occur under the assumption that these supplements contain pollen from soybean MON 87705 × MON 87708 × MON 89788. Since no data on the presence of newly expressed proteins in pollen were available, dietary exposure from this source was not estimated.

3.6.4.2. Animal dietary exposure[38]

Dietary exposure to CP4 EPSPS and DMO proteins in soybean MON 87705 × MON 87708 × MON 89788 was estimated across different animal species as below described, assuming the consumption of soybean products commonly entering the feed chain (i.e. soybean meal, protein concentrates, forage and hulls). A conservative scenario with 100% replacement of conventional soybean products by the three-event stack soybean products was considered.

Mean levels (dry weight) of CP4 EPSPS and DMO proteins in seeds and forage from the three-event stack soybean used for animal dietary exposure are listed Table 7.

The applicant estimated dietary exposure to CP4 EPSPS and DMO proteins via the consumption of soybean meal in broiler, finishing swine and dairy cattle, based on estimates for animal body weight, daily feed intake and inclusion rates (percentage) of soybean meal in diets (OECD, 2009).

To estimate the mean CP4 EPSPS and DMO levels in soybean meal, a factor of 1.28-fold was applied based on the protein content of soybean meal relative to soybean seed (OECD, 2012), assuming that no losses of proteins occur during processing. Estimated dietary exposure in livestock animals is reported in Table 10.

[37] EFSA (European Food Safety Authority), 2011. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097, 34 pp. https://doi.org/10.2903/j.efsa.2011.2097

[38] Dossier: Part II – Section 2.3.

Table 10: Dietary exposure to CP4 EPSPS and DMO proteins (μg/kg bw per day) in livestock animals based on the consumption of soybean meal

	Dietary exposure (μg/kg bw per day)	
	CP4 EPSPS	**DMO**
Broiler	5,060	470
Finishing swine	1,613	150
Dairy cattle	1,723	160

To further integrate the assessment, the GMO Panel estimated the animal dietary exposure to CP4 EPSPS and DMO proteins via the consumption of other soybean products entering the feed chain, i.e. protein concentrates, forage and hulls considering the concerned animals for each feed commodity:

a) Dairy cattle for forage. Consumption of soybean forage is based on estimates for animal body weight and daily feed intake (OECD, 2009), and inclusion rates of soybean forage in animal diets (OECD, 2012); estimated dietary exposure in dairy cattle is 1770 and 130 μg/kg bw per day, respectively, for CP4 EPSPS and DMO proteins.
b) Beef and dairy cattle, rams, lambs, breeding and finishing pigs, broiler and layer chickens for hulls. Consumption of soybean hulls is based on estimates for animal body weight, daily feed intake and inclusion rates of hull in animal diets (OECD, 2009, 2013). To estimate the mean NEP levels in soybean hulls a factor of 0.3-fold was applied based on the protein content of soybean hulls relative to soybean seed (OECD, 2012), assuming that no losses of these proteins occur during processing. Estimated dietary exposure in beef and dairy cattle, ram, lamb, breeding and finishing pigs, broiler and layer is reported in Table 11.

Table 11: Dietary exposure to CP4 EPSPS and DMO proteins (μg/kg bw per day) in livestock animals based on the consumption of soybean hull

	Dietary exposure (μg/kg bw per day)	
	CP4 EPSPS	**DMO**
Beef cattle	101	9
Dairy cattle	162	15
Ram	280	26
Lamb	357	33
Breeding pigs	97	9
Finishing pigs	126	12
Broiler	148	14
Layer	144	13

c) Piglets for protein concentrates. Consumption of soybean protein concentrates in piglet is based on estimates for animal body weight, daily feed intake (EFSA FEEDAP Panel, 2017, EFSA, 2019b) and inclusion rates of protein concentrates in diets (Guzmán et al., 2016). To estimate the mean NEP levels in soybean protein concentrates a factor of 1.75-fold was applied based on the protein content of soybean protein concentrates, relative to soybean seed (OECD, 2012), assuming that no losses of these proteins occur during processing. Estimated dietary exposure in piglets is 755 and 70 μg/kg bw per day, respectively, for CP4 EPSPS and DMO proteins.

3.6.5. Nutritional assessment of GM food/feed

The compositional analysis showed that palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), arachidic acid (C20:0), eicosenoic acid (C20:1), behenic acid (C22:0) and total fat were significantly different in seeds of MON 87705 × MON 87708 × MON 89788 soybean as compared to its conventional counterpart, and showed a lack of equivalence with the set of non-GM reference varieties (see Section 3.5.6).

Regarding total fat, the small decrease in total fat content (~ 2%) is not considered nutritionally relevant and was not further assessed. The biological relevance of the different fatty acids, the role of

soybean as contributor to their total intake and the magnitude and direction of the observed changes were considered during the nutritional assessment.

3.6.5.1. Human nutrition[39]

The main fat-containing processed product from soybean for human consumption as well as the most relevant from the nutritional point of view in this application is the oil. The applicant provided information on the fatty acid composition in RBD oil from seeds of MON 87705 × MON 87708 × MON 89788 soybean treated with the intended herbicides. As shown in Table 12, the fatty acid profile of the RBD oil was almost identical to that of the unprocessed seeds.

Table 12: Fatty acid composition of seeds from the non-GM comparator (n = 32), and of seeds (n = 32) and RBD oil (n = 2) produced from soybean MON87705 x MON87708 x MON89788

	% total fatty acids		
	MON87705 × MON87708 × MON89788 soybean[(a)]		Non-GM comparator
	Seeds[(b)]	RBD oil[(c)]	Seeds[(b)]
Palmitic acid (C16:0)	2.65 ± 0.1	2.58	11.60 ± 0.3
Stearic acid (C18:0)	3.37 ± 0.2	3.32	4.52 ± 0.2
Oleic acid (C18:1)	67.73 ± 1.9	68.15	18.98 ± 1.1
Linoleic acid (C18:2)	16.46 ± 1.7	16.32	54.57 ± 1.2
Linolenic acid (C18:3)	8.97 ± 0.4	8.68	9.58 ± 0.3
Arachidic acid (C20:0)	0.28 ± 0.02	0.28	0.33 ± 0.02
Eicosenoic acid (C20:1)	0.28 ± 0.02	0.29	0.13 ± 0.04
Behenic acid (C22:0)	0.26 ± 0.02	0.27	0.28 ± 0.02

(a): MON87705 × MON87708 × MON89788 soybean treated with intended herbicides.
(b): See Section 3.5.6.
(c): Mean value from duplicate fatty acid analyses of RBD oil.

The levels of all saturated fatty acids (palmitic acid, stearic acid, arachidic acid and behenic acid) decreased in the three-event stack soybean as compared to the non-GM comparator, in particular palmitic acid, the most abundant saturated fatty acid in soybean oil. Current nutritional recommendations for saturated fatty acids indicate that their intake should be as low as is possible within the context of a nutritionally adequate diet (EFSA NDA Panel, 2010). Based on this, the GMO Panel concludes that the observed decrease of saturated fatty acids in the RBD oil produced from the three-event stack soybean does not raise nutritional concerns.

The increase in the levels of two monounsaturated fatty acids (oleic acid and eicosenoic acid) was also assessed. This increase is particularly evident for oleic acid which constitutes the most abundant fatty acid in the RBD oil produced from the three-event stack soybean, with a concentration of more than three-fold as compared to the seeds of the non-GM comparator. No Dietary Reference Value (DRV) for cis- monounsaturated fatty acids is proposed by EFSA since these fatty acids are synthesised by the body (EFSA NDA Panel, 2010). Considering this information, the GMO Panel concludes that the observed increase of oleic acid and eicosenoic acid in the RBD oil produced from the three-event stack soybean does not raise nutritional concerns.

As previously identified during the nutritional assessment of the corresponding single event MON 87705 and the two-event stack MON 87705 × MON 89788 (Table 1), the main nutritional concern linked to the consumption of the RBD oil produced from MON 87705 × MON 87708 × MON 89788 soybean refers to its linoleic acid content. The concentration of linoleic acid is more than three-fold lower in the three-event stack soybean seeds as compared to the non-GM comparator (Section 3.5.6). Linoleic acid is an n-6 polyunsaturated fatty acid (n-6 PUFA) that represents ~99% of the total intake of n-6 PUFAs in the human diet (Sioen et al., 2017); it cannot be synthesised by the body and it is considered an essential fatty acid required to maintain metabolic integrity. EFSA has proposed an Adequate Intake (AI) for linoleic acid of 4 E%, although linoleic acid deficiency has not been observed with intakes > 1 E% (EFSA NDA Panel, 2010). Vegetable oils are important sources of linoleic acid, in particular corn oil, soybean oil and sunflower seed oil, where it is the predominant fatty acid. Other

[39] Dossier: Part I – Section 1.6.1. Spontaneous information on 4/9/2018; additional information: 16/12/2019; 12/3/2020.

relevant contributors to the intake of linoleic acid are cereals and cereal products (although the total fat content of these products is relatively low) and meat, in particular chicken (Wood et al., 2008).

Considering the biological relevance of linoleic acid, the magnitude and direction of the changes and the contribution of vegetable oils to its total intake, dietary intake estimations are considered necessary to assess the effect of introducing RBD oil produced from MON 87705 × MON 87708 × MON 89788 soybean in the diet. The estimated dietary intake of linoleic acid was determined using the fatty acid profile analysed in the RBD oil based on the fact that the fatty acid profile of the RDB oil produced from the three-event stack soybean seeds was almost identical to that of the unprocessed seeds (Table 13).

The dietary intake assessment relied on individual consumption data and nutrient intake estimations from the UK's 2008–2012 National Diet and Nutrition Survey (NDNS) that includes adult population (18–64 years) and toddlers (1.5–4 years), and on data from FAOSTAT databases.[40] The applicant provided a dietary intake scenario covering all possible uses of the RBD oil (scenario A), including both commercial and domestic uses as well as frying (e.g. salad dressing, margarine, mayonnaise and spreads, crackers and salty snacks etc.). A second scenario (scenario B) covering the replacement of all consumed vegetable oil by the RBD soybean oil was provided. The two different scenarios also differ on the source of information used to estimate the vegetable oil intake and its contribution to the total fat intake in the UK population, information used during the assessment. While scenario A relied on individual consumption data and the UK Food Standards Agency's Risk Recipe Database (for the oil composition in the different consumed foods), scenario B obtained the same data from the FAOSTAT database. In both scenarios, three replacement levels (100%, 50% and 25%) of vegetable oils with RBD oil from MON 87705 × MON 87708 × MON 89788 soybean were assessed. The GMO Panel considers both scenarios overly conservative and, therefore, protective for the consumers. As in the assessment of the corresponding double stack (EFSA GMO Panel, 2015b), estimations were provided considering mean, 5th, 50th and 95th percentile intakes of different fatty acids and total fat in the population; consumers with low intake (5th percentile) are those at the greatest risk of linoleic acid deficiency.

Following the evaluation of the nutritional assessment provided for the UK population, the GMO Panel requested additional data to assess the nutritional relevance of introducing RBD oil from MON 87705 × MON 87708 × MON 89788 soybean in the diet of other European populations. The request referred to countries with a consumption pattern of vegetable oils different from UK, in particular those consuming vegetable oils with relative high content of linoleic acid (e.g. sunflower oil). Based on FAOSTAT data on the vegetable oil profile consumed in different countries, Romania and Hungary, two countries with relatively high consumption of sunflower oil, were selected as requested by EFSA.[41] The relative change in linoleic acid intake was estimated comparing the intake in the baseline scenario using the vegetable oils consumed in Romania and Hungary to that in the replacement scenario considering the fatty acid profile of the RBD oil from MON 87705 × MON 87708 × MON 89788 soybean. The impact on the total intake of linoleic acid was estimated using the consumption data from the UK population as surrogate, applying the consumed vegetable oil profile and the vegetable oil contribution to total fat intake (from FAOSTAT database) in Romania and Hungary.

Table 13 shows the results of the nutritional assessments considering the most conservative scenario (i.e. 100% replacement scenario) and the group of population at the greatest risk of deficiency (5th percentile intake of linoleic acid). A decrease in the intake of PUFA n-6 was noted after the replacement of vegetable oils with RBD oil from the three-stack soybean, this decrease being particularly marked when the vegetable oil profiles consumed in Romania and Hungary were considered. However, in all cases the intakes were consistently above 1%E, a consumption level which does not result in linoleic acid deficiency (EFSA NDA Panel, 2010).

[40] http://www.fao.org/faostat/en/#data/FBS (accessed: 2/7/2017). FAOSTAT Food Balance Sheets (FBS) provide information on country's food supply during a specified reference period (food availability) considering the quantity of foodstuffs produced in the country, the quantity imported and any change in stocks.

[41] Hungary: soybean oil (8.1%), sunflower oil (56.1%), rape and mustard oil (10.8%), palm oil (23.4%); Romania: soybean oil (4.7%), sunflower oil (84.2%), palm oil (7.4%), olive oil (1.9%); UK: soybean oil (23.9%), sunflower oil (13.1%), rape and mustard oil (47.3%), olive oil (5.5%).

Table 13: Estimated dietary intake (E %) in the population with 5th percentile intake of PUFA n-6 before and after 100% replacement of all vegetable oils with RBD oil produced from MON 87705 × MON 87708 × MON 89788 soybean

		Male adults		Female adults		Toddlers	
		Predicted intake (% Energy)					
		Before replacement	After replacement	Before replacement	After replacement	Before replacement	After replacement
UK	**PUFA n-6**	2.6	1.6	2.7	1.7	2.4	1.5
Romania[(a)]	**PUFA n-6**	3.9	1.9	4.0	1.9	3.6	1.7
Hungary[(a)]	**PUFA n-6**	3.2	1.7	3.3	1.8	2.9	1.6

(a): The estimates intakes for Hungary and Romania were calculated using consumption data from the UK population as surrogate, applying the consumed vegetable oil profile and the vegetable oil contribution to total fat intake in those countries.

Although α-linolenic acid (omega-3 fatty acid) was not identified as a category III/IV endpoint in the compositional analysis (Section 3.5.6), the GMO Panel notes that a full replacement scenario where conventional oil is replaced by the three-event stack soybean oil would lead to an increase of its intake. This increase could be, for instance, particularly relevant when considering the vegetable oil profile consumed in Romania, as the RBD oil from the three-stack soybean contains much higher levels of α-linolenic acid than sunflower oil where it is essentially absent. However, this increase is not considered to raise nutritional concerns since no Tolerable Upper Intake Level (UL) for α-linolenic acid are set, neither specific values for the n-3/n-6 ratio (EFSA NDA Panel, 2010).

As already concluded by the GMO Panel for the two-event stack soybean MON 87705 × MON 89788 (Table 1), the contribution of other soybean processed products to the total intake of fatty acids is considered minor as compared to that of RBD oil, and is not expected to affect the outcome of the nutritional assessment.

Based on the assessment of the information provided and on the current scientific knowledge, the GMO Panel concludes that the consumption of MON 87705 × MON 87708 × MON 89788 soybean does not represent a nutritional concern in humans, in the context of the scope of this application.

3.6.5.2. Animal nutrition

Soybean is a valuable protein source of vegetable origin widely used in animal nutrition, mainly in ration formulations for farmed animal species (e.g. poultry, pigs, cattle and aquaculture).

The main soybean products entering the feed supply chain are seeds, meal and oil; although the use of soybean forage is less common, the aerial part of the plant (fresh, ensiled or dried to hay, EFSA, 2018) can enter the feed chain (mainly for ruminants). Other soybean products which may enter the feed chain consist of soybean hulls and soybean protein concentrates.

The use of unprocessed soybean seeds for animal feed is limited due to the presence of antinutritional factors, inactivated by adequate heat processing. Heated full fat soybean seeds (flakes) and defatted by-products (e.g. soybean toasted meal) are therefore commonly used as feed.

In the absence of compositional differences between the three-event stack soybean and to its non-GM comparator other than those regarding fatty acids levels in seeds, the GMO Panel considers that the consumption of defatted soybean products from soybean MON 87705 × MON 87708 × MON 89788 does not represent a nutritional concern for animals.

No compositional differences were found between forage from the three-event stack soybean and its non-GM comparator and no changes in the fatty acid profile are expected (Sections 3.1 and 3.5.6). In any case, forage contribution to the total fatty acid intake is rather limited. Therefore, the GMO Panel considers that the consumption of forage from the three-event stack soybean does not represent a nutritional concern for animals.

Considering the altered fatty acid profile of the three-event stack soybean (Section 3.5.6), a nutritional assessment was conducted on full-fat soybean products and oil. Dietary fat is not only classified as an energy source, but it is well recognised that specific fatty acids have also roles in lipid metabolism and organism defence systems in animals (Savoini et al., 2019; Waldron et al., 2012; Swiatkiewicz et al., 2015.

The increased oleic acid does not represent *per se* a nutritional concern for animals, as documented by the use of feed sources with different fatty acid content (Castellani et al., 2017;

Martins et al., 2018). Linoleic acid is an essential fatty acid in animal nutrition and must be included in the diet. Some of the most common sources of linoleic acid are soybean oil or heat-treated full fat soybean. The modified ratio between oleic and linoleic acid in the three-event stack soybean is not harmful per se, whenever fatty acids composition is properly balanced in rations to satisfy nutrient requirements of animals. Moreover, it is worth to remind that changes in the fatty acid composition of the fat of the diet affect also fatty acids profile of body, milk, eggs fat and could affect also sensory characteristics (aromatic profile) of products of animal origin.

The GMO Panel concludes that consumption of soybean MON 87705 × MON 87708 × MON 89788 does not represent a nutritional concern for animals, in the context of the scope of this application.

3.6.6. Conclusion of the food and feed safety assessment

The newly expressed proteins CP4 EPSPS and DMO and the dsRNAs and their deriving siRNAs present in soybean MON 87705 x MON 87708 × MON 89788 do not raise safety concerns for human and animal health. Interactions between the newly expressed proteins CP4 EPSPS and DMO raising food and feed safety concerns (in terms of toxicology, allergenicity and adjuvanticity) are not expected. There is no evidence that the genetic modification might change the overall allergenicity of the three-event stack soybean. Based on the outcome of the animal and human nutritional assessments, the consumption of soybean MON 87705 × MON 87708 × MON 89788 does not represent any nutritional concern, in the context of the scope of this application. Considering the altered fatty acid profile of the three-event stack soybean, a proposal for PMM needs to be provided by the applicant. (Section 3.8.1)

The GMO Panel notes that in the context of this application EFSA–GMO–NL–2015–126 the applicant did not provide a 90-day study on MON87705 soybean in line with the applicable legal requirements (i.e. no treatment with the intended herbicide was applied to MON 87705 soybean used to produce the test material). Therefore, the GMO Panel is not in the position to finalise the risk assessment of soybean MON 87705 × MON 87708 × MON 89788 under the current regulatory frame.

3.7. Environmental risk assessment[42]

Considering the scope of the application EFSA–GMO–NL–2015–126, which excludes cultivation, the environmental risk assessment (ERA) of soybean MON 87705 × MON 87708 × MON 89788 mainly takes into account: (1) the exposure of microorganisms to recombinant DNA in the gastrointestinal tract of animals fed GM material and of microorganisms present in environments exposed to faecal material of these animals (manure and faeces); and (2) the accidental release into the environment of viable soybean MON 87705 × MON 87708 × MON 89788 seeds during transportation and/or processing (EFSA GMO Panel, 2010a).

3.7.1. Persistence and invasiveness of the GM plant

Cultivated soybean (*Glycine max* (L.) Merr.) is a species in the subgenus *Soja* of the genus *Glycine.* The species originated from eastern Asia and is a highly domesticated crop, generally unable to survive in the environment without appropriate management (Lu, 2005).

Occasional feral GM soybean plants may occur outside cultivation areas, but survival is limited mainly by a combination of low competitiveness, absence of a dormancy phase and susceptibility to plant pathogens and cold climatic conditions (OECD, 2000). Soybean can grow as volunteers and the presence of volunteers of *G. max* was occasionally reported in some areas of Italy where soybean is intensively cultivated (Celesti-Grapow et al., 2010). However, as for the same reasons mentioned above, soybean seeds usually do not survive during the winter (Owen, 2005). Thus, the establishment and survival of feral and volunteer soybean in the EU are currently limited and transient.

It is unlikely that the intended traits of soybean MON 87705 × MON 87708 × MON 89788 will provide a selective advantage to soybean plants, except when they are exposed to glyphosate- and/or dicamba-containing herbicides. However, this fitness advantage will not allow the GM plant to overcome other biological and abiotic factors (described above) limiting plant's persistence and invasiveness. Therefore, the presence of the intended traits will not affect the persistence and invasiveness of the GM plant.

[42] Dossier: Part II – Section 5.

In conclusion, the GMO Panel considers it unlikely that soybean MON 87705 × MON 87708 × MON 89788 will differ from conventional soybean varieties in its ability to survive until subsequent seasons, or to establish occasional feral plants under European environmental conditions in case of accidental release into the environment of viable soybean MON 87705 × MON 87708 × MON 89788 seeds.

3.7.2. Potential for gene transfer

3.7.2.1. Plant-to-microorganism gene transfer

The probability and potential adverse effects of HGT of the recombinant DNA have been assessed in previous GMO Panel Scientific Opinions for the single events (see Table 1). This assessment included consideration of homology-based recombination processes, as well as non-homologous end joining and microhomology-mediated end joining. Possible fitness advantages that the bacteria in the receiving environments would gain from acquiring recombinant DNA were considered. No concern as a result of an unlikely, but theoretically possible, HGT of the recombinant genes to bacteria in the gut of domesticated animals and humans fed GM material or other receiving environments was identified.

The applicant submitted an updated bioinformatic analysis for each of the single events to assess the possibility for HGT by homologous recombination.

The updated bioinformatic analyses provided in this application for the events MON 87708 and MON 89788 have recently been assessed by the GMO Panel in the context of other applications (EFSA GMO Panel, 2019a,b).

The updated bioinformatics analysis for event MON 87705 revealed one element with sufficient length and sequence identity with Ti plasmids of *A. tumefaciens*. However, this element would not have the capacity to facilitate HGT by double homologous recombination with bacterial genomes in receiving environments.

Synergistic effects of the recombinant genes, for instance due to combinations of recombinogenic sequences, which would cause an increase in the likelihood for HGT or a selective advantage were not identified.

Therefore, the GMO Panel concludes that the unlikely, but theoretically possible, horizontal transfer of recombinant genes from this three-event stack soybean to bacteria does not raise any environmental safety concern.

3.7.2.2. Plant to plant-gene transfer

The potential for occasional feral soybean MON 87705 × MON 87708 × MON 89788 plants originating from seed import spills to transfer recombinant DNA to sexually compatible plants and the environmental consequences of this transfer were considered.

For plant to plant gene transfer to occur, imported GM soybean seeds need to germinate and develop into plants in areas containing sympatric wild relatives and/or cultivated soybean with synchronous flowering and environmental conditions favouring cross-pollination. It must be noted that most soybean MON 87705 × MON 87708 × MON 89788 seeds are processed in the countries of production or in ports of importation.

Vertical gene transfer from soybean (*G. max*) is limited to the species of the subgenus *Soja* to which *G. max* belongs to, as well as the wild relatives *G. soja* and *G. gracilis*. Although wild relatives exist elsewhere, no wild relatives of the subgenus *Soja* have been reported in Europe (Dorokhov et al., 2004; Lu, 2005). Therefore, vertical gene transfer from GM soybean is restricted to cultivated soybean (*G. max*).

Soybean is an annual, almost completely self-pollinating crop with a percentage of cross-pollination usually below 1% (OECD, 2000; Ray et al., 2003; Lu, 2005; Yoshimura et al., 2006; Abud et al., 2007), although natural cross-pollination rates can fluctuate significantly among different soybean varieties under particular environmental conditions, such as favourable climate for pollination and an abundance of pollinators (Caviness, 1966; Gumisiriza and Rubaihayo, 1978; Kikuchi et al., 1993; Ahrent and Caviness, 1994; Ray et al., 2003; Lu, 2005).

The potential of spilled soybean seeds to establish, grow and produce pollen is extremely low and transient (see Section 3.7.1). Therefore, the likelihood/frequency of cross-pollination between occasional feral GM soybean plants resulting from seed spillage, and weedy or cultivated soybean plants is also considered extremely low. Even if cross-pollination would occur, the GMO Panel is of the opinion that the likelihood of environmental effects as a consequence of the spread of genes from

occasional feral GM soybean plants in Europe will not differ from that of conventional soybean varieties for the reasons given in Section 3.7.1.

3.7.3. Interactions of the GM plant with target organisms

Taking the scope of application EFSA-GMO-NL-2015-126 and thus the absence of target organisms into account, potential interactions of occasional feral soybean MON 87705 × MON 87708 × MON 89788 plants with target organisms are not considered a relevant issue.

3.7.4. Interactions of the GM plant with non-target organisms

Given that environmental exposure of non-target organisms to spilled GM seeds or occasional feral GM soybean plants arising from spilled soybean MON 87705 × MON 87708 × MON 89788 seeds is limited, and because ingested dsRNA and proteins are degraded before entering the environment through faecal material of animals fed GM soybean, potential interactions of soybean MON 87705 × MON 87708 × MON 89788 with non-target organisms are not considered by the GMO Panel to raise any environmental safety concern.

3.7.5. Interactions with the abiotic environment and biogeochemical cycles

Given that environmental exposure to spilled seeds or occasional feral soybean MON 87705 × MON 87708 × MON 89788 plants arising from seed import spills is limited, and because ingested dsRNA and proteins are degraded before entering the environment through faecal material of animals fed GM soybean, potential interactions with the abiotic environment and biogeochemical cycles are not considered by the GMO Panel to raise any environmental safety concern.

3.7.6. Conclusion of the environmental risk assessment

The GMO Panel concludes that it is unlikely that soybean MON 87705 × MON 87708 × MON 89788 would differ from conventional soybean varieties in its ability to persist under European environmental conditions. Considering the scope of application EFSA-GMO-NL-2015-126, interactions of occasional feral soybean MON 87705 × MON 87708 × MON 89788 plants with the biotic and abiotic environment are not considered to be relevant issues. The analysis of HGT of recombinant DNA from soybean MON 87705 × MON 87708 × MON 89788 to bacteria does not indicate a safety concern. Therefore, considering the combined traits and their interactions, the outcome of the agronomic and phenotypic analysis, and the routes and levels of exposure, the GMO Panel concludes that soybean MON 87705 × MON 87708 × MON 89788 would not raise safety concerns in the event of accidental release of viable GM soybean seeds into the environment.

3.8. Post-market monitoring

3.8.1. Post-market monitoring of GM food/feed[43]

Considering the altered fatty acid profile of MON 87705 × MON 87708 × MON 89788 soybean (Section 3.5.6), in accordance with Regulation (EC) No 1829/2003 and Regulation (EU) No 503/2013 a proposal for post-market monitoring (PMM) needs to be provided by the applicant. As described in the regulation, the main objectives of PMM are to confirm the expected consumption, the application of conditions of uses or identified effects.

EFSA recommends that the post-market monitoring plan should initially focus on the collection of import data to Europe of MON 87705 × MON 87708 × MON 89788 soybean and/or its products, in particular RBD oil. Following the identification of imports, an updated nutritional assessment should be conducted in the case the available information on consumption (e.g. new dietary surveys, data from FAOSTAT database on amounts and type of vegetable oils consumed) differs from that used during the risk assessment. Likewise, the applicant should collect and provide any scientific information that might change the conclusions of the pre-market nutritional assessment.

For specific labelling, in accordance with Articles 13(2)(a) and 25(2)(c) of Regulation (EC) No 1829/2003 the applicant proposed that operators shall be required to label food and feed products containing or consisting of oil produced from MON 87705 × MON 87708 × MON 89788 soybean with

[43] Dossier Part IV – Labelling Proposal

the words 'produced from genetically modified soybean with increased monounsaturated fat and reduced polyunsaturated fat'. The GMO Panel considers that this proposal is consistent with the compositional data of this three-event stack soybean.

3.8.2. Post-market environmental monitoring

The objectives of a post-market environmental monitoring (PMEM) plan, according to Annex VII of Directive 2001/18/EC, are: (1) to confirm that any assumption regarding the occurrence and impact of potential adverse effects of the GMO, or its use, in the ERA are correct; and (2) to identify the occurrence of adverse effects of the GMO, or its use, on human health or the environment that were not anticipated in the ERA.

Monitoring is related to risk management, and thus, a final adoption of the PMEM plan falls outside the mandate of EFSA. However, the GMO Panel gives its opinion on the scientific rationale of the PMEM plan provided by the applicant (EFSA GMO Panel, 2011b).

As the ERA did not identify potential adverse environmental effects from soybean MON 87705 × MON 87708 × MON 89788, no case specific monitoring is required.

The PMEM plan proposed by the applicant for soybean MON 87705 × MON 87708 × MON 89788 includes: (1) the description of a monitoring approach involving operators (federations involved in import and processing), reporting to the applicant, via a centralised system, any observed adverse effect(s) of GMOs on human health and the environment; (2) a coordinating system established by EuropaBio for the collection of information recorded by the various operators; and (3) the review of relevant scientific publications retrieved from literature searches (Lecoq et al., 2007; Windels et al., 2008). The applicant proposes to submit a PMEM report on an annual basis and a final report at the end of the authorisation period.

The GMO Panel considers that the scope of the PMEM plan provided by the applicant is consistent with the intended uses of soybean MON 87705 × MON 87708 × MON 89788. The GMO Panel agrees with the reporting intervals proposed by the applicant in its PMEM plan.

In the context of annual PMEM reports, the applicant should improve future literature searches according to the GMO Panel recommendations given in Section 3.1.

4. Overall conclusions

The GMO Panel was asked to carry out a scientific assessment of soybean MON 87705 × MON 87708 × MON 89788 for import, processing and food and feed uses in accordance with Regulation (EC) No 1829/2003. No new information on the single soybean events MON 87705, MON 87708 and MON 89788 that would lead to a modification of the original conclusions on their safety were identified. The molecular characterisation, the comparative analysis (agronomic, phenotypic and compositional characteristics) and the outcome of the toxicological, allergenicity and nutritional assessment indicate that the combination of the single soybean events and of the newly expressed proteins or dsRNAs in the three event stack soybean does not give rise to food/feed safety and nutritional concerns.

Considering the altered fatty acid profile of soybean MON 87705 × MON 87708 × MON 89788, a proposal for post-market monitoring needs to be provided by the applicant. The GMO Panel considers that the specific labelling proposal provided by the applicant is consistent with the composition of this three-event stack soybean.

The GMO Panel concludes that there is a very low likelihood of environmental effects resulting from the accidental release of viable seeds from soybean MON 87705 × MON 87708 × MON 89788 into the environment. The PMEM plan and reporting intervals are in line with the intended uses of soybean MON 87705 × MON 87708 × MON 89788. In the context of annual PMEM reports, the applicant should improve future literature searches according to the GMO Panel recommendations.

In addition, the GMO Panel considered the additional unpublished studies listed in Appendix B. This new information does not raise any concern for human and animal health and the environment regarding the three-stack event GM soybean.

The GMO Panel notes that in the context of this application EFSA GMO NL-2015-126 the applicant did not provide a 90-day study on MON87705 soybean in line with the applicable legal requirements in the context of this three-event stack soybean application (i.e. no treatment with the intended herbicide was applied to MON 87705 soybean used to produce the test material). Therefore, the GMO Panel is not in the position to finalise the risk assessment of soybean MON 87705 × MON 87708 × MON 89788 under the current regulatory frame.

Documentation as provided to EFSA

- Letter from the Competent Authority of the Netherlands received on 22 September 2015 concerning a request for placing on the market of genetically modified soybean MON 87705 × MON 87708 × MON 89788 submitted by Monsanto Company in accordance with Regulation (EC) No 1829/2003 (application reference EFSA-GMO-NL-2015-126).
- Application validated by EFSA, 12 February 2016.
- Request for supplementary information to the applicant (EURL-GMFF), 15 February 2016.
- Reception of supplementary information by the applicant (to EURL-GMFF), 19 February 2016.
- Request for supplementary information to the applicant, 22 February 2016.
- Reception of supplementary information by the applicant, 23 March 2016.
- Request for supplementary information to the applicant, 5 April 2016.
- Reception of supplementary information by the applicant, 3 June 2016.
- Request for supplementary information to the applicant, 6 June 2016.
- Request for supplementary information to the applicant, 19 July 2016.
- Reception of supplementary information by the applicant, 29 September 2016.
- Request for supplementary information to the applicant, 9 November 2016.
- Reception of supplementary information by the applicant, 12 December 2016.
- Request for supplementary information to the applicant, 24 February 2017.
- Request for supplementary information to the applicant, 12 June 2017.
- Reception of supplementary information by the applicant, 19 June 2017.
- Request for supplementary information to the applicant, 27 July 2017.
- Reception of supplementary information by the applicant, 11 August 2017.
- Request for supplementary information to the applicant, 22 September 2017.
- Reception of supplementary information by the applicant, 6 October 2017.
- Request for supplementary information to the applicant, 22 November 2017.
- Reception of supplementary information by the applicant, 20 December 2017.
- Request for supplementary information to the applicant, 18 January 2018.
- Reception of supplementary information by the applicant, 22 January 2018.
- Request for supplementary information to the applicant, 7 February 2018.
- Request for supplementary information to the applicant, 15 February 2018.
- Reception of supplementary information by the applicant, 28 February 2018.
- Reception of supplementary information by the applicant, 3 April 2018.
- Reception of supplementary information by the applicant, 6 April 2018.
- Reception of supplementary information by the applicant, 24 April 2018.
- Reception of complementary information by the applicant, 30 April 2018.
- Reception of spontaneous information by the applicant, 14 June 2018.
- Reception of supplementary information by the applicant, 18 July 2018.
- Request for supplementary information to the applicant, 20 July 2018.
- Reception of supplementary information by the applicant, 4 September 2018.
- Reception of supplementary information by the applicant, 17 September 2018.
- Request for supplementary information to the applicant, 20 September 2018.
- Reception of supplementary information by the applicant, 5 October 2018.
- Request for supplementary information to the applicant, 9 October 2018.
- Reception of spontaneous information by the applicant 4 July 2019.
- Request for supplementary information to the applicant, 17 July 2019.
- Reception of supplementary information by the applicant, 10 October 2019.
- Request for supplementary information to the applicant, 21 October 2019.
- Request for supplementary information to the applicant, 3 December 2019.
- Reception of supplementary information by the applicant, 16 December 2019.
- Reception of supplementary information by the applicant, 24 January 2020.
- Request for supplementary information to the applicant, 7 February 2020.
- Request for supplementary information to the applicant, 10 March 2020.
- Reception of supplementary information by the applicant, 18 March 2020.

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Abbreviations

ADF	acid detergent fibre
Bw	body weight
DMO	dicamba mono-oxygenase
ELISA	enzyme-linked immunosorbent assay
EPSPS	5-enolpyruvylshikimate-3-phosphate synthase
ERA	environmental risk assessment
FA	fatty acid
GM	genetically modified
GMO	genetically modified organism
GMO	Panel EFSA Panel on Genetically Modified Organisms
HGT	horizontal gene transfer
HR	homologous recombination
IgE	immunoglobulin E
MS	Member States
NDF	neutral detergent fibre
OECD	Organisation for Economic Co-operation and Development
ORF	open reading frame
PAT	phosphinothricin acetyltransferase
PCR	polymerase chain reaction
PMEM	post-market environmental monitoring
PMM	post-market monitoring
UTR	untranslated region
WBC	white blood cell

Appendix A – Protein expression data

Means, standard deviation and ranges of protein levels (μg/g dry weight) from soybean MON 87705 × MON 87708 × MON 89788 (treated with dicamba and glyphosate), MON 87705 (treated with glyphosate), MON 89788 (treated with glyphosate) and MON 87708 (treated with dicamba), from field trials performed across five locations in Argentina in 2013–2014 (n = 20).

Protein	Event(s)	Leaf (V3–V4)	Leaf (V6–V7)	Leaf (R2–R3)	Leaf (R6)	Root (R6)	Forage (R6–R7)	Seed (R8)
CP4 EPSPS	**MON 87705 × MON 87708 × MON 89788**	450[(a)] ± 72[(b)] 350–610[(c)]	490 ± 70 340–640	450 ± 150 130–630	480 ± 37 410–570	65 ± 31 23–110	230 ± 37 160–290	140 ± 46 71–210
	MON87705	280 ± 33 230–370	250 ± 39 170–320	290 ± 87 110–420	330 ± 47 260–420	87 ± 24 56–150	170 ± 22 120–210	130 ± 36 63–200
	MON89788	230 ± 41 170–330	240 ± 60 150–360	240 ± 71 100–330	270 ± 46 140–350	50 ± 11 33–67	110 ± 22 68–140	63 ± 13 38–97
DMO	**MON 87705 × MON 87708 × MON 89788**	11 ± 4.8 3.6–22	9.4 ± 3.2 5.9–17	15 ± 6.8 9.1–31	39 ± 6.8 30–53	3.2 ± 2.4 0.7–8.2	17 ± 3.0 13–25	13 ± 5.8 5.4–27
	MON 87708	12 ± 3.7 5.6–19	11 ± 3.7 5.3–19	15 ± 5.9 9.2–28	42 ± 11 27–62	3.0 ± 2.1 0.9–7.0	18 ± 3.0 14–26	19 ± 3.3 13–25

(a): Mean.
(b): Standard deviation.
(c): Range.

Appendix B – List of additional unpublished studies performed by or on behalf of the applicant with regard to the evaluation of the safety of the food and feed for humans, animals and the environment for soybean MON 87705 × MON 87708 × MON 89788

Study identification	Title
MSL0026696	Southern Blot Analyses to Confirm the Presence of MON 87705, MON 87708 and MON 89788 in the Combined Trait Soybean Product MON 87705 × MON 87708 × MON 89788
MSL0023031	The Effect of Heat Treatment on Dicamba Mono-Oxygenase (DMO) Enzyme Immunodetection
MSL0026883	Comparison of Gly m 4 Expression Levels from MON 87705 × MON 87708 × MON 89788 and Conventional Soybeans
MSL0026838	Assessment of CP4 EPSPS and DMO Protein Levels in Soybean Tissues Collected from MON 87705 × MON 87708× MON 89788 Produced in Argentinean Field Trials During 2013-2014 and CP4 EPSPS Protein Levels in Soybean Tissues Collected from MON 87705 Produced in United States Field Trials During 2014
MSL0026197	An Acute Toxicity Study of E. coli-produced MON 87708 DMO protein by Oral Gavage in Mice
MSL0026454	An Acute Toxicity Study of E. Coli-produced CP4 EPSPS Protein by Oral Gavage in Mice
MSL0022648	Amended Report for MSL0021863: Characterization of the CP4 EPSPS Protein Purified from the Seed of MON 87705 and Comparison of the Physicochemical and Functional Properties of the Plant-Produced and E. coli-Produced CP4 EPSPS Proteins
MSL0026928	Amended from MSL0026912: Comparison of Broiler Performance and Carcass Parameters When Fed Diets Containing MON 87705 × MON 87708 × MON 89788, Control, or Reference Soybean Meal
MSL0027235	An Acute Oral Gavage Toxicity Study of E. coli-produced CP4 EPSPS Protein in CD-1 Mice
MSL0026669	Analyses of Minerals and B Vitamins of Soybean Seed from MON 87705 × MON 87708 × MON 89788 Grown in Argentina in 2013/2014