Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

# Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-NL-2016-131 (genetically modified maize MON 87427 x MON 89034 x MIR162 x NK603 and its subcombinations) from Monsanto under Regulation (EC) No. 1829/2003

17 September 2019
*Ref. SC/1510/BAC/2019_0745*

## Context

Application EFSA-GMO-NL-2016-131 was submitted by Monsanto for the marketing of genetically modified (GM) maize MON 87427 x MON 89034 x MIR162 x NK603 (Unique Identifier MON-87427-7 x MON-89Ø34-3 x SYN-IR162-4 x MON-ØØ6Ø3-6) and all of its subcombinations independently of their origin, for food and feed uses, import and processing (excluding cultivation) within the European Union, within the framework of Regulation (EC) No. 1829/2003[1].

The four-event stack maize MON 87427 x MON 89034 x MIR162 x NK603 was obtained by conventional crossing (no new genetic modification involved) of the corresponding single events:
- MON 87427, expressing the CP4 EPSPS protein that confers tolerance to herbicide products containing glyphosate;
- MON 89034, expressing the Cry1A.105 and Cry2Ab2 proteins for resistance to lepidopteran insect pests;
- MIR162, expressing the Vip3Aa20 protein, conferring resistance to certain lepidopteran insect pests, and the PMI protein, a selectable marker;
- NK603, expressing the CP4 EPSPS protein and its variant CP4 EPSPS L214P, that confer tolerance to herbicide products containing glyphosate.

The application was validated by EFSA on 31 May 2016. A formal three-month consultation period of the Member States was started, lasting until 12 September 2016, 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 Belgian Biosafety Advisory Council (BAC), under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier, chosen from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB). Nine 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 forwarded to EFSA.

The opinion of the EFSA Scientific Panel on GMOs was published on 8 July 2019 (EFSA Journal 2019;17(7):5734 [2]), toghether with the responses from the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period. On 22 July 2019 these two documents were forwarded to the Belgian experts. They were invited to give comments and to react if needed.

[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] See https://doi.org/10.2903/j.efsa.2019.5734

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In delivering the present advice the BAC considered in particular the following information:
- The comments formulated by the experts on application EFSA-GMO-NL-2016-135;
- The opinion of EFSA;
- The advices already adopted by the BAC on the single events and the lower-order stacks, which were as follows:

| Event | Application number | BAC advice | Conclusions |
|---|---|---|---|
| MON 87427 | EFSA-GMO-BE-2012-110 | BAC/2015/0585 (08/09/2015) | Unlikely to pose any risk to human and animal health.<br>No risk identified for the European environment. |
| MON 89034 | EFSA-GMO-NL-2007-37 | BAC/2009/0880 (03/02/2009) | No major risks for human and animal health or for the environment. |
| MIR162 | EFSA-GMO-DE-2010-82 | BAC/2012/0785 (29/08/2012) | No major risks for animal health or for the environment, no conclusion on human health.<br>The PMI protein has been positively assessed in subsequent applications. |
| NK603 | EFSA-GMO-NL-2005-22 | BAC/2009/1367 (02/10/2009) | No major risks for human and animal health or for the environment. |
| MON 89034 x NK603 | EFSA-GMO-NL-2007-38 | BAC/2009/1492 (06/11/2009) | No major risks for human and animal health or for the environment. |
| MON87427 x MON89034 x NK603 and its subcombinations | EFSA-GMO-BE-2013-117 | BAC/2017/0741 (19/09/2017) | Unlikely to pose any risk to human and animal health.<br>No risk identified for the European environment. |

All GM maize events mentioned in the table above are authorised in the EU for food and feed uses[3].

## Scientific evaluation

### 1. Environmental risk assessment

The Biosafety Advisory Council is of the opinion that it is unlikely that the accidental release of maize MON 87427 x MON 89034 x MIR162 x NK603 (i.e. during transport and/or processing) into the European environment[4] will lead to environmental harm.

### 2. Molecular characterisation

With regard to the molecular characterisation, the Biosafety Advisory Council is of the opinion that the information provided is sufficient and does not raise safety concerns.

### 3. Assessment of food/feed safety and nutritional value

3.1. Assessment of compositional analysis

Taking into account the previous assessment of the single events and the new data on compositional analysis provided by the applicant for the four-stacked event, the Biosafety Advisory Council agrees with the GMO panel of EFSA that the compositional data of GM maize MON 87427 x MON 89034 x MIR162 x NK603, in comparison with its conventional counterpart, do not raise safety concerns.

3.2. Assessment of toxicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed CP4 EPSPS, CP4 EPSPS L214P, Cry1A.105, Cry2Ab2, Vip3Aa20 and PMI proteins in the context of previous applications, and no safety concerns were identified. Taking into account the updated information

[3] See EU register of GM food and feed: http://ec.europa.eu/food/dyna/gm_register/index_en.cfm
[4] As the application doesn't imply cultivation of the GM crop in the EU, a full environmental assessment is as in the case of a cultivation file is not warranted.

considered in the current application, the Council is of the opinion that its previous conclusions remain valid.
The Biosafety Advisory Council is also of the opinion that the combined expression of the newly expressed proteins in the stacked event does not raise toxicological concerns.

3.3. Assessment of allergenicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed CP4 EPSPS, CP4 EPSPS L214P, Cry1A.105, Cry2Ab2, Vip3Aa20 and PMI proteins in the context of previous applications, and no concerns were identified. Since no new information on allergenicity of these proteins has become available, the Council is of the opinion that its previous conclusions remain valid.
The Biosafety Advisory Council is also of the opinion that the combined expression of the newly expressed proteins in the stacked event does not raise concerns regarding the allergenicity.

3.4. Nutritional value

The Biosafety Advisory Council is of the opinion that the information provided is sufficient to conclude that the nutritional characteristics of maize MON 87427 x MON 89034 x MIR162 x NK603-derived food and feed are not expected to differ from those of conventional maize varieties.

## 4. Monitoring

Since the allergenicity of the whole GM maize has not been fully assessed, it is recommended to take up monitoring of allergenicity as part of the general surveillance.

## Conclusion

Based on the whole set of data on maize MON 87427 x MON 89034 x MIR162 x NK603 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts, the opinion of EFSA, the answers of the EFSA GMO panel to the questions raised by the Belgian experts, and the advices already adopted by the BAC on the four single events and lower-order stacks, the Biosafety Advisory Council:

1) Agrees with the GMO panel of EFSA that the potential environmental release of maize MON 87427 x MON 89034 x MIR162 x NK603 and its subcombinations is unlikely to pose any threat to the European environment;
2) Agrees with the GMO panel of EFSA that there is no reason to expect interactions between the newly expressed proteins that could impact on the food or feed safety;
3) Agrees with the GMO panel of EFSA that in the context of its proposed uses, maize MON 87427 x MON 89034 x MIR162 x NK603 and its subcombinations are unlikely to pose any risk to human and animal health;
4) Considers that the conclusions of the Biosafety Advisory Council on the single events and lower order stacks that have been assessed previously (MON 87427, MON 89034, MIR162 and NK603 - see table on page 2) remain unchanged.

Dr. Corinne Vander Wauven
President of the Belgian Biosafety Advisory Council

*Annex I: Compilation of comments of experts in charge of evaluating the application EFSA-GMO-NL-2016-131 and Comments submitted on the EFSAnet on mandate of the Biosafety Council (ref. BAC_2016_0568)*

**Bioveiligheidsraad**
**Conseil de Biosécurité**

*12/09/2016*

**Secretariaat**
**Secrétariat**

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**Compilation of comments of experts in charge of evaluating the application EFSA/GMO/NL/2016/131**
**and**
**Comments submitted on the EFSAnet on mandate of the Biosafety Council**

**Mandate for the Group of Experts:** Mandate of the Biosafety Advisory Council (BAC) of 22 June 2016.
**Coordinator:** Geert Angenon
**Experts:** Eddy Decuypere (KUL), Jacques Dommes (ULg), Leo Fiems (ILVO), Johan Grooten (UGent), André Huyghebaert (UGent), Peter Smet (Consultant), Frank Van Breusegem (UGent), Jan Van Doorsselaere (KATO), Bart Van Droogenbroeck (ILVO)
**Domains of expertise of experts involved:** Molecular characterisation, DNA/RNA/protein analysis, herbicide tolerance, animal and human nutrition, food/feed processing, toxicology, general biochemistry, statistics, immunology, alimentary allergology, plant allergens, agronomy, ecology, breeding techniques, plant biology.
**SBB:** Didier Breyer, Fanny Coppens, Katia Pauwels.

- **INTRODUCTION**

Dossier **EFSA/GMO/NL/2016/131** concerns an application submitted by the company **Monsanto** for authorisation to place on the market genetically modified **maize MON87427 x MON89034 x MIR162 x NK603** in the European Union, according to Regulation (EC) No 1829/2003 on genetically modified food and feed.
The application has been officially acknowledged by EFSA on 10 June 2016.

The scope of the application is:
☒ 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)

Depending on their expertise, the experts were asked to evaluate the genetically modified plant considered in the application on its 1) molecular, 2) environmental, 3) allergenicity, 4) toxicity and/or 5)

food and feed aspects. It was expected that the expert should evaluate if the information provided in the application is sufficient in order to state that the marketing of the genetically modified plant for its intended uses, will not raise any problems for the environment or human or animal health. If information is lacking, the expert was asked to indicate which information should be provided and what the scientifically reasoning is behind this demand.

The comments are structured as in the "Guidance document of the scientific panel on genetically modified organisms for the risk assessment of genetically modified plants and derived food and feed" (EFSA Journal (2004), 99, 1-94). Items are left blank when no comments have been received either because the expert(s) focused on other related aspects, or because for this dossier the panel of experts who accepted to evaluate the dossier didn't have the needed expertise to review this part of the dossier.
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. Comments placed on the EFSAnet are indicated in grey.

**List of comments/questions received from the experts**

## GENERAL COMMENTS

*Comment 1*
It was interesting, under point 7 (p113-121), how the screening of scientific literature was done.

*Comment 2*
No question or comment, adequate information was provided.

*Comment 3*
MON87427 x MON89034 x MIR162 x NK603 maize may be as safe for human and animal health as conventional maize based on the results of the compositional analysis and the weight of evidence with regard to the toxicological and the allergenicity assessment.
The use of MON87427 x MON89034 x MIR162 x NK603 maize may increase the use of glyphosate-based herbicides. The safety of glyphosate is not within the remits of BAC, but a holistic approach of herbicide-tolerant GM crops is desirable. Therefore, the approval should be postponed until new epidemiological and toxicology studies clearly demonstrate the safety of glyphosate and its metabolites for human and animal health and the environment (see E.3.8.).

SBB comment:
The assessment of the safety of glyphosate is indeed not within the remits of the BAC.

*Comment 4*
No comments or questions.

*Comment 5*
No comments / questions.

## A. HAZARD IDENTIFICATION AND CHARACTERISATION

### A.1. INFORMATION RELATED TO THE RECIPIENT OR (WHERE APPROPRIATE) THE PARENTAL PLANT

*Comment 1*
No questions.

*Comment 2*
No question or comment, adequate information was provided.

*Comment 3*
No comments / questions.

### A.2. MOLECULAR CHARACTERISATION

**A.2.1. INFORMATION RELATING TO THE GENETIC MODIFICATION** including:

- Description of the methods used for the genetic modification

- Source and characterization of nucleic acid used for transformation
- Nature and source of vector(s) used

*Comment 1*
No comments.

*Comment 2*
No question or comment, adequate information was provided.

*Comment 3*
No comments.

*Comment 4*
- No specific comments or questions. Information provided is adequate. The applicant has summarized and referred to the information that was provided in previous applications related to the four single events.
- Word 'from' is missing on last sentence of first paragraph of section 1.2.1.3 (b), page 20
- Typo in the word 'anti-nutritional', first paragraph section 1.2.1.3. (c), page 20

*Comment 5*
No comments / questions.

**A.2.2. INFORMATION RELATING TO THE GM PLANT** including:
- Description of the trait(s) and characteristics which have been introduced or modified
- Information on the sequences actually inserted or deleted
- Information on the expression of the insert
- Genetic stability of the inserted/modified sequence and phenotypic stability of the GM plant

*Comment 1*
Why using MON87427 and NK603 in the stacked event (MON87427 x MON89034 x MIR162 x NK603), since both provide tolerance to glyphosate? Is the reason to have a higher level of EPSPS? And why is this needed?
See table 2 p 27: EPSPS levels, both in forage and grain in the stacked event are almost double the EPSPS levels in MON87427 or NK603 separately.

Coordinator comment:
This is indeed information on the introduced trait that is lacking. On the other hand, the increased EPSPS levels are as expected.

*Comment 2*
No question or comment, adequate information was provided.

*Comment 3*
No comments.
The application describes the stacking of events by traditional breeding. The separate events have been risk assessed by EFSA.

*Comment 4*

The information provided by the applicant is adequate. Sequence analysis indicated the intactness and stability of the inserts. Updated bioinformatics analysis did not provide any evidence that functional endogenous genes or ORFs were interrupted. From the updated *in silico* analysis of the inserted sequences it became clear that there are neither allergenic nor toxicological findings associated with the presence of the putative ORF polypeptides or putative products of predicted genes. Based on this information, no unintended changes and no indications of potential interactions between the single events or between the newly expressed proteins were identified. Therefore it can be concluded that the molecular characterization of maize MON87427 x MON89034 x MIR162 x NK603 does not indicate safety concerns.
Minor comments:

- In Table 5 and 6 on pgs. 30 and 31 respectively, the data describing the expression levels of the proteins on a fresh weight basis is missing, while this is included in Tables 3 & 4. What is the reason?
- The authors state that on pg. 33 “The inserts in MON87427 x MON89034 x MIR162 x NK603 are on different chromosomes, making this possibility extremely low”, without providing a reference.

Coordinator comment:
This is a general statement on meiotic recombination

- Typo in the word ‘inherited’ in section 1.2.2.2 (d), page 23

*Comment 5*
No comments / questions.

### A.3. COMPARATIVE ASSESSMENT

#### A.3.1. CRITERIA FOR THE SELECTION OF COMPARATOR(S)

*Comment 1*
No questions.

*Comment 2*
As it was the case in previous similar applications, no major effects on het overall composition are expected.
Maize LH244 x LH287, with similar genetic backgrounds, was selected as the conventional maize counterpart.
No remarks.

#### A.3.2. FIELD TRIALS: EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS

*Comment 1*
No questions.

*Comment 2*
Maize MON87427 x MON89034 x MIR162 x NK603 was grown at eight field sites in the US. In addition 17 commercial maize varieties were included in the study.
No remarks.

### A.3.3. COMPOSITIONAL ANALYSIS

*Comment 1*
No questions.

*Comment 2*
Relevant compounds from grain and forage of maize MON87427 x MON89034 x MIR162 x NK603 and 17 commercial varieties were analyzed according to the OECD consensus document of 2002.

For grain the analysis of 69 components were conducted whereas for forage 9 nutrients were included.
In the statistical analysis data of stack NT (non-treated) were compared with stack T (treated with glyphosate) and the conventional counterpart. The equivalence of stack NT and T to the conventional commercial maize hybrids was studied as well.
I have no further comments on the selection of the nutrients and anti-nutrients as this is in line with previous applications.

**Results of the statistical analysis.**
For **grain** a vast majority of results of proximate, fibre, protein and amino acids, fat and fatty acids, vitamins, ash and minerals and anti-nutrients were categorized in equivalence category I, outcome 1 and 2. Only palmitoleic acid was found to be in category non-equivalence but non-significant.

For **forage** all constituents were categorized in equivalence category I, outcome 1 and 2.

Based on these results the applicant concludes that maize MON87427 x MON89034 x MIR162 x NK603 is compositionally equivalent to the conventional comparator and that maize MON87427 x MON89034 x MIR162 x NK603 is not a significant contributor to compositionally variability in maize.

I agree with this conclusion.
Results obtained for palmitoleic acids are not relevant: non-equivalent but non-significant. Palmitoleic acid is not a major fatty acid in the composition of maize oil.

*Comment 3*
There seem to be no problems with the antinutrients and secondary metabolites.

The amount of CP4 EPSPS in the stacked event is higher compared to the single events (MON87427 and NK603) which is in line with the expectation. This raises no concerns since the margin of exposure still exceeds a factor of 1000.
The amounts of the other proteins involved in this combined event are comparable to the single events.

*Comment 4*
Some compounds of MON87427 x MON89034 x MIR162 x NK603 maize were different from conventional maize. However, there is some overlap between the component values of MON87427 x MON89034 x MIR162 x NK603 with those of LH244 × LH287 maize, so that differences are not really relevant.

No residue concentrations were given for glyphosate in case of MON87427 x MON89034 x MIR162 x NK603 maize treated with glyphosate. It is desirable to report the concentrations of glyphosate and its metabolites.

Coordinator comment:
The assessment of the safety of pesticides/herbicides or their residues is not within the remit of the BAC.

#### A.3.4. AGRONOMIC AND PHENOTYPIC CHARACTERISTICS

*Comment 1*
In the conclusions on p. 50 it is stated that the stacked event does not confer any increased susceptibility or tolerance to specific disease, abiotic stressors or insects. But does it confer a DECREASED susceptibility to insects and pests? I could not detect this throughout the text.

Coordinator comment:
Decreased susceptibility = increased tolerance

*Comment 2*
No comments.

#### A.3.5. EFFECTS OF PROCESSING

*Comment 1*
No questions.

*Comment 2*
As maize MON87427 x MON89034 x MIR162 x NK603 is compositionally equivalent to commercial maize hybrids, no particular effects are to be expected upon processing.

I agree with the conclusion of the applicant.

### A.4. TOXICOLOGICAL ASSESSMENT

#### A.4.1. METHODOLOGY USED FOR TOXICITY TESTS

*Comment 1*
No questions.

#### A.4.2. ASSESSMENT OF NEWLY EXPRESSED PROTEINS including:

- Molecular and biochemical characterisation of the newly expressed proteins
- Up-to-date bioinformatic search for homology
- Information on the stability of the protein under the relevant processing and storage conditions for the food and feed derived from the GM plant
- Data concerning the resistance of the newly expressed protein to proteolytic enzymes
- Repeated dose toxicity studies using laboratory animals

*Comment 1*

No questions.

*Comment 2*
No further testing is performed. At this moment there seems to be no need for extra information. Up-to-date homology searches showed no sequence similarities with known toxins.

*Comment 3*
The chance that the new proteins of MON87427 x MON89034 x MIR162 x NK603 maize (CP4 EPSPS, Cry1A.105, Cry2Ab2, Vip3Aa20 and PMI) will pose serious risks for toxicity is negligible, based on the biochemical characterization of the newly expressed protein, the bioinformatics analysis that uses sequence searches to identify any similarities to toxins and anti-nutrients, inactivation of new proteins during heat processing and the in-vitro protein stability. It is assumed that there is no biological pathway in which the newly-inserted genes would directly or indirectly interact with safety (Kok et al., 2014; Zdziarski et al., 2014). There is no plausible or testable hypothesis for an interaction of new proteins in MON87427 x MON89034 x MIR162 x NK603 maize (Steiner et al., 2013).

#### A.4.3. ASSESSMENT OF NEW CONSTITUENTS OTHER THAN PROTEINS

*Comment 1*
No questions.

#### A.4.4. ASSESSMENT OF ALTERED LEVELS OF FOOD AND FEED CONSTITUENTS

*Comment 1*
No questions.

#### A.4.5. ASSESSMENT OF THE WHOLE FOOD AND/OR FEED DERIVED FROM GM PLANTS

*Comment 1*
No questions.

*Comment 2*
No further testing is performed. At this moment there seems to be no need for extra information.

### A.5. ALLERGENICITY ASSESSMENT

**A.5.1. ASSESSMENT OF ALLERGENICITY OF THE NEWLY EXPRESSED PROTEIN** including:

- Amino acid sequence homology comparison between the newly expressed protein and known allergens using a comprehensive database
- Specific serum screening
- Pepsin resistance and in vitro digestibility tests
- Additional tests

*Comment 1*
No questions.

*Comment 2*
The stacked events lead to the combined expression throughout the maize plant and grain of CP4 EPSPS, Cry1A.105, Cry2Ab2, Vip3Aa20 and PMI proteins. All these proteins have been assessed

**individually** in the context of several previous applications and no indications pointing towards an increased risk for allergenicity were then identified. As some of these dossiers date back to 2009 and new information on allergens has since then become available, the applicants updated the amino acid sequence homology comparison between the newly expressed proteins and known allergens using a 2015 database. The results of this updated analysis indicate that no biologically relevant sequence similarities are present between the CP4 EPSPS, CrylA.105, Cry2Ab2, Vip3Aa20 and PMI proteins and allergens present in the 2015 database. Finally, there are no indications that the sequences would be intrinsically unstable when **combined** together by traditional breeding and/or engage in unintended interactions, hereby affecting the expression levels of the proteins. Accordingly, I agree with the applicant's conclusion that no concerns in relation to allergenicity of the (combined) newly expressed proteins were identified.
I have no further remarks.

#### A.5.2. ASSESSMENT OF ALLERGENICITY OF THE WHOLE GM PLANT

*Comment 1*
No questions.

*Comment 2*
The non-allergic profile of maize, its longstanding history of safe use for human food as well as the data and analyses provided by the applicant support the applicant's conclusion that "*it is unlikely that any interactions between the newly expressed proteins and metabolic pathways of maize would alter the pattern of expression of endogenous proteins/potential allergens and thereby significantly change the overall allergenicity of the whole plant*".
I have no further remarks.

*Comment 3*
It is assumed that MON87427 x MON89034 x MIR162 x NK603 maize is comparable with conventional maize with regard to allergenicity, and that it does not pose a serious allergenic risk.

#### A.5.3. ADJUVANTICITY

*Comment 1*
No questions.

*Comment 2*
I have no remarks.

### A.6. NUTRITIONAL ASSESSMENT

#### A.6.1. NUTRITIONAL ASSESSMENT OF FOOD DERIVED FROM GM PLANTS

*Comment 1*
No questions.

#### A.6.2. NUTRITIONAL ASSESSMENT OF FEED DERIVED FROM GM PLANTS

*Comment 1*

No questions.

*Comment 2*
There is no reason to assume that the genetic modification affects the nutritional value of the feed derived from MON87427 x MON89034 x MIR162 x NK603 maize based on the compositional equivalence.

## B. EXPOSURE ASSESSMENT - ANTICIPATED INTAKE/EXTENT OF USE

*Comment 1*
No questions.

## C. RISK CHARACTERISATION

*Comment 1*
No questions.

## D. POST MARKET MONITORING (PMM) OF FOOD AND FEED DERIVED FROM GM PLANTS

*Comment 1*
No questions.

## E. ENVIRONMENTAL RISK ASSESSMENT

### E.1. INTRODUCTION

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.2. GENERAL APPROACH OF THE ERA

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.3. SPECIFIC AREAS OF RISK

As stated in the EFSA guidance on the environmental risk assessment of genetically modified plants (EFSA Journal 2010, 8(11):1879) the objective of the ERA is on a case-by-case basis to identify and evaluate potential adverse effects of the GM plant, direct and indirect, immediate or delayed (including cumulative long-term effects) on the receiving environment(s) where the GM plant will be released. For each specific risk the ERA consists of the six steps described in Directive 2001/18/EC:
1. Problem formulation including hazard identification,
2. Hazard characterisation,

3. Exposure characterisation,
4. Risk characterisation,
5. Risk management strategies,
6. Overall risk evaluation and conclusions.

### E.3.1. PERSISTENCE AND INVASIVENESS INCLUDING PLANT-TO-PLANT GENE FLOW

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.3.2. PLANT TO MICRO-ORGANISMS GENE TRANSFER

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.3.3. INTERACTION BETWEEN THE GM PLANT AND TARGET ORGANISMS

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.3.4. INTERACTION BETWEEN THE GM PLANT AND NON-TARGET ORGANISMS (NTOS)

*Comment 1*
No questions.

*Comment 2*
No comment.

### E.3.5. IMPACTS OF SPECIFIC CULTIVATION AND MANAGEMENT AND HARVESTING TECHNIQUES

*Comment 1*
Not applicable.

*Comment 2*
No comment.

*Comment 3*

MON87427 x MON89034 x MIR162 x NK603 maize is glyphosate tolerant, which may result in an increased application of glyphosate-based herbicides. Health concerns with regard to the use of glyphosate have been reported (Mensah et al., 2015).

Coordinator comment:
The assessment of the safety of pesticides/herbicides is not within the remit of the BAC.

#### E.3.6. EFFECTS ON BIOGEOCHEMICAL PROCESSES

*Comment 1*
Not applicable.

*Comment 2*
No comment.

#### E.3.7. EFFECTS ON HUMAN AND ANIMAL HEALTH

*Comment 1*
No questions.

*Comment 2*
No comment.

*Comment 3*
The new proteins in MON87427 x MON89034 x MIR162 x NK603 maize are unlikely to be detrimental for human and animal health. However, there is a side effect of the use of MON87427 x MON89034 x MIR162 x NK603 maize: glyphosate residues and its metabolite may be harmful for human and animal health, although total glyphosate equivalents residue was not mentioned in the current dossier.

Coordinator comment:
The assessment of the safety of pesticides/herbicides is not within the remit of the BAC.

#### E.3.8. OVERALL RISK EVALUATION AND CONCLUSIONS

*Comment 1*
No questions.

*Comment 2*
No question or remark. I agree with the conclusion of this ERA.

*Comment 3*
Because of the controversy between the WHO (Guyton et al., 2015) and EFSA (EFSA, 2015) with regard to the safety of glyphosate, a new examination of glyphosate toxicity should be undertaken to adjust downward the acceptable daily intake for glyphosate, as proposed by Myers et al. (2016). Furthermore, the European Chemicals Agency is conducting an investigation into the wider human health effects of glyphosate: see http://echa.europa.eu/registry-of-submitted-harmonised-

classification-and-labelling-intentions/-/substance-rev/13201/term. In the meantime, the approval of MON87427 x MON89034 x MIR162 x NK603 maize may be postponed.

Coordinator comment:
The assessment of the safety of pesticides/herbicides is not within the remit of the BAC.

### E.4. Post Market Environmental Monitoring plan

#### E.4.1. Interplay between environmental risk assessment and monitoring

*Comment 1*
No questions.

#### E.4.2. Case-specific GM plant monitoring

*Comment 1*
No comments.

#### E.4.3. General surveillance for unanticipated adverse effects

*Comment 1*
No comments.

#### E.4.4. Reporting the results of monitoring

*Comment 1*
No comments.

## References


EFSA, 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J. 13, 4302, 107 pp.

Guyton, K.Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Mattock, H., Straif, K. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol. 16, 490-491.

Kok, E.J., Pedersen, J., Onori, R., Sowa, S., Schauzu, M., De Schrijver, A., Teeri, T.H. 2014. Plants with stacked genetically modified events: to assess or not to assess? Trends Biotechnol. 32, 70-73.

Mensah, P.K., Palmer, C.G., Odume, O.N. 2015. Ecotoxicology of glyphosate and glyphosate-based herbicides - Toxicity to wildlife and humans. In: Toxicity and hazard of agrochemicals. Eds.: M.L. Larramendy and S. Soloneski, In Tech, Rijeka, Croatia, pp.93-112.

Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll, L., Colborn, T., Everett, L.G., Hansen, M., Landrigan, P.J., Lanphear, B.P., Mesnage, R., Vandenberg, L.N., vom Saal, F.S., Welshons, W.V., Benbrook, C.M. 2016. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environ. Health 15, Article 19 (13 pp).

Steiner, H.Y., Halpin, C., Jez, J.M., Kough, J., Parrott, W., Underhill, L., Weber, N., Hannah, L.C. 2013. Evaluating the potential for adverse interactions within genetically engineered breeding stacks. Plant Physiol. 161, 1587-1594.

Zdziarski, I.M., Edwards, J.W., Carman, J.A., Haynes, J.I. 2014. GM crops and the rat digestive tract: A critical review. Environ. Int. 73, 423-433.