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KENMERK CGM/250515-04
ONDERWERP Advies import en verwerking van gg-mais Bt11 x MIR162 x MZIR098 x DP4114 x NK603

Geachte heer Jansen,

Naar aanleiding van een vergunningaanvraag voor import en verwerking van de genetisch gemodificeerde maïslijn Bt11 x MIR162 x MZIR098 x DP4114 x NK603 (GMFF-2024-22152) ingediend door Syngenta Crop Protection NV/SA, deelt de COGEM u het volgende mee.

Samenvatting:
De COGEM is gevraagd te adviseren over de mogelijke milieurisico's van import en verwerking van de genetisch gemodificeerde (gg-)maïs Bt11 x MIR162 x MZIR098 x DP4114 x NK603 en alle subcombinaties daarvan. De maïslijn is tot stand gekomen door middel van conventionele kruisingen van de vijf gg-ouderlijnen. In deze gg-maïs komen de *cry1Ab*-, *cry1F*-, *vip3Aa20*-, *mcry3A*-, *ecry3.1Ab*-, *cry34Ab1*-, *en cry35Ab1*-genen tot expressie, waardoor de plant beter beschermd is tegen vraat door vlinder- en keverachtigen. Introductie van het *cp4 epsps*-gen en twee kopieën van het *pat*-gen maakt dat de maislijn tolerant is voor bepaalde herbiciden.
Verwildering van maïsplanten is in Nederland nooit waargenomen. De wilde verwant van maïs, teosinte, komt niet in de natuurlijke omgeving in Nederland voor, waardoor de ingebrachte sequenties zich niet naar andere soorten kunnen verspreiden. De moleculaire karakterisering van Bt11 x MIR162 x MZIR098 x DP4114 x NK603 voldoet aan de eisen van de COGEM. Er zijn geen redenen om aan te nemen dat expressie van de ingebrachte genen ervoor zorgt dat deze gg-maïs zou kunnen verwilderen. Gezien het bovenstaande acht de COGEM de milieurisico's van de import en verwerking van de gg-maïs Bt11 x MIR162 x MZIR098 x DP4114 x NK603, en sub-combinaties hiervan, verwaarloosbaar klein. Omdat een voedselveiligheidsbeoordeling door andere instanties wordt uitgevoerd, heeft de COGEM bij deze vergunningaanvraag de risico's van incidentele consumptie niet beoordeeld.

De door de COGEM gehanteerde overwegingen en het hieruit voortvloeiende advies treft u hierbij aan als bijlage.

Hoogachtend,

Prof. dr. ing. Sybe Schaap
Voorzitter COGEM

c.c.

- Drs. Y. de Keulenaar, Hoofd Bureau ggo
- Ministerie van IenW, Directie Omgevingsveiligheid en milieurisico's, DG Milieu en Internationaal
- Ing. M.A.C. Möllers, Food-Feed loket

Advice Environmental risk assessment of import and processing of modified maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 and its subcombinations

COGEM advice CGM/250515-04

- The present application (GMFF-2024-22152) concerns the authorisation of genetically modified (GM) maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 and its subcombinations for import and processing for use in feed and food;
- The stacked event maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 was produced by conventional crossbreeding of the five GM parental maize lines;
- Previously, COGEM has advised positively on the import and processing of all five parental lines.

- The GM maize expresses the *cry1Ab*, *cry1F* and *vip3Aa20* genes, which each code for proteins conferring resistance against certain lepidopteran pests. In addition, it contains the *mcry3A, ecry3.1Ab, cry34Ab1, and cry35Ab1* genes coding for proteins that are active against certain coleopteran pests. Furthermore, it contains the *cp4 epsps* gene and two different copies of the *pat* gene, which encode proteins conferring tolerance to glyphosate and glufosinate-ammonium containing herbicides respectively. Lastly, it expresses the *pmi* gene as selectable marker.

- In the Netherlands, feral maize populations have never been observed and the appearance of volunteer maize plants is rare. Additionally, the wild relative of maize, teosinte is not present in the Dutch environment. Hybridisation of GM maize with other species is therefore not possible.

- The molecular characterisation of Bt11 x MIR162 x MZIR098 x DP4114 x NK603 has been updated and meets the criteria of COGEM;
- The updated bioinformatic analysis did not provide indications of potential environmental risks.
- There are no indications that the introduced traits allow the stacked event maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 to survive in the Netherlands;
- There are no indications that Bt11 x MIR162 x MZIR098 x DP4114 x NK603 could establish feral populations in the Netherlands.

- COGEM is of the opinion that import and processing of maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603, as well as GM maize consisting of subcombinations of its parental GM maize lines poses a negligible risk to the environment in the Netherlands;
- COGEM abstains from giving advice on the potential risks of incidental consumption as a food/feed assessment is carried out by other organisations.

1. Introduction

The present application (GMFF-2024-22152), filed by Syngenta, concerns the import and processing of genetically modified (GM) maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 (SYN-BTØ11-1 x SYN-IR162-4 x SYN-ØØØ98-3 x DP-ØØ4114-3 x MON-ØØ6Ø3-6) and its subcombinations. The GM maize was produced by conventional crossbreeding of the five GM parental maize lines. It contains the *cry1Ab*, *cry1F*, and *vip3Aa20* genes each coding for proteins conferring resistance against certain lepidopteran pests. In addition, it contains the *mcry3A*, *ecry3.1Ab*, *cry34Ab1*, and *cry35Ab1* genes coding for proteins that are active against certain coleopteran pests. Furthermore, it contains the *cp4 epsps* gene and two copies of the *pat* gene, which code for proteins conferring tolerance to glyphosate and glufosinate-ammonium containing herbicides, respectively. Lastly, the maize contains the *pmi* gene which encodes a protein that enables cells to utilize mannose as a primary carbon source, which was used as a selectable marker in de development of the line.

The parental lines NK603, MZIR098, Bt11, MIR162, DP4114, and the double stacked events BT11 x MIR162, MIR162 x NK603, DP4114 x NK603 have been authorised for import and processing for use in food and feed in the European Union.

2. Previous COGEM advice

Previously COGEM advised positively on the cultivation and import of NK603[1,2,3] and on import and processing of the parental lines Bt11,[4,5,6,7] MIR162,[8,9] DP4114,[10] and MZIR098[11]. COGEM also advised positively on the import and processing of many stacked events with these lines.[12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42]

3. Environmental risk assessment

The objective of an environmental risk assessment (ERA) is to identify and evaluate potential adverse effects of the genetically modified organism (GMO), direct or indirect, immediate or delayed, on human health and the environment. This ERA involves the import and processing of GM maize. Any concerns relating to cultivation, management or harvesting practices are beyond the scope of this advice. When assessing the environmental risk of incidental spillage of GM maize COGEM first considers the likelihood that the event could establish itself in the Netherlands or could hybridise with related species. Other so-called ‘areas of concern’ (e.g. effects on non-target organisms) are addressed only if there is a possibility that the event could establish itself or if gene flow to other species might occur.

3.1 Characteristics of the crop

Maize (*Zea mays*) is a member of the grass family *Poaceae*. It is a highly domesticated crop that originated from Central America and is nowadays cultivated globally. Maize is wind pollinated,[43,44] and has both male and female flowers that are spatially separated. The female flowers are not attractive to insect pollinators, because they do not produce nectar. Insect pollination of maize is highly limited but cannot be excluded.[45] Hybridisation of GM maize with species other than teosinte – the wild relative of maize – cannot occur.

Maize does not tolerate prolonged cold and frost, and requires warm conditions to grow.[46,45,47] In cultivation areas with warm climatic conditions, volunteers, i.e. maize not deliberately planted, can be present the year following maize cultivation due to spilled cobs or kernels. However, these volunteers are usually killed by common mechanical pre-planting soil preparation practices.[45]

Maize is very sensitive to weed competition.[48] During the long process of domestication, maize has lost the ability to persist in the wild.[44] A soil seed bank, small seeds, and an extended period of flowering and seed production are characteristics often observed in persistent weeds.[49] Maize lacks all these characteristics. After ripening, the seeds (the kernels) adhere to the cob and do not scatter naturally.[45,50] Consequently, seed dispersal is severely hampered.

3.2 Receiving environment

In the Netherlands, the appearance of volunteers is rare, although maize plants occasionally have been observed outside agricultural fields.[52,51] Any volunteers emerging will be killed by frost at the onset of winter.[52] COGEM is not aware of any reports of feral maize populations in the Netherlands.[52]

Maize can hybridise with teosinte, the wild relative of maize. However, as teosinte is absent in maize field and nature in the Netherlands,[52] hybridisation of GM maize with teosinte will not occur in the Netherlands.

Conclusion: In the Netherlands, feral maize populations do not occur and, therefore, hybridisation of maize with other species is impossible.

3.3 Description of the introduced genes and traits

GM maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 was created by conventional crossbreeding of the parental lines. For a description of the development of the parental lines, see previous COGEM advices (referenced in paragraph 2). A description of the inserted genetic elements in GM maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 is listed in the table below. The list is limited to information on the introduced genes, corresponding traits, and regulatory elements (promotors and terminators).

Introduced genes	Encoded proteins	Regulatory elements	Traits
cry1Ab (Bt11)	A variant of the Cry1Ab protein from *Bacillus thuringiensis* subsp. *kurstaki*[53]	35S promoter from *Cauliflower mosaic virus* (CaMV) and nopaline synthase (*nos*) terminator from *Agrobacterium tumefaciens*	Resistance to certain lepidopteran insects
pat (Bt11)	Variant of phosphinothricin N-acetyltransferase (PAT) originating from *Streptomyces viridochromogenes* strain Tü 494[64,65,66]	35S promoter from CaMV and *nos* terminator from *A. tumefaciens*	Tolerance to glufosinate-ammonium containing herbicides

vip3Aa20 (MIR162)	Variant of a native vegetative insecticidal protein (Vip) class A, subclass a, (Vip3Aa20) originating from *B. thuringiensis* strain AB88[54]	Polyubiquitin promoter and intron (Zm*Ubi*Int) from *Zea mays* and *35S* terminator from CaMV	Resistance against certain lepidopteran insects
pmi, also known as *manA* (MIR162)	Phosphomannose isomerase (PMI) enzyme derived from *Escherichia coli* K12[55]	Polyubiquitin promoter and intron (Zm*Ubi*Int) from *Z. mays* and nopaline synthase (*nos*) terminator from *A. tumefaciens*	Enables transformed plant cells to use mannose as a sole carbon source
cp4 epsps (NK603)	The 5-enolpyruvulshikimate-3-phosphate synthase (EPSPS) enzyme originating from *A. tumefaciens* strain CP4[56,57]	*Ract1* promoter from *Oryza sativa* and *nos* terminator from *A. tumefaciens*	Tolerance to glyphosate containing herbicides
cp4 epsps L214P (NK603)	The 5-enolpyruvulshikimate-3-phosphate synthase (EPSPS) L214P enzyme originating from *A. tumefaciens* strain CP4[56,57], functionally equivalent to the EPSPS enzyme.	*E35S* promoter from CaMV and *nos* terminator from *A. tumefaciens*	Tolerance to glyphosate containing herbicides
cry34Ab1 (DP4114)	Insecticidal δ-endotoxins Cry34Ab1 originating from *B. thuringiensis* strain PS149B1[58,59,60,61,62]	Polyubiquitin (*ubi*ZM1) promoter and intron from *Z. mays* and proteinase inhibitor II (*pin*II) terminator from *Solanum tuberosum*	Resistance to certain coleopteran insects
cry35Ab1 (DP4114)	Cry35Ab1 protein originating from *B. thuringiensis* strain PS149B1[58,59,60,61,62]	TA peroxidase promoter from *Triticum aestivum* and *pin*II terminator from *S. tuberosum*	Resistance to certain coleopteran insects
cry1F (DP4114)	A variant of the Cry1F protein originating from *B. thuringiensis* subsp. *aizawa*[63]	Polyubiquitin (*ubi*ZM1) promoter and intron from *Z. mays* and ORF25 terminator from *A. tumefaciens* strain pTi15955	Resistance to certain lepidopteran insects
pat (DP4114)	Variant of phosphinothricin N-acetyltransferase (PAT) originating from *Streptomyces viridochromogenes* strain Tü 494[64,65,66,67]	*35S* promoter and *35S* terminator from CaMV	Tolerance to glufosinate-ammonium containing herbicides

pat (MZIR098)	Variant of phosphinothricin N-acetyltransferase (PAT) originating from *Streptomyces viridochromogenes* strain Tü 494[68,69,70,71]	35S promoter from CaMV and *nos* terminator from *A. tumefaciens*	Tolerance to glufosinate-ammonium containing herbicides
ecry3.1Ab (MZIR098)	A chimera of a variant of the Cry3A protein from *B. thuringiensis* subsp. *tenebrionis* (mCry3A),[72,73,74] and the Cry1Ab protein from *B. thuringiensis* subsp. *Kurstaki*[72,75,76,77]	CMP promoter from *Cestrum yellow leaf curling virus* and *nos* terminator from *A. tumefaciens*	Resistance against certain coleopteran insects
mcry3A (MZIR098)	A variant of the Cry3A protein from *B. thuringiensis* subsp. *tenebrionis*[72,73,74]	Polyubiquitin (*ubi*ZM1) promoter and intron from *Z. mays* and *nos* terminator from *A. tumefaciens*	Resistance against certain coleopteran insects

3.4 Molecular characterisation

The COGEM has previously evaluated the molecular characterisation of each parental line and considered them to be adequate.[3,7,9,10,11]

The applicant updated the bioinformatics analyses of the Bt11, MIR162, MZIR098, DP4114, and NK603 inserts, and of the 5' and 3' flanking regions using recent databases. According to the applicant, the putative products of the open reading frames spanning the 5' and 3' junctions of the inserts did not generate any protein sequence similarity with known allergens, toxins, or other biologically active proteins.

The molecular characterisation was conducted according to the criteria previously laid down by COGEM.[78] The results from the updated molecular characterisation do not provide indications that the stacked event maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603could pose a risk to the environment.

Conclusion: The molecular characterisation of maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 is adequate and no indications of potential environmental risks were identified.

3.5 Phenotypic and agronomic characteristics

Previously, COGEM evaluated the phenotypic and agronomic characteristics of each parental line of Bt11 x MIR162 x MZIR098 x DP4114 x NK603 and found no deviations influencing the outcome of the environmental risk assessment.

The applicant analysed the phenotypic and agronomic characteristics of Bt11 x MIR162 x MZIR098 x DP4114 x NK603 and noted that these, except for the introduced traits, are not different compared to the non-GM near-isogenic control line, and are equivalent to the reference varieties, taking natural variation into account. The results of the phenotypic evaluation do not give reason to assume that the GM maize could pose an environmental risk. Therefore, COGEM is of the opinion that there are no indications that the introduced traits allow maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603 to survive or establish in the Dutch environment.

Conclusion: There are no indications that the introduced traits allow Bt11 x MIR162 x MZIR098 x DP4114 x NK603 to survive in the Netherlands. Bt11 x MIR162 x MZIR098 x DP4114 x NK603 has no increased potential for the establishment of feral populations in the Netherlands.

4. Food/feed assessment

This application is submitted under Regulation (EC) 1829/2003, therefore a food/feed assessment is carried out by the European Food and Safety Authority (EFSA) and national organisations involved in the assessment of food safety. In the Netherlands, a food and/or feed assessment for Regulation (EC) 1829/2003 applications is carried out by Wageningen Food Safety Research (WFSR). The outcome of the assessment by other organisations (EFSA, WFSR) was not known when this advice was completed.

5. Post-market environmental monitoring (PMEM)

The applicant supplied a general surveillance (GS) plan as part of the PMEM. COGEM has published several recommendations for further improvement of the GS plan, but considers the current GS and PMEM plan adequate for the import and processing of maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603.

Conclusion: The current PMEM plan is sufficient for the import and processing of GM maize Bt11 x MIR162 x MZIR098 x DP4114 x NK603.

6. Overall conclusion

Conclusion: The COGEM is of the opinion that import and processing of Bt11 x MIR162 x MZIR098 x DP4114 x NK603 maize and GM maize consisting of subcombinations of its parental GM maize lines pose a negligible risk to the environment in the Netherlands. COGEM abstains from giving advice on the potential risks of incidental consumption since other organisations carry out a food/feed assessment.

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