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

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Authors of the opinion

The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM (VKM, 2019). The principles reflect the collaborative nature of the work, and the authors have contributed as members of the VKM Panel on genetically modified organisms.

Members of the Panel on genetically modified organisms (in alphabetical order before chair of the Panel): Johanna Bodin (chair), Nur Duale, Monica Sanden, Tage Thorstensen and Rose Vikse.

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Summary

Stacked event MON87705 × MON87708 × MON89788 is a genetically modified soybean developed via conventional crossing, combining the three single events: MON87705, MON87708 and MON89788. All three single (parental) events were developed through *Agrobacterium*-mediated transformation of conventional soybean tissues. The stacked event MON87705 × MON87708 × MON89788, inherits endogenous soybean gene segments from MON87705 configured to suppress the genes *fatb* and *fad2. Fatb* and *fad2* are involved in fatty acid synthesis and regulation of fatty acid composition in the plant, hence the suppression leads to an altered fatty-acid profile in the stacked event. MON87705 also contributes with the *cp4epsps* gene from *Agrobacterium sp*. strain CP4 conferring tolerance to glyphosate-based herbicides. Likewise, the stacked event expresses the *dmo*-gene (dicamba mono-oxygenase) derived from *Stenotrophomonas maltophilia* from MON87708, conferring tolerance to the herbicide Dicamba. Finally, a second *cp4epsps* gene is inherited by the stack from MON89788.

The scientific documentation provided in the application for stacked event MON87705 × MON87708 × MON89788 is adequate for risk assessment, and in accordance with EFSA guidance on risk assessment of genetically modified plants for use in food or feed. The VKM GMO panel does not consider the introduced modifications in MON87705 × MON87708 × MON89788 to imply potential specific health or environmental risks in Norway, compared to EU-countries. The EFSA scientific opinion (EFSA, 2020) is adequate also for Norwegian considerations. Therefore, a full risk assessment of stacked event MON87705 × MON87708 × MON89788 was not performed by the VKM GMO Panel.

Sammendrag

MON87705 × MON87708 × MON89788 er en genmodifisert soya utviklet ved konvensjonell kryssing av de tre soyaene MON87705, MON87708, og MON89788.

De tre soyaene (foreldreplantene) er alle utviklet ved *Agrobacterium-mediert* transformasjon av celler fra konvensjonelle sorter. MON87705 × MON87708 × MON89788, har arvet gensekvenser, endogene for soya, fra MON87705 som undertrykker genene *fatb* og *fad2* . *Fatb* og *fad2* er involvert i produksjon og sammensetning av fettsyrer i planten, undertrykkelsen av disse endrer dermed fettsyreprofilen til den kryssede soyaen. MON87705 bidrar i tillegg med genet *cp4epsps* fra *Agrobacterium* sp. som gir økt toleranse for glyfosatbaserte ugressmidler. Tilsvarende, arver den kryssede soyaen *dmo-genet* (dicamba mono-oksygenase) fra *Stenotrophomonas maltofili* fra soyaen MON87708, som gir toleranse til ugressmiddelet Dicamba. MON89788 bidrar med enda et *cp4epsps*-gen*,* som øker toleransen for glyfosat ytterligere.

Den vitenskapelige dokumentasjonen i søknaden for den genmodifiserte soyaen er dekkende for risikovurdering, og i samsvar med EFSAs veiledning for risikovurdering av genmodifiserte planter til bruk i mat eller fôr. De genetiske endringene i soya MON87705 × MON87708 × MON89788 tilsier ingen økt helse- eller miljørisiko i Norge sammenlignet med EU-land. EFSAs vurdering (EFSA, 2020) er tilstrekkelig også for norske forhold. VKMs GMO panel har derfor ikke utført en fullstendig risikovurdering av soyaen.

Background as provided by the Norwegian Food Safety Authority and the Norwegian Environment Agency

The Norwegian Food Safety Authority (NFSA) and the Norwegian Environment Agency (NEA), have assigned VKM to perform assessments of genetically modified organisms (GMOs) and derived products thereof, for which there are sought approval of authorisation to the European market under the Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. VKM is requested to perform assessments for all GMO applications made accessible through the EFSA Document Management System (DMS), where the main focus should be on potential health or environmental risks specific to Norway compared to the EU.

1 Assessment of genetically modified Soybean MON 87705 × MON 87708 × MON 89788 and sub-combinations (application EFSA-GMO-NL-2015-126)

1.1 Comments during the EFSA scientific consultation-period

When EFSA submits an application for scientific consultation with a three-month commenting deadline, VKM shall initiate the scientific assessment. From the application is submitted for scientific consultation until EFSA has published its Scientific Opinion (6.5 months + the period when 'the clock stops') VKM should:

• Use this period to assess the scientific quality of the documentation presented in the application. Possible lack of essential information and other relevant scientific literature should be addressed. The application must be in compliance with Regulation (EU) No. 503/2013 and adhere to EFSA guidance (EFSA 2010, 2011) for risk assessment of genetically modified organisms.

• Provide comments to EFSA within the deadline and inform The Norwegian Food Safety Authority (NFSA) and the Norwegian Environment Agency (NEA) no later than two weeks before the deadline. If no comments are provided to EFSA, VKM notifies the NFSA and NEA for the reasons why no comment was submitted.

• Assess whether there are considerations specific to Norway that need to be addressed. If such considerations are identified VKM should immediately inform the NFSA and NEA.

Stage 1

1. Application	**EFSA-GMO-NL-2015-126** Genetically modified Soybean MON87705 × MON87708 × MON89788 and sub-combinations

2. Information related to the genetic modification:

Stacked event MON87705 × MON87708 × MON89788 is a genetically modified soybean developed via conventional crossing, combining the three single events: MON87705, MON87708 and MON89788. All three single (parental) events were developed through *Agrobacterium*-mediated transformation of conventional soybean tissues. The stacked event MON87705 × MON87708 × MON89788, inherits endogenous soybean gene segments from MON87705 configured to suppress the genes *fatb* and *fad2*. *Fatb* and *fad2* are involved in fatty acid synthesis and regulation of fatty acid composition in the plant, hence the suppression leads to an altered fatty-acid profile in the stacked event. MON87705 also contributes with the *cp4epsps* gene from *Agrobacterium* sp. strain CP4 conferring tolerance to glyphosate-based herbicides. Likewise, the stacked event expresses the *dmo*-gene (dicamba mono-oxygenase) derived from *Stenotrophomonas maltophilia* from MON87708, conferring tolerance to the herbicide Dicamba. Finally, a second *cp4epsps* gene is inherited by the stack from MON89788.

Genes	**Proteins**
CP4 epsps	CP4 EPSPS
dmo	Dicamba mono-oxygenase, DMO
fad2-1a	Partial sequence from intron #1 of the Glycine max *fad2-1a* gene that encodes the delta-12 desaturase which suppresses endogenous fad2-1a RNA levels
fatb1-a	Partial sequence from the 5' untranslated region and the plastid targeting sequence from *Glycine max fatb1-a* gene that encodes the palmitoyl acyl carrier protein thioesterase, which suppresses endogenous *fatb1-a* RNA levels

3. Previously assessed by VKM	YES:	NO:X

4. If yes in item 3. – comments from VKM:

5. Date when EFSA declared the application as valid in accordance with Articles 6(1) and 18(1)	
6. Deadline of EFSAs commenting period	
7. VKMs assessment of the documentation in the application	

Applicants' documentation:

Additional literature used by VKM:

Documentation in compliance with Regulation (EU) No. 503/2013: YES: NO: X

The conducted 90-day toxicological whole food feeding study for the single event MON 87705 was not in line with regulation No. 503/2013. The study did not use test material treated with the target herbicide, Glyphosate.

Documentation in accordance with EFSA guidance for risk assessment of genetically modified plants (EFSA 2010, 2011): YES: X NO:

8. Comments submitted from VKM during EFSAs public consultation	YES: X NO:
9. Date of submission from VKM	30.08.2016
10. Comment(s) to EFSA:	

A, 3.3 Compositional assessment

Worldwide, soybean oil is the second most produced oil after palm oil. Traditional soybean oil has high levels of unsaturated fatty acids, mainly 18:2n-6 (linoleic acid), making it unstable and prone to oxidation. The dietary shortcoming of soybean oil is its high n-6/n-3 ratio. Compared to its conventional counterpart and other conventional soybean cultivars, soybean MON 87705 × MON 87708 × MON 89788 has a significantly modified fatty acid profile with the main modifications being an increased level of 18:1n-9 oleic acid and lower levels of saturated fats (16:0 palmitic acid and 18:0 stearic acid) and 18:2n-6 linoleic acid, the latter an essential fatty acid for humans and animals. The mean values (as percentage total fatty acids (TFAs)) of the main fatty acids were Palmitic acid 2.65%, Stearic acid 3.37%, Linoleic acid 16.46% and Oleic acid 67.73%. Thus the point of the genetic modification was to induce significant compositional differences compared to conventional comparators. Comparing the above values with fatty acid profiles of other vegetable oils, the profile of soybean MON 87705 × MON 87708 × MON 89788 is similar to the fatty acid profile of rapeseed oil and olive oil. The applicant thus claims that with these compositional *changes, the oil from soybean MON 87705 × MON 87708 × MON 89788 may have health benefits. However, substituting conventional soybean oil with oil from soybean MON 87705 × MON 87708 × MON 89788 may lead to reduced intake of the essential fatty acid 18:2n-6 linoleic acid, as well as a changed intake pattern of other fatty acids and fat-soluble components (see below). Under certain circumstances this may introduce a possible safety risk for the consumers' nutritional status. However, if the applicant were to provide a thorough comparison of soybean MON 87705 × MON 87708 × MON 89788 with other commercial vegetable oils based on levels provided in the scientific literature, the risk may be partially mitigated. The Norwegian GMO panel therefore requests additional information that include a comparison of soybean MON 87705 × MON 87708 × MON 89788 with other commercial vegetable oils. The major components of vegetable oils are TAGs (triacylglycerides). In traditional soybean seeds the most abundant triacyl combinations are 1) 18:2n-6 in all three positions 2) 18:1n-9 in sn-1 position and 18:2n-6 in sn2/3 and 3) 18:2n-6 in sn1/2 and 18:3n-3 in position sn-3 (Li, Butka and Wang 2014). The acyl combinations in soybean MON 87705 × MON 87708 × MON 89788 is not given by the applicant and we do not know if positional redistribution of fatty acids has occurred in soybean MON 87705 × MON 87708 × MON 89788. Fatty acid position on the TAG molecule may affect digestibility of the individual fatty acids and largely determines the physical behavior of dietary fats as a whole in food products (Karupaiah and Sundram 2007). Preferential hydrolysis by pancreatic and lipoprotein lipases target the fatty acids in the sn-1 and sn-3 positions resulting in free fatty acids (FFAs) and sn-2 monoacylglycerols (Nillson-Ehle et al 1973; Yang et al 1991). In order to assess the effect of soybean MON 87705 × MON 87708 × MON 89788 compared to traditional soybean on nutrition and health, it would be valuable to see the alteration in TAG structure. This is also of importance in light of soybean as a major source of phospholipids. The soybean phospholipids represent a mixture of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS) and phosphatidic acid (PA). The most frequent fatty acid component of soybean phospholipids is 18:2n-6 linoleic acid (Liu and Ma 2011). The genetic modification conducted on soybean MON 87705 × MON 87708 × MON 89788, with the significantly reduced fraction of 18:2n-6 linoleic acid is thus likely to also influence the nature and possibly also amount of soybean phospholipids. This should have been characterised by phospholipid analysis and also argues for the need for in vivo nutritional studies. The modern rapeseed (also called canola with low levels of erucic acid and glucosinolates) is the third largest source of oil for human consumption and is the main vegetable oil used in Norwegian salmon feed (Ytrestøyl et al 2014). Rapeseed oil is characterized as a high phytosterol-oil, while soybean oil and olive oil are in the group low/intermediate-phytosterols. Phytosterols have the ability to inhibit the uptake of cholesterol from the intestine and lower plasma cholesterol and triacylglycerol (TAG) in humans (Bernacer et al. 2015). The effects of phytosterols on Atlantic salmon metabolism and health, however, are not completely known, but it has been suggested that high concentrations of dietary phytosterols (>1.1 g kg-1 diet) can lead to some unwanted metabolic changes, like increased liver and plasma TAGs (Liland 2014). We do not know if the levels of phytosterols or other lipid-soluble components in the soybean MON 87705 × MON 87708 × MON 89788 have been affected by the genetic modification. If there are changes in phytosterol levels in soybean MON 87705 × MON 87708 × MON 89788, this may affect bioavailability of other sterols. Thus, analysis of phytosterol levels would be of importance to help mitigate possible negative effects that any changes in their concentration may have on consumer health. Furthermore, other unintended effects in soybean MON 87705 × MON 87708 × MON 89788 regarding saponin and lectin levels are not provided by the applicant. These are not among the list of suggested components in the OECD guideline for new varieties of soybeans, but with major nutrient changes as observed in soybean MON 87705 × MON 87708 × MON 89788, a more thorough compositional screening should be performed and this should also be* *requested in an updated OECD guideline. Lectins and heat-stable, amphipathic saponins present in soybean have been implicated as contributing factors in the development of soybean meal-induced enteropathy in Atlantic salmon and rainbow trout (Krogdahl et al. 2015; Iwashita et al. 2008). Their involvement in the development of a similar condition observed in calves and piglets cannot be excluded. Thus any changes in the levels of these antinutritional factors in MON 87705 × MON 87708 × MON 89788 soybean would be of practical importance for the aquafeed industry.*

References Iwashita Y., Yamamoto T., Furuita H., Sugita T., Suzuki N. (2008) Influence of certain soybean antinutritional factors supplemented to a casein-based semipurified diet on intestinal and liver morphology in fingerling rainbow trout Oncorhynchus mykiss. Fisheries Sci 74, 1075-1082. Karupaiah T and Sundram K (2007). Effects of stereospecific positioning of fatty acids in triacylglycerol structures in native and randomized fats: a review of their nutritional implications. NUTRITION & METABOLISM Volume: 4 Article Number: 16 Krogdahl Å., Gajardo K., Kortner T.M., Penn M., Gu M., Berge G.M., Bakke A.M. (2015) Soya saponins induce enteritis in Atlantic salmon (Salmo salar L.) J Agric Food Chem 63, 3887-3902.Li, My, Butka E, Wang XM (2014). Comprehensive Quantification of Triacylglycerols in Soybean Seeds by Electrospray Ionization Mass Spectrometry with Multiple Neutral Loss Scans. SCIENTIFIC REPORTS. Volume: 4. Li, My, Butka E, Wang XM (2014). Comprehensive Quantification of Triacylglycerols in Soybean Seeds by Electrospray Ionization Mass Spectrometry with Multiple Neutral Loss Scans. SCIENTIFIC REPORTS. Volume: 4. Liu D and Ma F (2011). Soybean Phospholipids, Recent Trends for Enhancing the Diversity and Quality of Soybean Products, Prof. Dora Krezhova (Ed.), ISBN: 978-953-307-533- 4, InTech, http://www.intechopen.com/books/recent-trends-for-enhancing-thediversity-and-quality-of-soybeanproducts/soybean-phospholipids Liland NS (2014) Atlantic salmon (Salmo salar L.) sterol metabolism and metabolic health impact of dietary lipids. University of BergenKarupaiah T and Sundram K (2007). Effects of stereospecific positioning of fatty acids in triacylglycerol structures in native and randomized fats: a review of their nutritional implications. NUTRITION & METABOLISM Volume: 4 Article Number: 16 Nillson-Ehle P, Egelrud T, Belfrage P, Olivecrona T, Borgstrom B: Positional specificity of purified milk lipoprotein lipase. J Biol Chem 1973, 248: 6734-7. Yang LY, Kuksis A: Apparent convergence (at 2-monoacylglycerol level) of phosphatidic acid and 2-monoacylglycerol pathways of synthesis of chylomicron triacylglycerols. J Lipid Res 1991, 32: 1173-86. Ytrestøyl T, Aas TS, Åsgård T (2014) Resource utilisation of Norwegian salmon farming in 2012 and 2013. vol 36. Nofima report.

A, 6.2. Nutritional assessment of the GM food and feed

We agree with the applicant that soybean MON 87705 × MON 87708 × MON 89788 with its changes in fatty acid profile can represent a nutritional improvement in both food and feed. Soybean MON 87705 × MON 87708 × MON 89788 could improve the disequilibrium in the intakes of n-6 to n-3 fatty acids, as we know today that the ratios between n-6 and n-3 FAs in traditional soybean oil are above the recommended levels for humans. In the case of GM plants modified for altered content of nutrients, livestock studies with model or target species should be performed in order to determine the bioavailability of individual nutrients in the feed derived from a GM plant compared to its comparator (ILSI, 2003, 2007). The Norwegian GMO panel is of the opinion that a nutritional assessment study should have been performed with the stacked soybean MON 87705 × MON 87708 × MON 89788.

References ILSI (2003) Best Practices for the Conduct of Animal Studies to Evaluate Crops Genetically Modified for InputTraits http://www.ilsi.org/FoodBioTech/Documents/BestPractices2003.pdf IlSI (2007) Best Practices for the Conduct of Animal Studies to Evaluate Crops Genetically Modified for Output Traits
http://www.ilsi.org/FoodBioTech/Documents/BestPractices2007.pdf

11. If NO in item 8. – comments from VKM:

12. Need for national consideration(s)

YES: NO: X

13. If YES in item 12. – comments from VKM:

14. If NO in item 12. – comments from VKM:

The VKM GMO Panel does not consider the modifications in stacked event MON 87705 × MON 87708 × MON 89788 to imply potential specific health or environmental risks in Norway compared to EU-countries.

15. VKMs conclusion regarding the application:

The scientific documentation provided in the application is adequate for risk assessment, and in accordance with the EFSA guidance on risk assessment of genetically modified plants for use in food or feed.

1.2 Considerations after EFSAs publication of their scientific opinion – part 1

When EFSA publishes their scientific opinion together with the comments from the member states, VKM shall within a month inform the NFSA and EEA on the following:

• Are EFSA's answer(s) to the Norwegian comments satisfactorily answered, or do VKM still have scientific objections to EFSA's conclusions

• Do EFSA's answers to comments from member states indicate need for follow-up by VKM

• Considerations specific to Norway

Stage 2		
1. Date of publication of EFSA opinion	02.04.2020	
2. VKMs deadline for informing NFSA and EEA		
3. If YES in item 8. (table 1)– Answer from EFSA has been considered by VKM as satisfactory (Annex G)	YES: X	NO:
4. If YES in item 3 – Comments from VKM:		
EFSA has given a thorough and adequate reply to the VKM comments		
5. If NO in item 3 – Comment(s) and further considerations from VKM:		
6. Follow-up item 12 (table 1) – comments from VKM:		
The VKM GMO Panel does not consider the modifications in stacked event MON 87705 × MON 87708 × MON 89788 to imply potential specific health or environmental risks in Norway compared to EU-countries. The EFSA scientific opinion (EFSA, 2020) is adequate also for Norwegian considerations.		
7. Considerations from VKM regarding comments from EU member states and other countries under Annex G:		
No member state comments imply the need for follow-up by VKM.		

1.3 Considerations after EFSAs publication of their scientific opinion – part 2

If VKM's comments regarding health and environmental risk are not considered to be satisfactorily answered by EFSA, VKM shall within three months carry out a risk assessment of these conditions, as well as conditions specific to Norway. VKM shall highlight uncertainty and knowledge gaps. It shall be stated in what area there are knowledge gaps, and whether the uncertainty, quality of the data, and knowledge gaps will affect the conclusion.

Stage 3		
1. Need for further assessment(s)	YES:	NO: X
2. If YES in item 1. – Further considerations from VKM:		
3. If NO in item 1. – comments from VKM:		
The scientific documentation provided in the application is adequate for risk assessment, and in accordance with the EFSA guidance on risk assessment of genetically modified plants for use in food or feed. The EFSA scientific opinion (EFSA, 2020) is adequate also for Norwegian considerations.		
4. Need for national considerations	YES:	NO: X
5. If YES in item 4. – comments from VKM:		
6. If NO or NA in item 4. – comments from VKM		
The VKM GMO Panel does not consider the modifications in stacked event MON87705 × MON87708 × MON89788 to imply potential specific health or environmental risks in Norway compared to EU-countries.		
7. Need for a risk assessment	YES:	NO: X
8. Date of deadline for risk assessment	Not applicable	
9. Date of publication of assessment		

2 Conclusions

The VKM GMO Panel has performed an assessment of genetically modified Soybean MON87705 × MON87708 × MON89788.

The VKM GMO panel has assessed the documentation in the application EFSA-GMO-NL-2015-126 and the EFSAs scientific opinion (EFSA, 2020) on genetically modified Soybean MON 87705 × MON 87708 × MON 89788. The scientific documentation provided in the application is adequate for risk assessment, and in accordance with the EFSA guidance on risk assessment of genetically modified plants for use in food or feed.

The GMO panel does not consider the introduced modifications in Soybean MON 87705 × MON 87708 × MON 89788 to imply potential specific health or environmental risks in Norway, compared to EU-countries. The EFSA scientific opinion is adequate also for Norwegian considerations. Therefore, a full risk assessment of stacked soybean event MON87705 × MON87708 × MON89788 was not performed by the VKM GMO Panel.

3 References

EFSA (2010) Guidance on the environmental risk assessment of genetically modified plants. Scientific option from the EFSA Panel on Genetically Modified Organisms (GMO). The EFSA Journal 8 (11):1-111 http://www.efsa.europa.eu/en/efsajournal/doc/1879.pdf

EFSA (2011) Guidance for risk assessment of food and feed from genetically modified plants. The EFSA Journal 9(5): 2150. http://www.efsa.europa.eu/en/efsajournal/doc/2150.pdf

EFSA (2020) Scientific Opinion on the assessment of genetically modified soybean MON 877059MON 877089MON 89788, for food and feed uses, under Regulation (EC) No1829/2003 (application EFSA-GMO-NL-2015-126) EFSA Journal 2020;18(5):6111, 36 pp. https://doi.org/10.2903/j.efsa.2020.6111ISSN:1831-4732