Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-RX-014 (maize MON 88017) from Monsanto under Regulation (EC) No. 1829/2003

23 April 2020
Ref. SC/1510/BAC/2020_0362

Context

Application EFSA-GMO-RX-014 was submitted by Monsanto for the renewal of authorisation for the marketing of genetically modified (GM) maize MON 88017 for food and feed uses, import and processing (excluding cultivation) within the European Union within the framework of Regulation (EC) No. 1829/2003[1].

Maize MON 88017 expresses a modified Cry3Bb1 protein which provides protection to certain coleopteran pests and the CP4 EPSPS protein which confers tolerance to glyphosate herbicides. The placing on the market of maize MON 88017 for food/feed uses, except cultivation, is currently authorised by Commission Decision 2009/814 of 30 October 2009, amended by Commission Implementing Decision (EU) 2019/1579 of 18 September 2019, following a positive opinion of EFSA (EFSA Journal 2009;1075, 1-28)[2] on 21 April 2009, and a positive advice of the Belgian Biosafety Advisory Council (BAC) on 13 July 2009.

The renewal application was validated by EFSA on 17 December 2018 and a formal three-month consultation period of the Member States was started, lasting until 21 March 2019, in accordance with Articles 6.4 and 18.4 of Regulation (EC) No. 1829/2003 (consultation of national Competent Authorities within the meaning of Directive 2001/18/EC designated by each Member State in the case of genetically modified organisms being part of the products).

Within the framework of this consultation, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the updated bioinformatics study provided in the dossier, chosen from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB). Four experts answered positively to this request, and formulated a number of comments to the dossier. See Annex I for an overview of all the comments and the comments sent to EFSA on 19 March 2019.

The opinion of the EFSA Scientific Panel on GMOs was published on 11 March 2020 (EFSA Journal 2020;18(3):6008)[3], together with the responses from the Panel to comments submitted by the Member States during the three-month consultation period. These documents were sent to the experts who evaluated the application on 13 March 2020, while inviting them to react if needed.

The comments formulated by the experts on the renewal application together with the opinion of EFSA, as well as the previous advice of the BAC on maize MON 88017 (BAC_2009_01045)[4], form the basis of the advice of the Biosafety Advisory Council on application EFSA-GMO-RX-014 given below.

[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).
[2] https://doi.org/10.2903/j.efsa.2009.1075
[3] https://doi.org/10.2903/j.efsa.2020.6008
[4] http://www.bio-council.be/Advices/BAC_2009_01045.pdf

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Scientific evaluation

The data for application EFSA-GMO-RX-014 provided by the applicant at the time of submission included the annual post-market environmental monitoring (PMEM) reports covering the years of import, two systematic literature searches covering the period from January 2008 till September 2019, an updated bioinformatic package including an analysis of the potential similarity of the newly expressed proteins and newly created open reading frames within the insert or spanning the junctions with genomic DNA to known toxins or allergens, an analysis of possible horizontal gene transfer, a safety assessment of the newly expressed proteins Cry3Bb1 and CP4 EPSPS regarding their capacity to trigger celiac disease, and reports of additional studies performed by the applicant over the course of the authorisation period.

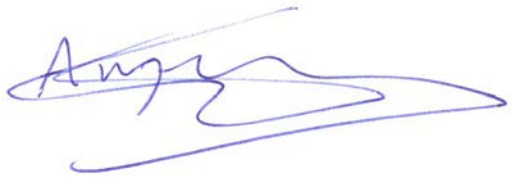
The Belgian experts and the members of the Biosafety Advisory Council did not identify any information elements in the renewal application EFSA-GMO-RX-014 that would raise a safety concern for human or animal health or the environment.

Conclusion

Based on the whole set of data on maize MON 88017 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion of EFSA, and the original advice of the BAC on maize MON 88017, the Biosafety Advisory Council is of the opinion that in the context of its proposed uses, maize MON 88017 is unlikely to pose any risk to human and animal health.

The Biosafety Advisory Council did not identify any risk that the import and processing of this GM maize could pose to the European environment.

In addition, the Biosafety Advisory Council recommends following up any unanticipated allergenicity aspects of the GM maize in the existing allergenicity monitoring systems.



Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex I: Compilation of comments of experts in charge of evaluating the application EFSA/GMO/RX-014 (ref. BAC_2019_0245)

Adviesraad voor Bioveiligheid
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Outcome of the assessment of application EFSA/GMO/RX-014 by the Biosafety Council during the formal consultation of the Member States (3-month commenting period in accordance with Articles 6.4 and 18.4 of Regulation (EC) No 1829/2003)

19 March 2019
Ref. SC/1510/BAC/2019_0245

Coordinator: René Custers
Experts: Peter Smet (Consultant), Frank Van Breusegem (UGent), Jan Van Doorsselaere (Vives), Nicolas Van Larebeke (UGent)
SBB: Fanny Coppens

Application for renewal: **EFSA/GMO/RX-014**
Applicant: **Bayer**
GMO: **Maize MON 88017**
Validation of dossier by EFSA: **21 December 2018**

Scope of the application:
☒ GM plants for food use
☒ Food containing or consisting of GM plants
☒ Food produced from GM plants or containing ingredients produced from GM plants
☒ GM plants for feed use
☒ Feed produced from GM plants
☒ Import and processing (Part C of Directive 2001/18/EC)
☐ Seeds and plant propagating material for cultivation in European Union (Part C of Directive 2001/18/EC)

Since the previous application for this event had received a positive advice from the Biosafety Advisory Council, and given the new information provided in the current application for renewal, experts were only requested to evaluate the **updated bioinformatics studies**.

The comments are structured as in the "Guidance for renewal applications of genetically modified food and feed authorised under Regulation (EC) 1829/2003" (EFSA Journal 2015;13(6):4129).
Comments sent to EFSA are indicated in grey. It should be noted that all the comments received from the experts are considered in the evaluation of this dossier and in formulating the final advice of the Biosafety Advisory Council.

List of comments/questions received from the experts

A. GENERAL COMMENTS

N/A

B. DATA REQUIREMENTS

B.1. COPY OF AUTHORISATION FOR PLACING THE FOOD/FEED ON THE MARKET

N/A

B.2. POST-MARKET MONITORING AND POST-MARKET ENVIRONMENTAL MONITORING REPORTS

N/A

B.3. NEW INFORMATION

B.3.1. SYSTEMATIC SEARCH AND EVALUATION OF LITERATURE:

N/A

B.3.2. UPDATED BIOINFORMATICS

- similarity searches for known toxic and/or allergenic proteins, using up-to-date databases, for all ORFs between stop codons without applying a size limit.
- information on the similarities of DNA sequences inserted in the plant genome with microbial DNA sequences, with an assessment of potentially altered likelihood for horizontal gene transfer, together with an evaluation of the consequences for human and animal health and the environment.

Have evaluated this section and consider the information adequate: 3 experts

Comment 1

Remarks concerning the document Annex 3

As to reference publications concerning safety: *Healy et al. (2008). Results of a 13-week safety assurance study with rats fed grain from corn rootworm-protected, glyphosate-tolerant MON 88017 corn. Food and Chemical Toxicology, 46, 2517-2524.*
An experiment on rats with a duration of 13 weeks gives insufficient information concerning cancer and other chronic diseases.

Coordinator comment: The reference describes the results of a 90-day sub-chronic toxicity study. These are not carcinogenicity studies. Carcinogenicity studies are not required by law.

As to the exclusion of studies: (Tabel 7 in Annex3_MON_88017_Renewal)
In my opinion the papers by Bernillon et al.(2018), Fedorenko et al.(2012) en Nakajima et al. (2010) have a certain relevance.

Coordinator comment: Agree that Nakajima does have relevance. It confirms a certain safety aspect of the Cry3Bb protein. The other two references are not relevant.

Remarks concerning Skottke and Silvanovich 2018a

In the Skottke and Silvanovich 2018a document " Expanded Bioinformatic Evaluation of MON 88017 Utilizing 2018 Databases" following statement is of particular interest:

"*To identify the insert location and nearest neighboring genomic features, the insert site conventional sequence was used to query a maize genome assembly (Zmays_2018). The results indicated that a putative endogenous ORF, encoding Putative Purine Permease 11, was disrupted by the insertion of T-DNA in MON 88017. Currently there is no evidence to suggest that this ORF produces biologically significant protein in conventional or MON 88017 maize and there is no indication that MON 88017 produces unintentional proteins that are harmful to human health. Regardless, the MON 88017 T-DNA is placed within chromosome 4 of the maize genome*."

Coordinator comment: That's OK: no indications that the ORF produces biologically significant proteins. But what about the disruption of the putative purine permease 11 gene? Apparently there are also no indications that this disruption would have any negative consequences as the plant grows normally and has a composition that is comparable to the non-GM counterpart.

The purine permeases (PUPs) constitute a large plasma membrane-localized transporter family in plants that mediates the proton-coupled uptake of nucleotide bases and their derivatives, such as adenine, cytokinins, and caffeine (Kato t al., 2015). Apparently Purine permease genes are involved in growth regulation of plants. See:

> X. Ji, Y. Du, F. Li, H. Sun, J. Zhang, J. Li, T. Peng, Z. Xin, and Q. Zhao. The basic helix-loop-helix transcription factor, OsPIL15, regulates grain size via directly targeting a purine permease gene OsPUP7 in rice. *Plant Biotechnol.J.*, 2019.
>
> Y. Xiao, D. Liu, G. Zhang, S. Gao, L. Liu, F. Xu, R. Che, Y. Wang, H. Tong, and C. Chu. Big Grain3, encoding a purine permease, regulates grain size via modulating cytokinin transport in rice. *J.Integr.Plant Biol.*, 2018.

Purine permease genes are involved in the cytokinin signaling pathway in plants as cytokinin transporters See

> K. Zhang, L. Zhao, X. Yang, M. Li, J. Sun, K. Wang, Y. Li, Y. Zheng, Y. Yao, and W. Li. GmRAV1 regulates regeneration of roots and adventitious buds by the cytokinin signaling pathway in Arabidopsis and soybean. *Physiol Plant*, 2018.
>
> J. Kang, Y. Lee, H. Sakakibara, and E. Martinoia. Cytokinin Transporters: GO and STOP in Signaling. *Trends Plant Sci.* 22 (6):455-461, 2017.

Cytokinins are phytohormones essential for cytokinesis and many other physiological and developmental processes in planta. Long-distance transport and intercellular transport have been postulated. For these processes, the existence of cytokinin transporters has been suggested. Recently, a transporter loading the xylem (AtABCG14) and another for cellular import (AtPUP14) have been discovered. AtABCG14 participates in the xylem loading process of cytokinins and contributes to the positive regulation of shoot growth. The cellular importer AtPUP14 is required to suppress cytokinin signaling. A role of a transporter as stop signal is a new paradigm for a hormone transporter. Plant development is regulated by cytokinin sinks such as PURINE PERMEASE 14. (E. Zurcher, J. Liu, Donato M. di, M. Geisler, and B. Muller. Plant development regulated by cytokinin sinks. *Science* 353 (6303):1027-1030, 2016.)

Purine permease genes can play a role in the stability of biofilms. See:

> R. Gallegos-Monterrosa, S. Kankel, S. Gotze, R. Barnett, P. Stallforth, and A. T. Kovacs. Lysinibacillus fusiformis M5 Induces Increased Complexity in Bacillus subtilis 168 Colony Biofilms via Hypoxanthine. *J.Bacteriol.* 199 (22), 2017.

In the Skottke and Silvanovich 2018a document " Expanded Bioinformatic Evaluation of MON 88017 Utilizing 2018 Databases" following statement is of particular interest:
"*The FASTA analysis revealed that two translated frames yielded a protein sequence which exceeded the threshold of >35% identity over 80 amino acids (Codex Alimentarius 2009) to sequences in the AD_2018 database. However, each of the parsed protein sequences displayed an extreme compositional bias towards proline and/or glycine; therefore, these alignments do not reflect*

conserved structure or function indicating that its potential for inducing an allergenic response is highly unlikely."
While it is certain that conserved structure increases the probability of allergic reactions, its absence does probably not exclude allergic reactions.

Coordinator comment: See comments below regarding Skottke and Silvanovich 2018b.

Remarks concerning Skottke and Silvanovich 2018b

In the Skottke and Silvanovich 2018b document " Updated Bioinformatics Evaluation of MON 88017 Utilizing the AD_2018, TOX_2018, PRT_2018, EST_2018, NT_2018, and NR_2018 Databases" following statement is of particular interest:

When using the translated frame sequences to search the AD_2018 database a single frame, frame_6, returned alignments with E-score of ≤1e-5 (Table 8, Appendices 12-17). Frame_6 also resulted alignments that exceeded the (Codex Alimentarius, 2009) threshold of 35% identity over 80 amino acids and yielded 8-mer matches (Appendix 17). All 4 of the threshold exceeding alignments were to putative ragweed homologues of Art v 1. The top alignment to CBK62695.1 yielded an E-score of 1e-6 and displayed 46.5% identity in a window of 71 amino acids. While this alignment length is less than 80 amino acids, the percentage of identical aligning amino acids is sufficient to produce 35% identity in 80 amino acids even if nine non-identical amino acids were added to the alignment. Further inspection of the ragweed homologues of Art v 1 alignments revealed they were heavily biased by glycine identities. Of the 33 identical aligning amino acids in the top alignment, 27 were between glycine residues while the remaining six were with proline, lysine, or glutamic acid. As such, these alignments are not likely to reflect conserved structure or function between the Art v 1 homologues due to the extreme compositional bias favoring glycine.

Coordinator comment: We could make the following remark to EFSA: "The dismissal of the relevance of the 35% homology within a 80 amino-acid window is based upon the observation that the vast majority of identical amino acids were glycine residues , while the remaining were with proline, lysine or glutamic acid. This is judged by the applicant not to reflect a conserved structure or function between the ORF and the Art v1 homologues. We think it is important that this judgement is validated by 3D protein experts."

Ragweed homologue of Art v 1has some similarity with Scorpion_toxin-like. A close relative of mugwort, ragweed (Ambrosia artemisiifolia) is an important allergen source in North America, and, since 1990, ragweed has become a growing health concern in Europe as well (Leonard et al., 2010). Apparently ragweed induced allergies are a mounting problem in America, Europe and Asia as described below (Ihler & Canis, 2014):

> *"Ragweed (Ambrosia spp.) is an annually flowering plant whose pollen bears high allergenic potential. Ragweed-induced allergic rhinoconjunctivitis has long been seen as a major immunologic condition in Northern America with high exposure and sensitization rates in the general population. The invasive occurrence of ragweed (A. artemisiifolia) poses an increasing challenge to public health in Europe and Asia as well. Possible explanations for its worldwide spread are climate change and urbanization, as well as pollen transport over long distances by globalized traffic and winds. Due to the increasing disease burden worldwide, and to the lack of a current and comprehensive overview, this study aims to review the current and emerging treatment options for ragweed-induced rhinoconjunctivitis. Sound clinical evidence is present for the symptomatic treatment of ragweed-induced allergic rhinoconjunctivitis with oral third-generation H1-antihistamines and leukotriene antagonists. The topical application of glucocorticoids has also been efficient in randomized controlled clinical trials. Combined approaches employing multiple agents are common. The mainstay of causal treatment to date, especially in Northern America, is subcutaneous immunotherapy with the focus on the major allergen, Amb a 1. Beyond this, growing evidence from several geographical regions documents the benefit of sublingual immunotherapy. Future treatment options promise more specific symptomatic treatment and fewer side effects during causal therapy. Novel antihistamines for symptomatic treatment are aimed at the histamine H3-receptor. New adjuvants with toll-like receptor 4 activity or the application of the monoclonal anti-immunoglobulin E antibody, omalizumab, are supposed to enhance conventional immunotherapy. An approach targeting*

toll-like receptor 9 by synthetic cytosine phosphate–guanosine oligodeoxynucleotides promises a new treatment paradigm that aims to modulate the immune response, but it has yet to be proven in clinical trials."

In the Skottke and Silvanovich 2018b document " Updated Bioinformatics Evaluation of MON 88017 Utilizing the AD_2018, TOX_2018, PRT_2018, EST_2018, NT_2018, and NR_2018 Databases" following statement is of particular interest:
" *Frame 1 yielded a single threshold-exceeding alignment to BAB11757.1, which corresponds to the 81-kDa leukemia toxin from Bacillus thuringiensis. This alignment displayed 23.6% identity over 445 amino acids, with an E-score of 3e-6. Inspection of this alignment revealed that while it required numerous gaps to optimize the alignment, it is classified as the non-insecticidal Cry protein, Cry31Aa1 (Crickmore et al., 2016; Mizuki et al., 2000). Identification of a Cry family protein related to the MON 88017- produced Cry3Bb1 protein is not unexpected and does not suggest potential adverse biological activity."*

Bacillus thuringiensis is a gram-positive bacterium producing insecticidal proteins against agricultural and medical pests during sporulation. Lee et al (2000) characterized a novel strain producing a protein with toxic effects on human cells resembling the effect of insecticidal Cry toxins in lepidopteran insect cells. These toxic effects were more pronounced on leukemia cells than on normal cells. The statement by Monsanto "*Identification of a Cry family protein related to the MON 88017- produced Cry3Bb1 protein is not unexpected and does not suggest potential adverse biological activity"* should be more substantiated. Monsanto should explain clearly why there is no reason for concern.

In the Skottke and Silvanovich 2018b document " Updated Bioinformatics Evaluation of MON 88017 Utilizing the AD_2018, TOX_2018, PRT_2018, EST_2018, NT_2018, and NR_2018 Databases" following statements are of particular interest:

Frame 2 yielded a single threshold-exceeding alignment. However, this alignment was punctuated with numerous stop codons and required numerous gaps to optimize the alignment, which indicate a lack of highly conserved structural homology and therefore this alignment does not suggest a potential for toxicity.

Frame 3 yielded two threshold-exceeding alignments. However, these alignment were punctuated with numerous stop codons and required numerous gaps to optimize the alignment, which indicate a lack of highly conserved structural homology and therefore this alignment does not suggest a potential for toxicity.

Is it certain that a highly conserved structural homology is a necessary condition for toxicity?

Coordinator comment: No as such it is not. But in the risk assessment we use the bio-informatics analysis to identify identities with known allergens and toxins, and if they are not identified, we conclude that the risks of something being toxic or allergenic is acceptably low.

In the Skottke and Silvanovich 2018b document " Updated Bioinformatics Evaluation of MON 88017 Utilizing the AD_2018, TOX_2018, PRT_2018, EST_2018, NT_2018, and NR_2018 Databases" following statement is of particular interest:
"*Inspection of the remaining alignments that displayed 95% or greater identity revealed that they were all within the aligned regions described above. These data indicate that the T-DNA insert in MON 88017 may have disrupted 18 bp of the 5' end of a maize cDNA sequence. Based upon the observed proximity of the cDNA sequence to the T-DNA insertion site and results of the BLASTx alignment described in Section 6.3.3, it is possible that the T-DNA is inserted into the 5¢ UTR of a putative gene.*"

Is there any means of knowing what kind of gene might be involved?

Coordinator comment: I propose that we send the following remark: “In Skottke and Silvanovich 2018a the applicant states that the insert has disrupted a native putative purine permease, while in Skottke and Silvanovich 2018b it is concluded that the T-DNA insert is ‘possibly inserted into a putative gene’. Can the applicant explain these different conclusions?”

Some considerations related to allergy and to the potential link with GMO

According to the World Allergy report allergic diseases are increasing in prevalence worldwide (Pawankar et al., 2008) .In the UK, the prevalence of allergic disorders has risen importantly over several decades, but rates have stabilized over the past decade (Gupta et al., 2007). In the UK admissions for some systemic allergic diseases have however risen sharply in the last decade which may indicate a rising incidence of these Conditions (Gupta et al., 2007). In most countries, the prevalence of asthma has been reported to increase in the last few decades (Eder et al., 2006).
It should be noted that inflammation induced by allergic reactions can contribute through mast cell activation to a certain degree to many diseases including atherosclerosis, pulmonary hypertension, ischemia-reperfusion injury, male infertility, autoimmune disorders such as rheumatoid arthritis and multiple sclerosis, bladder pain syndrome (interstitial cystitis), anxiety, Alzheimer's disease, nociception, obesity and diabetes mellitus (Anand et al., 2012).
The incidence and prevalence of allergic conditions has been on the rise in the last decadesIgE-mediated food allergies are regarded as a relevant health concern and affect up to 0.1–3.2% adults and 0.1–5.7% children in Europe. According to structural, biochemical, and functional characteristics, the so far identified allergenic proteins are found within a fairly limited number, i.e. approximately 2%, of protein families compared to all known protein families (Mazzucchelli et al., 2018)

According to Herman & Ladics (2018), some of the debate surrounding the weight-of evidence criteria for predicting the allergenic risk of GM crops can be resolved by explicitly distinguishing between sensitization risk and elicitation risk.

The established and currently applied methods are based on a homology assessment to already identified allergens. Thus, these methods are of limited applicability for novel proteins lacking homology to already identified proteins (Mazzucchelli et al., 2018). As far as I understood, in this renewal application the newly introduced gene and its product are checked for potential sequence and/or structure similarity to known allergens. But no attempt was made to investigate whether significant higher IgE binding is observed in the GMO-product as compared to its isogenic counterpart (specific serum screening) by using sera from allergic donors in in vitro assays. Also, to assess the de novo sensitizing capacity of such novel foods, in vivo testing in animals, or cell culture systems have been proposed and some have shown experimental evidence of principle applicability (Mazzucchelli et al., 2018).

A reassuring message is found in a systematic review by Dunn et al. 2017, but the authors are collaborators of Monsanto and have conflicts of interest. According to these authors no animal or human study was identified that demonstrated evidence that a GM food item was more allergenic than its conventional counterpart. No studies were identified that demonstrated that direct consumption of a GM food was associated with an increased rate of clinical allergy (eg, allergy being defined as typical signs or symptoms of IgE-mediated mast cell reactivity in human or animal models) compared with its conventional counterpart. Of the 83 studies identified, only 3 noted increased sensitization to the GM product.

Interestingly, it has been shown that genetic modification can be used to reduce allergenicity of food by genetic modification of apples to reduce Mal d 1 gene expression (Dubois et al., 2015).

Coordinator comment: These are general comments about the allergenicity assessment and are not comments on this specific dossier. There may be merit however to feed these remarks into general discussions on allergenicity assessment at the level of EFSA.

Concerns

The main problem associated with the import of plants genetically modified to be resistant to herbicides may be, certainly on the longer term, the increase in human exposure to herbicides. According to new research from University of Virginia economist Federico Ciliberto (Perry et al., 2016), widespread adoption of genetically modified crops has decreased the use of insecticides, but increased the use of weed-killing herbicides as weeds become more resistant. On average, adopters of GE glyphosate-tolerant (GT) soybeans used 28% (0.30 kg/ha) more herbicide than nonadopters,

adopters of GT maize used 1.2% (0.03 kg/ha) less herbicide than nonadopters. In addition, the results indicate that the difference in pesticide use between GE and non-GE adopters has changed significantly over time. For both soybean and maize, GT adopters used increasingly more herbicides relative to nonadopters. The estimated pattern of change in herbicide use over time is consistent with the emergence of glyphosate weed resistance (Perry et al., 2016).

I am of the opinion that an "Application for renewal of the authorization" should comprise a study of the recent literature (2008-2018) concerning possible biological or adverse effects of Cry3Bb1 protein 5-enolpyruvylshikimate-3-phosphate synthase, MON 88017 maize and food containing MON 88017 maize as well in vitro, in vivo and in epidemiological studies.
Purine permeases are important genes involved in the regulation of the development of the plant. It is however likely that purine permease 11 is not essential.

Monsanto argues with respect of possible similarities with allergenic or toxic proteins that " *lack of highly conserved structural homology"* renders allergenic or toxic activities highly unlikely. This is probably correct, but does not totally exclude allergenic or toxic activities. In terms of allergenicity these methods are of limited applicability for novel proteins lacking homology to already identified proteins (Mazzucchelli et al., 2018). As far as I understood, in this renewal application the newly introduced gene and its product are checked for potential sequence and/or structure similarity to known allergens. But no attempt was made to investigate whether significant higher IgE binding is observed in the GMO-product as compared to its isogenic counterpart (specific serum screening) by using sera from allergic donors in in vitro assays. Also, to assess the de novo sensitizing capacity of such novel foods, in vivo testing in animals, or cell culture systems have been proposed and some have shown experimental evidence of principle applicability (Mazzucchelli et al., 2018). In my opinion thorough tests in vitro and in vivo are necessary to exclude allergenicity and toxicity.

CONCLUSION
I am of the opinion that the present renewal application does not provide sufficient guaranties to exclude potential adverse effects of MON 88017 maize on human health. At least a thorough study of the published literature in the period 2008-2018 is necessary as mentioned in the paragraph on concerns. Although I belief firmly that genetically modified organisms can contribute importantly to the production of healthy food in sufficient quantities, the use of plants made resistant to herbicides will lead to an increase in human internal exposure to herbicides, what will probably increase the risk of a series of diseases

SBB and coordinator comments:

- Updated literature studies were provided in the dossier by the applicant, this evaluation is only aimed at the updated bioinformatics studies that were provided in the frame of this renewal application.
- The evaluation of the safety of pesticides is not within the remit of the Biosafety Advisory Council.

References not already included in the text:

Anand, P., B. Singh, A. S. Jaggi, and N. Singh. Mast cells: an expanding pathophysiological role from allergy to other disorders. *Naunyn Schmiedebergs Arch.Pharmacol.* 385 (7):657-670, 2012.

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Gupta, R., A Sheikh, D P Strachan, H R Anderson (2007) Time trends in allergic disorders in the UK. Thorax 2007;62:91–96. doi: 10.1136/thx.2004.038844

Herman R.A. and G. S. Ladics. Allergenic sensitization versus elicitation risk criteria for novel food proteins. *Regul.Toxicol.Pharmacol.* 94:283-285, 2018.

Kato K., N. Shitan, T. Shoji, and T. Hashimoto. Tobacco NUP1 transports both tobacco alkaloids and vitamin B6. *Phytochemistry* 113:33-40, 2015.

Lee, Dae-Weon * Tetsuyuki Akao,* Satoko Yamashita,* Hideki Katayama,*Leonard‡, Renaud1, Nicole Wopfner§1, Martin Pabst‡1, Johannes Stadlmann‡, Bent O. Petersen¶, Jens Ø. Duus¶,Martin Himly§, Christian Radauer, Gabriele Gadermaier§, Ebrahim Razzazi-Fazeli**, Fatima Ferreira§,and Friedrich Altmann‡ A New Allergen from Ragweed (Ambrosia artemisiifolia) withHomology to Art v 1 from Mugwort. THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 285, NO. 35, pp. 27192–27200, August 27, 2010Mazzucchelli, G., T. Holzhauser, Velickovic T. Cirkovic, A. az-Perales, E. Molina, P. Roncada, P. Rodrigues, K. Verhoeckx, and K. Hoffmann-Sommergruber. Current (Food) Allergenic Risk Assessment: Is It Fit for Novel Foods? Status Quo and Identification of Gaps. *Mol.Nutr.Food Res.* 62 (1), 2018.

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Pawankar[1, 2] Ruby, Carlos E Baena-Cagnani[1, 3], Jean Bousquet[1, 4], G Walter Canonica[1, 5], Alvaro A Cruz[1, 6], Michael A Kaliner[1, 7], Bobby Q Lanier[1, 8] and Karen Henley. State of World Allergy Report 2008: Allergy and Chronic Respiratory Diseases. *World Allergy Organization Journal*2008**1**:130

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B.3.3. ADDITIONAL DOCUMENTS OR STUDIES PERFORMED BY OR ON BEHALF OF THE APPLICANT

N/A

C. OVERALL ASSESSMENT

N/A

D. MONITORING PLAN AND PROPOSAL FOR IMPROVING THE CONDITIONS OF THE ORIGINAL AUTHORISATION

N/A