ANNEX I

Assessment of the grounds for the review in request for internal review of Commission Implementing Decision (EU) 2021/66[1] authorising the placing on the market of products containing, consisting of or produced from genetically modified soybean MON 87751 × MON 87701 × MON 87708 × MON 89788 pursuant to Regulation (EC) No 1829/2003[2]

1. Risk assessment conducted by EFSA and the applicant

1.1 Molecular characterisation: assessment of open reading frames

In section 2.1.1 of your request, you claim that the European Food Safety Authority (EFSA) did not take into account all the relevant data required by Annex II to Commission Implementing Regulation (EU) No 503/2013[3] for the assessment of open reading frames ('ORFs')[4] *in* genetically modified (GM) soybean MON 87751 × MON 87701 × MON 87708 × MON 89788 ('GM stack soybean'). In particular, you claim that (1) EFSA assumed that the proteins that might emerge from these ORFs would raise no safety concerns and it did not carry out any further investigations in that regard; (2) it did not assess other gene products, such as non-coding RNA ('ncRNA') that might emerge from ORFs; and (3) it did not take into consideration the potential synergistic or antagonistic effects resulting from the combination of the transformation events.

As regards your first and second claims, according to the EFSA *Guidance for risk assessment of food and feed from genetically modified plants*[5], which implements the requirements set out in Regulation (EU) No 1829/2003 and in Commission Implementing Regulation (EU) No 503/2013[6], new peptides, including proteins, likely to be produced from ORFs are assessed, while ncRNAs are not assessed unless justified by the nature of the insert[7].

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1 OJ L 26, 26.1.2021, p. 44–49.

2 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).

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 L 157, 8.6.2013, p. 1–48).

4 Regulation (EU) No 503/2013 defines "open reading frames" as "any nucleotide sequence that contains a string of codons that is uninterrupted by the presence of a stop codon in the same reading frame" (Part II, section 1.2.2.2. point (f) of Annex II).

5 EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2011. *Scientific Opinion on Guidance for risk assessment of food and feed from genetically modified plants*. EFSA Journal 2011;9(5): 2150, 37 pp. https://doi.org/10.2903/j.efsa.2011.2150.

6 According to part II, section 1.2.2.2, point (f) and section 1.2.2.3 point (d) and (e) of Annex II to Regulation (EC) No 503/2013.

7 In line with part II, section 1.2.2.3, point (e) of Annex II to Regulation (EU) No 503/2013

In the case at hand, regarding new peptides, including proteins, likely to be produced from ORFs, EFSA assessed them, as required by Regulation (EU) 503/2013, based on the information provided by the applicant, and concluded, in section 3.2 of its scientific opinion on the assessment of genetically modified soybean MON 87751 × MON 87701 × MON 87708 × MON 89788 for food and feed uses, under Regulation (EC) No 1829/2003 (hereafter, 'EFSA scientific opinion on the GM stack soybean')[8], that the production of a new peptide, including protein, showing significant similarities to toxins or allergens in the GM stack soybean is highly unlikely.

As already stated in section 3.1.1 of the EFSA *Scientific advice to the European Commission on the internal review submitted under Regulation (EC) No 1367/2006 on the application of the provisions of the Aarhus Convention against the Commission Implementing Decision (EU) 2015/687 to authorise genetically modified oilseed rape MON 88302*[9], EFSA recognises that there is evidence in the peer-reviewed scientific literature for ncRNAs to be produced from different sequences of the insert. These ncRNAs would be unintended and linked to the genetic transformation. In the case at hand, possible unintended effects in the GM stack soybean, resulting from the potential production of such ncRNAs, were covered by a comprehensive comparative analysis, consisting of compositional and agronomic/phenotypic characterisation of the GM stack soybean, as explained in section 3.5 of the EFSA scientific opinion on the GM stack soybean.

With regard to your third claim, contrary to your allegations, the possible impact of the combination of the transformation events on the integrity of each of them, on the expression levels of the newly expressed proteins and on the biological functions conferred by the individual inserts were considered by EFSA and reflected in section 3.4 of its scientific opinion on the GM stack soybean, in line with the requirements of part II, section 1.2.2.4. of Annex II to Regulation (EU) No 503/2013. In that regard, the sequencing of the events in the GM stack soybean and an updated bioinformatics analysis confirmed previous results from the EFSA scientific opinions on the GM single soybeans[10], indicating that no known endogenous genes were disrupted by any of the inserts and that no new significant similarities of the newly expressed proteins and ORFs to toxins and allergens were identified. Considerations on the assessment of ORFs were previously discussed by EFSA, in section 3.1.1 of its scientific advice on the internal review concerning GM oilseed rape MON88302, referred to above[11]. In the present case, EFSA assessed the sequences

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[8] EFSA GMO Panel, Naegeli H, Bresson JL, Dalmay T, Dewhurst IC, Epstein MM, Firbank LG, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogué F, Rostoks N, Sánchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Álvarez F, Ardizzone M, De Sanctis G, Devos Y, Fernández Dumont A, Gennaro A, Gómez Ruiz JA, Lanzoni A, Neri FM, Papadopoulou N, Paraskevopoulos K and Raffaello T, 2019a. *Scientific Opinion on the assessment of genetically modified soybean MON 87751 × MON 87701 × MON 87708 × MON 89788 for food and feed uses, under Regulation (EC) No 1829/2003* (application EFSA-GMO-NL-2016-128). EFSA Journal 2019; 17(11):5847, 31 pp. https://doi.org/10.2903/j.efsa.2019.5847

[9] EFSA, 2015a. *Scientific advice to the European Commission on the internal review submitted under Regulation (EC) No 1367/2006 on the application of the provisions of the Aarhus Convention against the Commission Implementing Decision 2015/687 to authorise genetically modified oilseed rape MON88302.* EFSA supporting publication 2015:EN-864. 44 pp. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2015.EN-864.

[10] EFSA Scientific opinions on GM soybean MON 87751 (https://doi.org/10.2903/j.efsa.2018.5346), MON 87701 (https://doi.org/10.2903/j.efsa.2011.2309), MON 87708 (https://doi.org/10.2903/j.efsa.2013.3355) and MON 89788 (https://doi.org/10.2903/j.efsa.2018.5468).

[11] See *supra* footnote 9.

of the events in the GM stack soybean and found them identical to the sequences originally reported for the single events, thus confirming that the integrity of these events was maintained in the stack.

In view of the above considerations, your claims must be rejected as unfounded.

1.2 Impact of environmental factors, agricultural practice and genetic backgrounds on gene expression, plant composition and phenotypic characteristics

As a preliminary remark, this section addresses the claims made under sections 2.1.2 and 2.2 of your request. Those claims, which are of a similar nature, have been grouped in this reply under the type of information concerned, i.e. data on environmental factors and stress conditions, data on herbicide application rates, data on stacking and genetic backgrounds and data from compositional analysis.

According to those claims, the data presented by the applicant do not satisfy the requirements of Regulation (EU) No 503/2013, based on the following grounds: (1) the field trials were not conducted in all relevant regions where the GM stack soybean will be cultivated and no extreme weather conditions were taken into account; (2) the field trials did not take into account current agricultural management practices; (3) the field trials only included one transgenic stacked variety, and (4) the data from compositional analysis showed the need for further investigations.

1.2.1. Data on environmental factors, stress conditions and their impact on gene expression and on plant composition and phenotype

In sections 2.1.2.1 and 2.2.1 of your request, you allege that the data presented by the applicant were insufficient to conclude on the impact of environmental factors and stress conditions on gene expression, plant composition and the biological characteristics of the plant, because the GM stack soybean could be subject to more extreme climate conditions in other soybean producing countries.

In that regard, you refer to a number of publications. Among others, you refer to a paper by Tritkova *et al*. (2015)[12], concerning the impact of climate conditions on the content of the *Bacillus thuringiensis* ('Bt') protein in the plant tissue. Furthermore, you refer to publications by Wang *et al*. (2014)[13], Yang *et al*. (2017)[14], Fang *et al*. (2018)[15], Beres *et al*. (2018)[16] and Beres

[12] Trtikova M, Wikmark OG, Zemp N, Widmer A and Hilbeck A, 2015.Transgene expression and Bt protein content in transgenic Bt maize (MON 810) under optimal and stressful environmental conditions. PLoS ONE, 10(4): e0123011.

[13] Wang, W., Xia, H., Yang, X., Xu, T., Si, H.J., Cai, X.X., Wang, F., Su, J., Snow, A.A., Lu, B.-R. (2014) A novel 5-enolpyruvoylshikimate-3-phosphate (EPSP) synthase transgene for glyphosate resistance stimulates growth and fecundity in weedy rice (Oryza sativa) without herbicide. New Phytol, 202(2): 679-688. https://doi.org/10.1111/nph.12428.

[14] Yang, X., Li, L., Jiang, X., Wang, W., Cai, X., Su, J., Wang, F., Lu, B.-R. (2017) Genetically engineered rice endogenous 5-enolpyruvoylshikimate-3-phosphate synthase (epsps) transgene alters phenology and fitness of crop-wild hybrid offspring. Sci Rep, 7(1): 1-12. https://doi.org/10.1038/s41598-017-07089-9.

(2019)[17], showing effects of the EPSPS enzyme, one of the newly expressed protein from the GM stack soybean, on plant growth hormone metabolism and common breeding parameters[18]. On that basis, you claim that interference in the plant metabolism might cause changes in gene activity, and that extreme weather conditions can cause unexpected stress reactions in GM plants expressing additional EPSPS enzymes. In that regard, you claim that the concentration of EPSPS enzyme in the GM stack soybean is higher compared to the parental plants and that, therefore, even if no such effects were observed in the parental plants, the likelihood of interaction of the EPSPS enzyme with the plant growth hormone metabolism is higher in the stack.

It should be noted that, since the receiving environments are highly diverse and dynamic over time, it is considered unfeasible, in practice, to assess GM events under all possible receiving environments. Therefore, applicants must select sufficiently different locations to capture the environmental variability within the set of possible receiving environments in which the GM stack soybean may be cultivated. In the case at hand, EFSA considered that the experimental design and the tested materials for this GM stack soybean were adequate to identify possible unintended changes introduced with the genetic modifications.

Regarding the findings reported by Trtikova *et al*. (2015), EFSA has already assessed them in the past[19]. The authors based their findings on their experiments with plants grown in controlled environments, claiming that genetic background and environmental conditions, especially abiotic environments, could affect Cry1Ab transgene expression and Bt protein levels in GM maize MON810. EFSA is of the opinion that, taking those findings into account, the risk assessment conclusions and risk management recommendations on all Cry1Ab-expressing Bt-maize events remain valid and applicable.

As regards the findings reported by Wang *et al*. (2014), Yang *et al*. (2017), Fang *et al*. (2018), Beres *et al*. (2018) and Beres (2019), these were observed in rice, *Arabidopsis* and *Conyza canadensis* and not in soybean. In any case, as highlighted in Vila-Aiub *et al*., 2019[20], reports on benefits on common breeding parameters from EPSPS overexpression in transgenic events need to be further validated before it can be confirmed that this remarkable finding is solely due to the

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[15] Fang, J., Nan, P., Gu, Z., Ge, X., Feng, Y.-Q., Lu, B.-R. (2018) Overexpressing exogenous 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) genes increases fecundity and auxin content of transgenic Arabidopsis plants. Front Plant Sci, 9: 233. https://doi.org/10.3389/fpls.2018.00233.

[16] Beres, Z.T., Yang, X., Jin, L., Zhao, W., Mackey, D.M., Snow, A.A. (2018) Overexpression of a native gene encoding 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) may enhance Fecundity in Arabidopsis thaliana in the absence of glyphosate. Int J Plant Sci, 179(5):390–401. https://doi.org/10.1086/696701.

[17] Beres, Z.T. (2019) Ecological and evolutionary implications of glyphosate resistance in Conyza canadensis and Arabidopsis thaliana. Dissertation presented in partial fulfillment of the requirements for the degree Doctor of Philosophy in the graduate school of the Ohio State University. http://rave.ohiolink.edu/etdc/view?acc_num=osu1555600547328876.

[18] Such as yield, plant morphology, flowering time, day degrees to maturity, duration of pollen viability, response to plant pathogens and insect pests, sensitivity to abiotic stress (according to part II, section 1.3.5 of Annex II to Regulation (EU) No 503/2013).

[19] EFSA, 2015. *Relevance of a new scientific publication (Trtikova et al., 2015) on previous EFSA GMO Panel conclusions on the risk assessment of maize MON 810 and other Cry1Ab-expressing Bt-maize events*. EFSA supporting publication 2015:EN-878. 11. https://doi.org/10.2903/sp.efsa.2015.EN-878

[20] Vila-Aiub M, Yu Q, Powles S, 2019. Do plants pay a fitness cost to be resistant to glyphosate? New Phytologist, 223(2): 532-547. https://doi.org/10.1111/nph.15733

intended glyphosate resistance. In addition, in the case at hand, the agronomic and phenotypic characterisation submitted by the applicant included the assessment of common breeding parameters and revealed no biologically relevant differences between the GM stack soybean and its conventional counterpart.

Regarding the other publications you are referring to concerning the impact of climate conditions on protein expression levels, EFSA recognises that there is evidence in the peer-reviewed scientific literature suggesting that stressful conditions could in some instances be a factor influencing protein expression levels[21]. However, EFSA notes that the possible consequences for protein expression levels are unpredictable and may result in either higher or reduced protein expression levels (Hendawey, 2009[22]; Merewitz *et al*., 2011[23]; Parvaiz, 2014[24]).

For the compositional and agronomic/phenotypic characterisation, the applicant selected field trial sites located in major soybean producing areas of the United States, and each of these sites reflect different meteorological and agronomic conditions under which the crop is to be grown. EFSA considered that the meteorological and agronomic variability at the sites selected for the compositional and agronomic/phenotypic characterisation of the application were able to ensure a sufficient range of environmental and agronomic conditions reflecting those under which the GM stack soybean might be cultivated in practice. In any case, the lack of reported extreme events during the field trials does not imply that the plants were not exposed at all to any abiotic and biotic stressors, as these occur naturally during cultivation under uncontrolled environmental conditions.

In view of the above considerations, your claims on this point must be rejected.

1.2.2. Data on herbicide application rates and their impact on gene expression and on plant composition and agronomic and phenotypic characteristics

In sections 2.1.2.2 and 2.2.2 of your request, you claim that the field trials for the GM stack soybean did not take into consideration current agricultural management practices. You claim that, due to increased weed pressure, the GM stack soybean will be exposed to much higher dosages and repeated spraying of glyphosate alone or in combination with dicamba. You claim

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[21] EFSA, Neri FM, Afonso A, De Sanctis G, Devos Y, Fernandez Dumont A, Lanzoni A and Papadopoulou N, 2021. *Technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of the Commission's decisions authorising the placing on the market of genetically modified soybean MON 87751 x MON 87701 × MON 87708 x MON 89788 (application EFSA-GMO-NL-2016-128), maize MON 87427 × MON 87460 × MON 89034 × MIR162 × NK603 and subcombinations (application EFSA-GMO-NL-2016-134) and maize MON 87427 × MON 89034 × MIR162 × MON 87411 and subcombinations* (application EFSA-GMO-NL-2017-144). EFSA supporting publication 2021:EN-6590. 182 pp. https://doi.org/10.2903/sp.efsa.2021.EN-6590

[22] Hendawey MH, 2009. Effect of salinity on proteins in some wheat cultivars. Australian Journal of Basic and Applied Sciences 3:80-88.

[23] Merewitz EB, Gianfagna T, Huang B, 2011. Protein accumulation in leaves and roots associated with improved drought tolerance in creeping bentgrass expressing an iptgene for cytokinin synthesis. Journal of Experimental Botany 62:5311-5333.

[24] Parvaiz A, 2014. Legumes under environmental stress: yield, improvement and adaptations. John Wiley & Sons. ISBN 978-1-118-91708-4.

that this should have been considered because higher rates of herbicide application can influence the expression of the transgenes or other genome activities of the plants, as well as the plant composition and its biological characteristics.

In support of your claim, you refer to the publications by Miyazaki *et al*. (2019)[25], Campos *et al*. (2020)[26] and Zanatta *et al*. (2020)[27], among others, which show, in your view, that higher dosages of the intended herbicides may influence gene expression and the composition of the GM stack soybean and that these changes may have serious effects on health.

Similar criticisms on the non-representativeness of the herbicide regime applied on herbicide tolerant GM plants have been previously rebutted in section 3.1.2.1 of the EFSA *Assessment of the outcomes of the project "Risk Assessment of Genetically Engineered Organisms in the EU and Switzerland" (RAGES)*[28].

Part II, sections 1.3.1 and 1.3.3 of Annex II to Regulation (EU) No 503/2013 require that herbicide tolerant GM plants are exposed to the intended herbicide. In line with those provisions, the application of the intended herbicide in the field trials for the comparative assessment of herbicide tolerant GM plants is a mandatory requirement of the EFSA *Guidance for risk assessment of food and feed from genetically modified plants*[29]. Later on, in the EFSA *Guidance on the agronomic and phenotypic characterisation of GM plants*[30], the GMO Panel provided further clarifications on the type of information that applicants should report with regard to the application of the complementary herbicides (e.g. timing, dose, volumes, coadjuvants) to ensure a proper evaluation of their correct application.

In the field trials for comparative analysis of herbicide tolerant GM plants, the intended herbicides are to be kept at a similar application rate across sites, to ensure comparability between locations, while the combinations of conventional herbicides applied at the selected sites are to reflect different weed management practices, chosen to maintain the weed pressure under control. EFSA verifies that the timing and rate of the applied intended herbicides are in line with the recommendations of the manufacturers. This information is routinely verified by EFSA and specifically discussed in the section of its scientific opinions on management practices.

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[25] Miyazaki J et al., 2019. Insufficient risk assessment of herbicide-tolerant genetically engineered soybeans intended for import into the EU. Environmental Sciences Europe, 31(1): 92.

[26] de Campos, B.K., Galazzi, R.M., dos Santos, B.M., Balbuena, T.S., dos Santos, F.N., Mokochinski, J.B., Eberlin, M.N., Arruda, M.A.Z. (2020) Comparison of generational effect on proteins and metabolites in non-transgenic and transgenic soybean seeds through the insertion of the cp4-EPSPS gene assessed by omics-based platforms, Ecotoxicol Environ Saf, 202: 110918. https://doi.org/10.1016/j.ecoenv.2020.110918

[27] Zanatta, C.B., Benevenuto, R.F., Nodari, R.O., Agapito-Tenfen, S.Z. (2020) Stacked genetically modified soybean harboring herbicide resistance and insecticide Cry1Ac shows strong defense and redox homeostasis disturbance after glyphosate-based herbicide application. Environ Sci Eur, 32: 104. https://doi.org/10.1186/s12302-020-00379-6

[28] EFSA, Gennaro A, Álvarez F, Devos Y, Fernandez Dumont A, Gómez Ruiz JÁ, Lanzoni A, Paoletti C, Papadopoulou N, Raffaello T, Waigmann E, 2020a. Assessment of the outcomes of the project "Risk Assessment of Genetically Engineered Organisms in the EU and Switzerland" (RAGES). EFSA supporting publication 2020:EN-1890. 31 pp. https://doi.org/10.2903/sp.efsa.2020.EN-1890

[29] See *supra* footnote 5.

[30] EFSA GMO Panel, 2015. *Guidance on the agronomic and phenotypic characterisation of genetically modified plants*. EFSA Journal 2015;13(6):4128, 44 pp. https://doi.org/10.2903/j.efsa.2015.4128.

In the case of the GM stack soybean in question, which is tolerant to dicamba- and glyphosate-based herbicides, the plots containing the GM stack soybean were exposed to two sequential applications, the first one with a dicamba-based herbicide, and a second one with a glyphosate-based herbicide[31]. Those herbicide applications were conducted at standard doses and both those doses and the timing of the applications were in accordance with the manufacturer's recommendations. On that basis, EFSA concluded that the tested materials in the GM stack soybean application were in line with the requirements of Regulation (EU) No 503/2013 as well as with the EFSA *Guidance on the agronomic and phenotypic characterisation of genetically modified plants*[32]. The Commission agrees with that assessment.

Regarding the publication by Miyazaki *et al*. (2019), it should be noted that it was already assessed in EFSA's *Scientific advice on the Testbiotech's requests for internal review of Commission Implementing Decisions (EU) No 2019/2083 and 2019/2084 on soybean MON 89788 and soybean A2704-12 (applications EFSA-GMO-RX-011 and EFSA-GMO-RX-009)*[33] and in the frame of specific discussions of a working group organised by the GMO Panel[34].

The findings of Zanatta *et al*. (2020) on the glyphosate-based herbicide impact on plant physiological processes are certainly relevant but, in the case at hand, EFSA considered, in section 3.5.6 of its opinion on the GM stack soybean, that the compositional data generated on seed and forage exposed to the intended herbicides and on materials grown under natural conditions were adequate to inform the risk assessment.

Finally, the publication by de Campos *et al*. (2020) is, in the Commission's view, not relevant to your claim concerning the application rates of herbicides. That paper investigates the stability of metabolites and proteins in a GM soybean variety versus a conventional one over two generations without application of glyphosate-based herbicides.

Regarding the other publications you cite, the experimental data mentioned in those publications are considered important evidence of potential impact of herbicide treatment on plant metabolism. However, they are not directly relevant to this GM stack soybean because they were generated using material produced in a glyphosate-free environment or using material not produced from a specific event or they were generated from material not produced from seeds/grain.

In view of the above considerations, your allegations on this point must be rejected.

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[31] Described in section 3.5.4.3 of EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

[32] See *supra* footnote 30.

[33] EFSA, 2020b. *Scientific advice on the Testbiotech's requests for internal review of Commission Implementing Decisions (EU) No 2019/2083 and 2019/2084 on soybean MON 89788 and soybean A2704-12* (applications EFSA-GMO-RX-011 and EFSA-GMO-RX-009). EFSA supporting publication 2020:EN-1805. 11 pp. https://doi.org/10.2903/sp.efsa.2020.EN-1805

[34] Minutes of the 207th meeting of the Working Group on comparative analysis and environmental risk assessment, available at https://www.efsa.europa.eu/sites/default/files/wgs/gmo/gmocompera2019.pdf.

1.2.3. Impact of stacking and influence of genetic backgrounds on gene expression and on plant composition and agronomic and phenotypic characteristics

In sections 2.1.2.3 and 2.2.3 of your request, you claim that the level of some compounds from the GM stack soybean is lower compared to its conventional counterpart. According to you, this fact indicates the influence from the stacking process and the resulting overall genomic background of the stacked event. You also claim that the data in the application showed a much lower number of significant findings in plant composition and phenotypic characteristics when the plants were sprayed with the complementary herbicides, which, according to you, indicates that such spraying might have impacted metabolic pathways.

According to the requirements of Regulation (EU) No 503/2013[35], the EFSA *Guidance on the environmental risk assessment of GM plants*[36] and the EFSA *Guidance on the agronomic and phenotypic characterisation of genetically modified plants*[37], agronomic and phenotypic characteristics for each transgenic event are to be assessed in the comparison of the GM plant with its conventional counterpart and with non-GM reference varieties with a history of safe use. Applicants are required to perform field trials for the agronomic/phenotypic and compositional characterisation of GM plants, which include common breeding parameters covering growth habit and vegetative vigour, phenology and reproductive behaviour, and susceptibility to pests, diseases and abiotic stress. If the GM plant contains a trait for herbicide tolerance, agronomic/phenotypic data must be generated with and without the intended herbicide[38]. Consequently, common breeding parameters of GM herbicide tolerant plants treated or untreated with the intended herbicides are assessed in field trials designed for comparative analysis.

For the GM stack soybean, the compositional analysis and the agronomic and phenotypic characterisation were performed with and without application of the intended herbicides.

As regards the compositional analysis, EFSA assessed all the significant differences in composition between the GM stack soybean and its conventional counterpart, taking into account the potential impact on plant metabolism and the natural variability observed for the non-GM reference varieties. It considered that none of those differences required further assessment except for changes in Gly m 4 protein levels in seed, as it is the only compound showing significant differences between the GM stack soybean and the conventional counterpart. EFSA further assessed those changes and did not find that they had a safety impact[39].

As regards the agronomic and phenotypic characterisation, it included the assessment of common breeding parameters and EFSA found no relevant differences between the GM stack soybean and its conventional counterpart[40].

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[35] Part II, section 1.3.5 of Annex II.

[36] EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2010a *Guidance on the environmental risk assessment of GM plants*. EFSA Journal 2010;8(11):1879, 111 pp. https://doi.org/10.2903/j.efsa.2010.1879.

[37] See *supra* footnote 30.

[38] Part II, section 1.3.1 of Annex II to Regulation (EU) No 503/2013.

[39] Sections 3.5.7 and 3.6.4.2 of EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

[40] Section 3.5.7 of EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

Regarding, in particular, the potential impact of stacking of the transformation events, EFSA assessed all the significant differences between the GM stack soybean and its conventional counterpart, taking into account the potential impact on plant metabolism and the natural variability observed for the set of non-GM reference varieties. It concluded that none of those differences required further assessment except for changes in Gly m 4 protein levels in seed. EFSA further assessed those changes and did not find that they had a safety impact. In addition, the EPSPS enzymes in GM stack soybean is expressed at similar levels as in the parental line MON 89788.

Based on the grounds above, your claims on this point must be rejected.

1.2.4. Data from compositional analysis

In section 2.2.4 of your request, you claim that only data from a low number of agronomic parameters, as required by the EFSA *Guidance on the agronomic and phenotypic characterisation of genetically modified plants*, were subjected to statistical analysis and that those data showed significant differences in the GM stack soybean treated and untreated compared to the conventional counterpart. On that basis, you claim that EFSA should have requested much more data.

According to EFSA, the statistical outcomes for the treated and untreated GM stack soybean compared to the conventional counterparts were not expected to be identical because the statistical analysis was carried out on experimental data with a limited (albeit large) sample size. Furthermore, differences in outcome due to natural background variability were expected. In that regard, the pattern of significant differences (and magnitude thereof) has to be considered in order to determine whether there could be an indication of an altered metabolism[41]. Such pattern is systematically considered by EFSA in its assessment.

In this specific case, the significant differences, in the level of some compounds, unique to the untreated GM stack soybean were very small in magnitude and did not show any consistent pattern that could point to metabolic changes. As shown by the test of equivalence[42], the level of those compounds was within the range of natural variability. Therefore, EFSA considered that the different number of significant results between the GM stack soybean treated and untreated compared to the conventional counterpart was not a reason for concern[43].

In view of the above considerations, your claims on this point must be rejected.

[41] EFSA GMO Panel *(2010), Statistical considerations for the safety evaluation of GMOs.* EFSA Journal, 8: 1250. https://doi.org/10.2903/j.efsa.2010.1250.

[42] Part II, section 1.3.2.1, point (ii) of Annex II to Regulation (EU) No 503/2013.

[43] Section 3.5.6 of the EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

1.3 Toxicity

In section 2.3 of your request, you claim that the EFSA evaluation of the potential toxicity and adverse health effects caused by consumption of food and feed derived from the GM stack soybean does not fulfil the legal requirements. You base your claims on four grounds: (1) the testing of the GM stack soybean was not requested and, therefore, data was lacking to determine the true impact of the intended effects on health; (2) the basic data for the toxicity assessment of Bt proteins in the GM stack soybean are neither valid nor reliable; (3) the potential enhancement of toxic or immunogenic effects caused by interaction of Bt proteins with plant components was not considered; (4) the effects from residues of spraying with intended herbicide specific to the GM stack soybean and their mixed toxicity were not considered.

1.3.1. No testing of the whole stacked plant in spite of findings from molecular characterisation and comparative approach

In section 2.3.1 of your request, you claim that significant changes were identified in the plant composition and agronomic characteristics, and that uncertainties were identified in the feeding studies of the parental lines, which would, according to you, require a feeding study to be carried out with the GM stack soybean.

Regarding the lack of animal studies testing the toxicity of the whole food and feed, the Commission would like to note that they are not required by Regulation (EU) No 503/2013 for stacked transformation events obtained by conventional crossing of GM plants containing a single transformation event, unless the specific hypotheses mentioned in the second paragraph of part II, section 1.4.4.1 of Annex II to the Regulation are identified. EFSA has confirmed that no specific hypotheses requiring animal feeding studies were identified by EFSA to conclude on the safety assessment of this GM stack soybean[44].

However, as required in part II, section 1.4.4.1 of Annex II of Regulation (EU) No 503/2013, animal feeding studies on the parental lines were re-scrutinised in the context of the GM stack soybean application dossier with regard to their adherence to the methodology, and clarification questions were asked to the applicant, as necessary. EFSA confirmed that the studies adhered to the legal requirements and that they did not identify adverse effects[45]. Interpretation of the results of these studies by Member States were duly taken into consideration and assessed by EFSA in the context of the assessment of the single events[46].

As explained in section 1.2.4 above, the significant differences unique to the untreated GM stack soybean were very small in magnitude, did not show any consistent pattern and were within the range of natural variability. Therefore, your claim that those changes justify a more detailed investigation of the impact of the application of the intended herbicide on metabolic pathways is unfounded.

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[44] Section 3.6.3.4 of the EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

[45] Section 3.6.3.4 of the EFSA scientific opinion on the GM stack soybean (see *supra* footnote 8).

[46] Appendix A of the *EFSA technical and scientific assistance on the internal review request* (see *supra* footnote 24).

In view of the above considerations, your allegations on this point must be rejected.

1.3.2. Claims regarding the toxicity of the Bt proteins

In section 2.3.2 of your request, you claim that the assessment of the toxicity of Bt proteins alone or in combination with other stressors was not sufficient. In particular, you consider that the assessment of the potential synergistic or combinatorial effects of Bt proteins was not sufficient considering the uncertainties on the mode of action of these proteins, their differences with the natural templates and the potential stressor effects of herbicides on herbicide tolerant crops, leading to higher levels of expression of such proteins.

You also claim that EFSA did not carefully examine publications by MacIntosh *et al*. (1990)[47] and by Mesén-Porras *et al*. (2020)[48], and other publications showing potential synergistic effects between Bt proteins and other compounds present in the plant such as protease inhibitors and strongly enhancing their toxicity.

Regarding the toxicity of Bt proteins alone or in combination with other stressors, EFSA has previously assessed the publications cited in your request in its *Scientific advice on the internal review under Regulation (EC) No 1367/2006 of the Commission's decision authorising the placing on the market of genetically modified maize MON 87427 × MON 89034 × 1507 × MON 88017 × 59122 and subcombinations*[49]. It found that those publications do not to invalidate its assessment of the safety of Bt proteins (alone or in combination) in food and feed from the assessed GMO.

Regarding, in particular, the publications by MacIntosh *et al*. (1990) and Mesén-Porras *et al*. (2020), a working group organised by the EFSA GMO Panel recently discussed them and concluded that the findings on Bt proteins of those publications do not raise concerns for human and animal health[50].

In view of the above considerations, your allegations on this point must be rejected.

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[47] MacIntosh, S.C., G.M. Kishore, F.J. Perlak, P.G. Marrone, T.B. Stone, S.R. Sims, and R.L. Fuchs. 1990. Potentiation of Bacillus thuringiensis insecticidal activity by serine protease inhibitors. J. Agric. Food Chem. 38:1145-1152. https://doi.org/10.1111/1744-7917.12713.

[48] Mesen-Porras, E., Dahdouh-Cabia, S., Jimenez-Quiros, C., Mora-Castro, R., Rodriguez, C. and Pinto-Tomas, A. 2020. Soybean protease inhibitors increase Bacillus thuringiensis subs. israelensis toxicity against Hypothenemus hampei. Agronomia Mesoamericana, vol.31, n.2, pp.461-478. ISSN 2215-3608. http://dx.doi.org/10.15517/am.v31i2.36573.

[49] EFSA, 2019. Scientific advice on the internal review under Regulation (EC) No 1367/2006 of the Commission's decision authorising the placing on the market of genetically modified maize MON 87427 × MON 89034 × 1507 × MON 88017 × 59122 and subcombinations. EFSA supporting publication 2019:EN-1603. 25 pp. https://doi.org/10.2903/sp.efsa.2019.EN-1603.

[50] Minutes of the 122nd Meeting of the Working Group on Food and Feed Safety, available at https://www.efsa.europa.eu/sites/default/files/wgs/gmo/wg-applications-foodfeed-2018-2021.pdf.

1.3.3. Claims concerning the immunogenicity of the Bt proteins

In section 2.3.3 of your request, you claim that EFSA did not consider the potential enhancement of toxic or immunogenic effects caused by interaction of Bt proteins with plant components in food and feed products derived from the GM stack soybean, and that the GM stack soybean needs to be much more carefully risk assessed for its impact on the immune system compared to genetically engineered plants producing just one Bt protein.

Furthermore, you claim that the safety assessment of this GM stack soybean should have included animal feeding studies on the whole food and feed to investigate long-term organ toxicity, immune responses and impact on the gut microbiome, also taking into account combinatorial effects and mixed toxicity.

EFSA conducted its assessment of the combination of the events in line with the requirements of part I, section 2.2, point (c) of Annex II to Regulation (EU) No 503/2013 and the *EFSA GMO Panel approach to the risk assessment of sub-combinations as required by Implementing Regulation (EU) No 503/2013*[51]. With regard in particular to the assessment of the individual proteins newly expressed in the GM stack soybean, elements considered included, among others, updated bioinformatic searches for their homology to toxic proteins, updated literature searches and an over-conservative exposure assessment in both humans and animals, as provided in part II, section 1.4.1, point (b), and section 1.5.1, point (a) of Annex II to Regulation (EU) No 503/2013.

Regarding potential immunogenic effects of Bt proteins, EFSA has published in the past comprehensive scientific reports addressing similar criticism to its assessments of GM plants and the potential effects of Bt proteins on the immune system[52,53,54]. In those scientific reports, EFSA did not find indications that Bt proteins in the GM stack soybean might act as adjuvants with the potential to enhance a specific immunoglobulin E response and to favour the development of an allergic reaction. Furthermore, as none of the newly expressed proteins in the assessed GM stack soybean showed potential for allergenicity, considering current knowledge, no reasons for concern regarding the simultaneous presence of these newly expressed proteins in the GM stack soybean were expected.

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[51] Annex I to the minutes of the 115th EFSA GMO Panel plenary meeting, available at https://www.efsa.europa.eu/sites/default/files/event/170517-m.pdf.

[52] EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H, Birch AN, Casacuberta J, De Schrijver A, Gralak MA, Guerche P, Jones H, Manachini B, Messéan A, Nielsen EE, Nogué F, Robaglia C, Rostoks N, Sweet J, Tebbe C, Visioli F, Wal J-M, Eigenmann P, Epstein M, Hoffmann-Sommergruber K, Koning F, Lovik M, Mills C, Moreno FJ, van Loveren H, Selb R and Fernandez Dumont A, 2017b. Guidance on allergenicity assessment of genetically modified plants. EFSA Journal 2017;15(5):4862, 49 pp. https://doi.org/10.2903/j.efsa.2017.4862.

[53] EFSA, Dumont AF, Lanzoni A, Waigmann E and Paoletti C, 2018b. Relevance of new scientific information (Santos-Vigil et al., 2018) in relation to the risk assessment of genetically modified crops with Cry1Ac. EFSA supporting publication 2018:EN-1504. 13 pp. https://doi.org/10.2903/sp.efsa.2019.EN-1504.

[54] Parenti MD, Santoro A, Del Rio A, Franceschi C, 2019. Literature review in support of adjuvanticity/immunogenicity assessment of proteins. EFSA supporting publication 2019:EN-1551. 68 pp. https://doi.org/10.2903/sp.efsa.2019.EN-1551.

In conclusion, the Commission is of the view that EFSA assessment of this GM stack soybean fulfils the requirements of the GMO legislation as regards evaluation of potential synergistic or antagonistic effects resulting from the combination of the transformation events in the GM stack soybean, in particular with regard to potential toxicity and adverse health effects from the consumption of food and feed derived from it. In addition, in relation to allergenicity and immunogenicity, EFSA performed its risk assessment according to part II, section 1.5 of Annex II to Regulation (EU) No 503/2013 and its *Guidance for risk assessment of food and feed from genetically modified plants*, the principles of which are aligned with the *Codex Alimentarius* (2009)[55].

In view of the above considerations, your claims on this point must be dismissed.

1.3.4. Effects from residues of intended herbicides and their mixed toxicity

In section 2.3.3 of your request, you recall that residues from spraying were considered by EFSA to be outside its remit, and claim that without a detailed assessment of these residues, no conclusion can be drawn on the safety of the imported products.

You state that it should be taken into account that EFSA, in its review of the maximum residue level ('MRL') for glyphosate, explicitly stated that no conclusion can be drawn on the safety of residues from spraying with glyphosate occurring in genetically engineered plants made resistant to this herbicide.

You also claim that glyphosate is known to cause shifts in the microbial composition and associated microbiomes of plants and animals, thus leading to a specific situation with regard to chronic exposure from food consumption.

You further claim that the analysis of the toxicity data for glyphosate and dicamba indicate higher toxicity if the two herbicides are combined, and state that EFSA should have at least requested data on the combined toxicity of the residues from spraying with the intended herbicides.

The Commission would like to clarify that under Articles 4(1)(a) and 16(1)(a) of Regulation (EC) No 1829/2003, GM food and feed must not have adverse effects on human health, animal health or the environment. However, these conditions for the authorisation of GM food and feed under Regulation (EC) No 1829/2003 do not cover the assessment of the potential effects of pesticide residues on human health, including possible cumulative effects.

This has been confirmed by the Court of Justice of the European Union in its judgment of 12 September 2019 in Case C-82/17P, *TestbioTech and Others v. Commission*[56] (par. 106 and 107), which upheld the General Court's interpretation that the assessment of the effects of pesticide residues on health is not covered by Regulation (EC) No 1829/2003 but by Regulation (EC)

[56] ECLI:EU:C:2019:719.

No 396/2005 of the European Parliament and of the Council on maximum residue levels[57] (Case T-177/13[58], par. 233 and 289). The safety of GM food and feed products with a possible presence of pesticide residues is therefore guaranteed by the combined application of Regulations (EC) No 1829/2003 and No 396/2005.

In any event, Regulation (EC) No 396/2005 applies to pesticide residues on all food and feed placed on the market in the EU, including food and feed imported from third countries, and whether they are conventional or GM products. As any other food and feed, GM products placed on the EU market have to comply with the corresponding MRLs under Regulation (EC) No 396/2005.

In addition, in its reasoned opinion on the review of MRLs for glyphosate, EFSA proposed soybeans MRLs based only on conventional soybean crops (the only existing uses in the EU) given that no data on import tolerances within the meaning of Regulation (EC) No 396/2005 was available as regards GM soybean crops. Consumer safety is further increased by the fact that the residue definitions included metabolites that occur on both conventional and glyphosate tolerant GM crops. Moreover, EFSA performed an acute and chronic consumer exposure assessment resulting from the authorised uses on conventional and GM crops reported in the frame of that review and concluded that there was no risk to consumers.

The Commission would also like to note that, together with EFSA and the Member States, it is working on developing methodologies for assessing the risk from combined exposures to pesticide residues. Based on monitoring data, EFSA recently published pilot assessments of dietary exposures with effects on the nervous system[59,60] and the thyroid[61]. Work is further evolving for the MRL-setting scenario in accordance with the recent Action Plan[62] published by EFSA and the European Commission, which also includes possible expansion to non-dietary evaluations. Further discussion on a risk management level will determine alternatives for regulatory application of the methodology.

Finally, regarding your claim that glyphosate has an impact on plants and animal microbiomes, EFSA recently launched a call for a thematic grant on the evaluation of the impact of microbiomes in risk assessment, including gastrointestinal tract microbiomes (human and domestic animals) and environmental microbiomes (plants, wildlife, soil)[63]. The microbiome is also being considered as a possible future scientific theme by the Science Studies and Project Identification & Development Office of EFSA (SPIDO)[64]. Furthermore, the need to explore the

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57 Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (OJ L 70, 16.3.2005, p. 1).

58 Judgment of 15 December 2016, *Testbio Tech and Others v. Commission*, ECLI:EU:T:2016:736.

59 https://www.efsa.europa.eu/en/efsajournal/pub/6087

60 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2021.6392

61 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6088

62 https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_cum-risk-ass_action-plan.pdf

63 https://www.efsa.europa.eu/en/news/new-grant-opportunity-microbiomes-and-plant-pests

64 https://www.efsa.europa.eu/en/events/event/79th-advisory-forum-meeting, item 2.5

integration of microbiomes in EFSA risk assessment is included in the draft EFSA 2027 strategy, currently under public consultation.

In view of the above considerations, your allegations on this point must be rejected.

1.4 Allergenicity

Firstly, in section 2.4.1 of your request, you claim that EFSA's assessment of the GM stack soybean does not fulfil the legal requirements for assessing allergenicity of the source of the transgene, because the allergenicity of the Bt protein Cry1Ac, which was used as a source for the Cry1A.105 toxin expressed in the GM stacked soybean, was not investigated in detail. In support of your claim, you refer to the publication of Santos-Vigil *et al*. (2018)[65], according to which Cry1Ac is thought to be allergenic. You claim that this publication is also relevant in the case of Cry1A.105 and that the EFSA technical report on this publication[66] is biased.

Secondly, in section 2.4.2 of your request, you claim that potential synergistic effects between Bt proteins and other compounds present in the plant, such as protease inhibitors, were not carefully examined regarding potential adjuvanticity of Bt proteins.

With regard to your first claim, the Commission does not share your views that EFSA's assessment of the Santos-Vigil *et al.* (2018) publication is biased. In that regard, an external report on immunogenicity commissioned by EFSA, Parenti *et al*. (2019), has been published[67]. This report also discusses the adjuvanticity of Bt proteins and concludes that:

> "*The adjuvanticity and immunogenicity of Cry proteins in certain experimental conditions seems plausible but due to low dosage, oral route of administration, food and feed processing and digestion, it is unlikely to emerge as a safety issue in food and feed. This assessment is consistent with the assessment by the EFSA GMO panel whereby they concluded that there is not a safety concern for the health of humans or animals that consume food/feed derived from GM plants containing Cry proteins. […]*"[68]

This conclusion confirms the EFSA conclusions on immunogenicity and adjuvanticity of Bt proteins.

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[65] Santos-Vigil, K.I., Ilhuicatzi-Alvarado, D., García-Hernández, A.L., Herrera-García, J.S., Moreno-Fierros, L. (2018) Study of the allergenic potential of Bacillus thuringiensis Cry1Ac toxin following intra-gastric administration in a murine model of food-allergy. Int Immunopharmacol, 61: 185-196. https://doi.org/10.1016/j.intimp.018.05.029.

[66] See *supra* footnote 54.

[67] Parenti, M.D., Santoro, A., Del Rio, A., Franceschi, C. (2019) Literature review in support of adjuvanticity/immunogenicity assessment of proteins. EFSA Supporting Publications, 16(1): 1551E. https://doi.org/10.2903/sp.efsa.2019.EN-1551.

[68] Section 4, point vi.

In addition, as mentioned above, EFSA has published in the past comprehensive scientific reports addressing similar questions on its assessment of GM plants and the potential effects of Bt proteins on the immune system and has found no reason for concern (see section 1.3.3 above).

It should also be noted that EFSA performed its risk assessment according to relevant guidelines, the principles of which are aligned with the *Codex Alimentarius* (2009).

In addition, the assessment of allergenicity of the whole GM stack soybean was also considered. Protease inhibitors are compounds naturally occurring in specific crops. In that respect, it is noted that the composition of the GM stack soybean was also analysed, and it included an analysis of the Kunitz trypsin inhibitor. Considering all the information available, EFSA considered that there was no evidence that the genetic modification might substantially change the overall allergenicity of the GM stack soybean assessed when compared to their non-GM comparators and non-GM reference varieties tested[69].

In view of the above considerations, your claims on this point must be rejected.

2. Post-market monitoring requirement in the Commission Implementing Decision

In section 3.2 of your request, you claim, firstly, that the detection methods provided by the applicant should not have been accepted because they do not allow, under practical conditions, to identify the GM stack soybean and to distinguish it from other already authorised stacked or single events that inherit the same gene constructs and that can be mixed in the diets. Secondly, you indicate that the post-market monitoring plan should have included some pieces of information, such as import volumes and volumes used in the EU. Finally, you make a number of observations regarding where and how environmental monitoring should be carried out.

Regarding the first claim, in accordance with Articles 5(3)(i) and 17(3)(i) of Regulation (EC) No 1829/2003, the applicant must provide the methods of detection, sampling and identification of the transformation event, in accordance with the requirements set out in Article 8 and Annex III to Regulation (EU) No 503/2013.

For GMOs with stacked events, the Commission's Joint Research Centre ('JRC'), which is the European Union Reference Laboratory for GM food and feed ('EURL GMFF')[70], carries out a verification study to assess the performance of the event-specific methods, previously validated on parental lines, to detect and quantify the transformation event(s) on DNA from the stacked GMO containing several transgenic events. The results of the EURL GMFF verification are available online[71].

The detection methods validated by the EURL GMFF for the purposes of carrying out its tasks pursuant to Regulation (EC) No 1829/2003 are event-specific. Therefore, by applying several of

[69] Section 3.6.4.2 of EFSA Scientific opinion on the GM stack soybean (see *supra* footnote 8).

[70] The JRC/EURL GMFF is in charge of testing and validating the methods of detection and identification proposed by the applicants in accordance with Articles 6(3)(d) and 18(3)(d) of Regulation (EC) No 1829/2003.

[71] Available at: http://gmo-crl.jrc.ec.europa.eu/statusofdossiers.aspx.

such methods, it is possible to appropriately identify multiple GMO events in a food or feed sample, may the events correspond to different GMOs or to the same GMO. However, distinguishing between the potential presence of an equimolar mixture of single-event GMOs and a stacked-event GMO in a food or feed product usually requires additional information besides the laboratory measurement results.

In any case, in your request, you do not provide any evidence to support your claim that the GM soybean in question cannot be distinguished from other GM stacked or single events. Therefore, your allegation on this point must be rejected.

As regards your second claim, the Commission notes that, in accordance with Article 5(3)(k) of Regulation (EC) No 1829/2003, the application for authorisation may include, *'where appropriate, a proposal for post-market monitoring regarding the use of the food for human consumption'*. Article 6(5)(e) provides that post-market monitoring requirements may be imposed ('*where applicable'*), *'based on the outcome of the risk assessment'*. In the case at hand, the applicant did not propose a post-market monitoring regarding the use of the GM stack soybean in food, and EFSA in its opinion did not identify the need for such monitoring on the basis of the risk assessment. Your request does not provide any argumentation or evidence showing that such a monitoring was needed based on the outcome of the risk assessment.

Finally, concerning the monitoring plan for environmental effects, the Commission notes that, as stated in recital 6 of Commission Implementing Decision (EU) 2021/66, EFSA concluded that the plan submitted by the applicant, consisting of a general surveillance plan, was in line with the intended uses of the products. In your request, you simply mention aspects, including where and how environmental monitoring should be carried out, which were not included in the plan, without providing any argumentation or evidence as to the reasons why they should have been included or as to the way in which they were at odds with the requirements of Annex VII to Directive 2001/18/EC[72].

Based on the above considerations, the Commission is of the view that your claims regarding the detection methods and the post-market monitoring requirement in Commission Implementing Decision (EU) 2021/66 are unfounded.

[72] 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, 17.4.2001, p. 1–39)