

Aan de minister van
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Ordening en Milieubeheer
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KENMERK CGM/090917-05
ONDERWERP Advies "Import and processing of gm-maize Bt11xMIR162xMIR604xGA21"

Geachte mevrouw Cramer,

Naar aanleiding van een adviesvraag (EFSA/GMO/DE/2009/66) betreffende de import van de genetisch gemodificeerde maïslijn Bt11xMIR162xMIR604xGA21 van Syngenta Crop Protection AG, deelt de COGEM u het volgende mee.

Samenvatting

De COGEM is gevraagd om te adviseren over de mogelijke milieurisico's van import en verwerking van maïslijn Bt11xMIR162xMIR604xGA21. Deze maïslijn is verkregen door vier genetisch gemodificeerde maïslijnen met elkaar te kruisen.

Bt11xMIR162xMIR604xGA21 brengt de genen *cry1Ab*, *mcry3A*, *vip3Aa20*, *mepsps*, *pat* en *pmi* tot expressie. Als gevolg hiervan is Bt11xMIR162xMIR604xGA21 resistent voor bepaalde insecten uit de orde van de Lepidoptera en de Coleoptera en tolerant voor glufosinaat en glyfosaat bevattende herbiciden.

De moleculaire karakterisering van Bt11xMIR162xMIR604xGA21 en van de individuele ouderlijnen voldoet aan de criteria van de COGEM.

Verwildering van maïsplanten is in Nederland nooit waargenomen. Daarnaast is opslag van maïsplanten in Nederland nagenoeg uitgesloten. Er zijn geen redenen om aan te nemen dat expressie van de geïnserteerde genen of interacties tussen de transgene eiwitten het verwilderingspotentieel van maïs vergroten. Bovendien zijn er in Europa geen wilde verwanten van maïs aanwezig waardoor uitkruising niet mogelijk is. Daarom acht de COGEM de kans dat incidenteel morsen tot verspreiding van deze maïslijn leidt verwaarloosbaar klein. Omdat andere instanties een voedselveiligheidsbeoordeling uitvoeren heeft de COGEM bij deze vergunningaanvraag de risico's van incidentele consumptie niet beoordeeld.

Concluderend heeft de COGEM in het licht van de door haar uitgevoerde risicobeoordeling geen bezwaar tegen import en verwerking van maïslijn Bt11xMIR162xMIR604xGA21 en acht zij de risico's voor mens en milieu verwaarloosbaar klein.

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

Hoogachtend,

A handwritten signature in black ink, consisting of a large loop on the left and a long horizontal stroke extending to the right.

Prof. dr. ir. Bastiaan C.J. Zoeteman

Voorzitter COGEM

c.c. Drs. H.P. de Wijs
Dr. I. van der Leij

Import and processing of genetically modified maize Bt11xMIR162xMIR604xGA21

COGEM advice CGM/090917-05

The present application by Syngenta Crop Protection AG (file EFSA/GMO/DE/2009/66) concerns import and processing for use in feed and food of the genetically modified maize line Bt11xMIR162xMIR604xGA21. Cultivation is not part of this application.

*Maize line Bt11xMIR162xMIR604xGA21 expresses the *cry1Ab*, *mcry3A* and *vip3Aa20* genes conferring resistance to certain lepidopteran and coleopteran insects. In addition, this maize line contains the genes *mepsps* and *pat* resulting in tolerance to glufosinate-ammonium and glyphosate containing herbicides. Finally, Bt11xMIR162xMIR604xGA21 contains two copies of the *pmi* gene which acts as a selectable marker enabling transformed plant cells to utilize mannose as a carbon source.*

Bt11xMIR162xMIR604xGA21 was produced by conventional cross-breeding of four genetically modified maize lines. Previously, COGEM issued positive advices on import and processing of maize lines Bt11, MIR604, GA21, Bt11xMIR604, Bt11xGA21, MIR604xGA21 and Bt11xMIR604xGA21. In addition, COGEM issued positive advices on cultivation of Bt11 and GA21. Maize line MIR162 has never been evaluated by COGEM but was evaluated in the current application.

The molecular characterization of maize line Bt11xMIR162xMIR604xGA21 and its individual parental lines (including MIR162) meets the criteria of COGEM.

During its long domestication process, maize has lost its ability to survive in the wild. In the Netherlands, the appearance of maize volunteers is rare and establishment of volunteers in the wild has never been reported. There are no reasons to assume that the introduced traits or interactions between the transgenic proteins will increase the potential of maize to establish feral populations. The introduced genes cannot spread to closely related species since wild relatives of maize are not present in Europe.

In view of the above, COGEM is of the opinion that the risks for humans and the environment associated with import and processing of maize line Bt11xMIR162xMIR604xGA21 are negligible. A food/feed safety assessment is carried out by other organizations. Therefore, COGEM abstained from advice on the potential risks of incidental consumption.

Introduction

The scope of the present notification (EFSA/GMO/DE/2009/66) by Syngenta Crop Protection AG concerns import and processing of maize line Bt11xMIR162xMIR604xGA21. Maize line Bt11xMIR162xMIR604xGA21 contains the *cry1Ab*, *mcry3A*, *vip3Aa20*, *mepsps*, *pat*, and *pmi* genes which are constitutively expressed. As a result, the maize line is resistant to certain lepidopteran and coleopteran insects, tolerant to glufosinate-ammonium and glyphosate containing herbicides, and able to use mannose as a carbon source.

Simultaneous with the present application an application concerning import and processing of maize Bt11xMIR162xGA21 was filed. In the applications several studies are delivered that contain data relevant to the risk assessment of the maize line. The majority of these studies is

relevant to and presented in both applications. The COGEM advices on import and processing of Bt11xMIR162xMIR604xGA21 and Bt11xMIR162xGA21 will be published simultaneously.

Previous COGEM advices and EFSA opinions

In 1997, COGEM issued a positive advice on import and processing of maize line Bt11,¹ and in 2008 and 2009 COGEM advised positively on the renewal of this application.^{2,3} A positive advice on cultivation of this maize line has been issued in 2005.⁴ In the same year, COGEM issued a positive advice on import and processing of maize line MIR604.⁵ COGEM has also advised on maize line GA21 and concluded that the ecological risks associated with import and processing and with cultivation of this maize line are negligible.^{6,7,8} In 2008, COGEM issued positive advices on import and processing of hybrid maize lines Bt11xGA21, Bt11xMIR604, MIR604xGA21 and Bt11xMIR604xGA21.^{9,10,11,12}

Maize line MIR162 has not been assessed previously by COGEM. Favorable EFSA opinions have been published on import and processing of Bt11, MIR604 and GA21, and on cultivation of Bt11.^{13,14,15,16,17}

Aspects of the crop

Maize (*Zea mays* L.) is a member of the grass family *Poaceae*. Maize is cultivated as an agricultural crop, originating from Central America. Although insect pollination cannot be completely excluded, maize is predominantly wind pollinated.^{18,19} According to literature, pollen viability varies between 30 minutes and 9 days.^{19,20,21} In Europe, no wild relatives of maize are present and, therefore, hybridization with other species cannot occur.

The appearance of volunteers is very rare under Dutch conditions. Grains exhibit no germination dormancy, resulting in a short persistence. In addition, only few seeds remain on the field after the harvest of fodder maize.¹⁸ Establishment of maize plants in the wild has never been observed in the Netherlands.

Molecular characterization

Maize line Bt11xMIR162xMIR604xGA21 was produced by conventional cross-breeding of the genetically modified maize lines Bt11, MIR162, MIR604 and GA21. Information on the elements introduced in these maize lines is given below.

Maize line Bt11

Bt11 maize was generated by transformation of *Z. mays* protoplasts using a *NotI* restriction fragment which contains the *cryIAb* and *pat* gene cassettes.

The *cryIAb* gene cassette consists of the following elements:

- 35S promoter, derived from *Cauliflower mosaic virus* (CaMV)
- IVS6-ADH1 intron, intervening intron sequence 6 derived from the alcohol dehydrogenase 1 (*adh1*) gene of maize
- truncated *cryIAb* gene, derived from *Bacillus thuringiensis* var. *kurstaki* HD-1, truncated at the 3' end and modified to enhance expression in plants. The Cry1Ab protein confers resistance to certain lepidopteran insects

- NOS terminator, derived from the nopaline synthase (*nos*) gene of *Agrobacterium tumefaciens*

The *pat* gene cassette consists of the following elements:

- 35S promoter, derived from CaMV
- IVS2-ADH1 intron, intervening intron sequence 2 derived from the alcohol dehydrogenase 1 (*adh1*) gene of maize
- *pat* gene, derived from *Streptomyces viridochromogenes* strain Tu494 and codon-optimized to enhance expression in maize. The *pat* gene encodes phosphinothricin acetyl transferase which confers resistance to glufosinate ammonium containing herbicides
- NOS terminator, derived from the nopaline synthase (*nos*) gene of *A. tumefaciens*

Besides these gene cassettes the *NotI* restriction fragment contains a 1.1 kb fragment of vector sequence upstream of the *cry1Ab* gene cassette. This fragment contains the ColE1 *ori*, the origin of replication that permits replication of plasmids in *Escherichia coli*, but which is not functional in plants.

Maize line Bt11 contains a single DNA insertion with one copy of the *NotI* restriction fragment.

Maize line MIR162

The *vip3Aa19* and *pmi* gene cassettes were introduced in maize line MIR162 via *A. tumefaciens* mediated transformation.

The *vip3Aa19* gene cassette consists of the following elements:

- ZmUbiInt promoter, derived from the *Z. mays* polyubiquitin gene; provides constitutive expression in monocots
- *vip3Aa19* gene, modified version of the native *vip3Aa1* gene from *B. thuringiensis* strain AB88
- iPEPC9 intron, intron #9 from the phosphoenolpyruvate carboxylase gene from *Z. mays*
- 35S terminator, derived from CaMV

The *pmi* gene cassette consists of the following elements:

- ZmUbiInt promoter, derived from the *Z. mays* polyubiquitin gene; provides constitutive expression in monocots
- *pmi* gene, from *Escherichia coli*; catalyzes the isomerization of mannose-6-phosphate to fructose-6-phosphate
- NOS, terminator sequence from the nopaline synthase (*nos*) gene of *A. tumefaciens*

Maize line MIR604

The *mcry3A* and *pmi* gene cassettes were introduced in maize line MIR604 via *Agrobacterium*-mediated transformation.

The *mcry3A* gene cassette consists of the following elements:

- MTL promotor, derived from the *Z. mays* metallothionein-like gene; provides root-preferential expression
- *mcry3A* gene, from *B. thuringiensis* subsp. *tenebrionis* and optimized for expression in maize; confers resistance to certain coleopteran insects
- NOS, terminator sequence from the nopaline synthase (*nos*) gene of *A. tumefaciens*

The *pmi* gene cassette consists of the following elements:

- ZmUbiInt promotor, derived from the *Z. mays* polyubiquitin gene; provides constitutive expression in monocots
- *pmi* gene, from *Escherichia coli*; catalyzes the isomerization of mannose-6-phosphate to fructose-6-phosphate
- NOS, terminator sequence from the nopaline synthase (*nos*) gene of *A. tumefaciens*

Maize line MIR604 contains a single DNA insertion with one copy of the *mcry3A* and *pmi* gene cassettes.

Maize line GA21

GA21 maize was produced by microprojectile bombardment of *Z. mays* suspension cells using a *NotI* restriction fragment which contains the *mepsps* gene cassette.

The *NotI* restriction fragment contains the following elements:

- *ract1* promoter, first intron and exon, derived from the rice actin 1 (*ract1*) gene
- optimized CTP, N-terminal chloroplast transit peptide (CTP) based on CTP sequences from sunflower and maize
- *mepsps* gene, modified 5-enolpyruvylshikimate-3-phosphate synthase (*mepsps*) gene from maize
- NOS terminator, derived from the nopaline synthase (*nos*) gene of *A. tumefaciens*

Maize line GA21 contains a single DNA insertion with six (partial) copies of the *NotI* restriction fragment.

Molecular analysis

The molecular characterization of maize lines Bt11, MIR604 and GA21 has been discussed in several previous advices.^{1,2,3,4,5,6,7,8,9,10,11}

In recent applications concerning import and processing of Bt11xGA21, Bt11xMIR604, MIR604xGA21 and Bt11 (renewal) the original sequence data of maize lines Bt11 and MIR604 was revised.^{2,3,9,10,11,12} The original sequence data of maize line GA21 was recently revised in the application for cultivation of this maize line.⁸ Apparently the data presented in the first applications contained flaws. COGEM commented on the revised sequence data as a proper risk assessment can only be carried out if correct and clear-cut information is provided to the competent authorities. However, as mentioned in previous advices concerning these applications,

COGEM is of the opinion that both the original and the revised sequence data give no reason to expect any adverse effects on the environment.^{2,3,8,10,11,12}

Last year COGEM reconsidered the elements of the molecular characterization that are needed for the environmental risk analysis and formulated revised criteria for the molecular characterization of commercial releases of GM crops.²² COGEM concluded that analyses for putative ORFs and their theoretical products are necessary for the risk analysis. COGEM defines an ORF as beginning with any of the three stop codons and ending with one. COGEM is of the opinion that ORFs encoding for smaller proteins than fifty amino acids should also be analyzed.

In previous advices on maize lines GA21 and MIR604 COGEM made remarks on the analyses that were carried out for putative ORFs and their products^{8,10,11} However, in the mean time additional information has been supplied by the applicants. The additional information contains bioinformatic analyses that meet the criteria of COGEM. The applicant identified eleven nucleotide sequences for GA21 and twelve nucleotide sequences for MIR604 that were delimited by putative stop codons. None of these nucleotide sequences were homologous to toxins or allergens.

Maize line MIR162 has not been assessed previously by COGEM. Therefore, the molecular characterization of this maize line is discussed in more detail hereafter.

By Southern blot hybridization with a probe spanning the entire backbone region of the vector the applicant showed that the vector backbone is not present in maize MIR162. In addition, Southern blot hybridizations with a *vip3Aa19*-, *pmi*-, ZmUbiInt promoter- and with a NOS terminator-specific probe showed that one copy of the *vip3Aa19* gene, *pmi* gene and NOS terminator and two copies of the ZmUbiInt promoter were present. These results are expected when one copy of the insertion cassette is present in maize MIR162.

Sequence analysis of the insert confirmed that the insert is intact, but indicated that the right border (RB) and the left border (LB) ends of the insert are truncated. In MIR162 the entire RB along with two non-coding base pairs is missing, and the entire LB is missing along with 32 non-coding base pairs. Sequence analysis indicated that in MIR162 two nucleotides of the *vip3Aa19* gene had changed. To indicate the difference the applicant designated the *vip* gene that is present in MIR162 *vip3Aa20*. One of the nucleotide changes leads to a different amino acid, whereas the other nucleotide change does not influence the amino acid sequence.

The applicant also sequenced 1000 base pairs of the 5' and 3' flanking regions and showed by BLAST analysis that these regions are maize genomic DNA. Bioinformatic analysis of the 5' flanking region indicated that part of this region is significantly homologous to a *Dissociation1* (*Ds1*) related transposable element. The region of homology is located 500 base pairs from the insert. A *Ds1* transposable element can only transpose if an *Activator* (*Ac*) element is present. If the *Ds1* element would transpose part of the maize genomic DNA that flanks the *Ds1* element may be deleted. However, in maize deletions caused by *Ds1* transposable elements rarely extend into the host genome.²³ The largest amount of host DNA reported to be deleted was 36 base pairs.²⁴ Since the *Ds1* transposable element is located at 500 base pairs from the insert, it is unlikely that the insert would be affected.

Bioinformatic analysis of the 3' flanking region showed that this region is homologous to maize genomic DNA.

In addition, bioinformatic analysis of the junctions of the insert and the maize genomic DNA identified twelve nucleotide sequences that were delimited by putative stop codons. None of these nucleotide sequences were homologous to toxins or allergens.

Properties of the introduced genes conferring insect resistance

Maize line Bt11xMIR162xMIR604xGA21 contains the *cry1Ab*, *mcry3A* and *vip3Aa20* genes. These genes were derived from *B. thuringiensis*. The *cry1Ab* gene encodes a δ -endotoxin specific for certain lepidopteran insects, e.g. the European corn borer (*Ostrinia nubilalis*) and the Mediterranean corn borer (*Sesamia nonagrioides*), whereas the *mcry3A* gene encodes a δ -endotoxin specific for certain coleopteran insects, e.g. the Western corn rootworm (*Diabrotica virgifera virgifera*) and the Northern corn rootworm (*Diabrotica barberi*). The δ -endotoxins are solubilized in the midgut of susceptible insects and are activated by midgut proteases to release a toxin fragment. The toxin fragment binds to specific receptors on the epithelial surface of the midgut. Subsequently, pores are formed in the membranes of the gut cells of the insect, enabling midgut bacteria to enter the body cavity, which leads to septicemia and death.²⁵

The *vip3Aa20* gene is a modified version of the *vip3Aa1* gene which encodes a vegetative insecticidal protein (VIP3Aa20) with activity against certain lepidopteran insect orders. Susceptible insects are e.g. the corn earworm (*Heliothis zea*), the black cutworm (*Agrotis ipsilon*), the fall armyworm (*Spodoptera frugiperda*) and the Western bean cutworm (*Striacosta albicosta*).^{26,27} Although the Vip3A protein shows no sequence homology to known δ -endotoxins its mode of action is similar to that of δ -endotoxins. Like δ -endotoxins, Vip3A is processed in the insect gut. The resulting fragment binds to epithelial cells of the midgut of susceptible insects which results in the formation of pores in the membranes of the gut cells of the insect and finally in the insect's death.²⁶

Although the mode of action of Vip3A is similar to the mode of action of δ -endotoxins experimental data shows that the binding site of Vip3A in the midgut differs from the binding site of Cry1Ab. In addition, the ion channels formed when Vip3A binds to the epithelial cells of the midgut are structurally and functionally different from those that are formed by Cry1Ab.²⁶

Properties of the introduced genes conferring herbicide tolerance

In addition to the *cry1Ab*, *mcry3A* and *vip3Aa20* genes, Bt11xMIR162xMIR604xGA21 contains the *pat* and *mepsps* genes.

In non-transgenic plants glufosinate ammonium inhibits the activity of glutamine synthetase, an enzyme necessary for the production of glutamine and for ammonia detoxification. The application of glufosinate ammonium leads to reduced glutamine and increased ammonia levels in non-transgenic plants.²⁸ Photosynthesis is inhibited and eventually the plant dies.²⁹ In Bt11xMIR162xMIR604xGA21 the PAT protein acetylates L-phosphinothricin, the active isomer of glufosinate ammonium. The resulting compound N-acetyl-L-phosphinothricin does not inhibit the activity of glutamine synthetase.²⁸ As a result maize line Bt11xMIR162xMIR604xGA21 is tolerant to L-phosphinothricin and thus to glufosinate ammonium containing herbicides.

In non-transgenic plants glyphosate inhibits 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), an enzyme involved in the biosynthesis of aromatic amino acids. Application of glyphosate results in a lack of amino acids essential for growth and development of plants and

ultimately causes plant death.³⁰ Maize line Bt11xMIR162xMIR604xGA21 expresses a modified EPSPS protein, which is not inhibited by glyphosate, and is therefore tolerant to glyphosate containing herbicides.

Properties of the introduced selection marker

Bt11xMIR162xMIR604xGA21 also contains the *pmi* (*manA*) gene, which encodes the phosphomannose isomerase (PMI) enzyme. As a result maize plants are able to use mannose as a carbon source. Mannose is phosphorylated to mannose-6-phosphate (M6P) which can be converted to fructose-6-phosphate with the help of PMI. In non-transgenic maize plants conversion of M6P will not occur. M6P will accumulate, block glycolysis, and inhibit plant growth.

The ability to use mannose as a carbon source is used to select transformed cells in cell cultures.

Environmental risk assessment

During the long process of domestication, maize has lost the ability to survive in the wild. In addition, maize needs human intervention to disseminate its seed. Maize kernels exhibit no dormancy and can only survive within a narrow range of climatic conditions. Furthermore, maize is very sensitive to weed competition and cannot persist as a weed.^{31,32} In the Netherlands, volunteers are rarely found and establishment of maize plants in the wild has never been observed.

Maize Bt11xMIR162xMIR604xGA21 expresses the *cry1Ab*, *mcry3A*, *vip3Aa20*, *mepsps*, *pat*, and *pmi* genes. As a result, the maize line is resistant to certain lepidopteran and coleopteran insects, tolerant to glufosinate-ammonium and glyphosate containing herbicides, and able to use mannose as a carbon source. The current application concerns import and processing. In case of spillage maize kernels may be released into the environment. Maize kernels can only survive within a narrow range of climatic conditions. The introduced traits do not increase the ability of maize kernels to survive. In addition, according to the agronomic assessment of Bt11xMIR162xMIR604xGA21 the ecological characteristics of this maize line have not been influenced by the introduced traits. Interactions between the expressed transgenic proteins could theoretically change the potential to establish feral populations. COGEM is of the opinion that the chance that interactions between the expressed transgenic proteins increase the possibility to establish feral populations is negligible. In view of the above, there are no reasons to assume that maize Bt11xMIR162xMIR604xGA21 has an increased potential for the establishment of feral populations in case of incidental spillage.

Recently, COGEM abstains from advices on the potential risks of incidental consumption in case a food/feed safety assessment is already carried out by other organizations. This application is submitted under Regulation (EC) 1829/2003, therefore a food/feed safety assessment is carried out by EFSA. Other organizations who advice the competent authorities can perform an additional assessment on food safety although this is not obligatory. In the Netherlands a food and/or feed safety assessment for Regulation (EC) 1829/2003 applications is carried out by

RIKILT. Regarding the risks for food and feed, the outcome of the assessment by other organizations (EFSA, RIKILT) was not known at the moment of the completion of this advice.

General surveillance

General surveillance has been introduced to be able to observe unexpected adverse effects of genetically modified crops on the environment. The setting or population in which these effects might occur is either not, or hardly predictable.

The general surveillance plan describes that unanticipated adverse effects will be monitored by existing systems which include the authorization holder and operators involved in the handling and use of viable Bt11xMIR162xMIR604xGA21 maize. Although the general surveillance plan could be improved by a guarantee that operators will monitor for unanticipated effects, COGEM considers the general surveillance plan sufficient for import and processing of Bt11xMIR162xMIR604xGA21 maize.

Advice

COGEM has been asked to advice on import and processing of maize line Bt11xMIR162xMIR604xGA21. The molecular characterization of maize line Bt11xMIR162xMIR604xGA21 and of its individual parental maize lines meets the criteria of COGEM.

Maize has lost the ability to survive in the wild. In addition, maize needs human intervention to disseminate its seed. In the Netherlands, volunteers are rare and establishment of maize plants in the wild has never been observed. There is no reason to assume that expression of the *cry1Ab*, *mcry3A*, *vip3Aa20*, *pat*, *mepsps* and *pmi* genes or interactions between the transgenic proteins increase the potential of maize to establish feral populations in case of incidental spillage. In addition, introgression of the introduced genes into closely related species cannot occur, as wild relatives of maize are not present in Europe.

In view of the above, COGEM is of the opinion that the risks for humans and the environment associated with import and processing of maize line Bt11xMIR162xMIR604xGA21 are negligible. A food/feed safety assessment was carried out by other organizations. Therefore, COGEM abstained from advice on the potential risks of incidental consumption.

Additional remark

Bt11xMIR162xMIR604xGA21 expresses the *vip3Aa20* gene. This gene is a modified version of the *vip3Aa19* gene which is a codon optimized version of the *vip3Aa1* gene. Although some information on the specificity of the Vip3Aa1 and the Vip3Aa19 proteins is available, this information cannot be directly extrapolated to the Vip3Aa20 protein since the amino acid sequence of Vip3Aa20 is not completely identical to the Vip3Aa19 or the Vip3Aa1 protein.

In case of import and processing the exposure of non-target organisms is limited to unintended release of Bt11xMIR162xMIR604xGA21 maize by spillage. Therefore, COGEM is of the opinion that in the current application, the lack of data on the specificity of the Vip3Aa20 is not a reason for concern. However, in case of cultivation non-target organisms will be exposed to the Vip3Aa20 protein. For such an application COGEM considers data on the specificity of the Vip3Aa20 protein essential.

Maize line Bt11xMIR162xMIR604xGA21 expresses the *cry1Ab*, *mcry3A*, *vip3Aa20*, *pat*, *mepsps* and *pmi* genes. These transgenic proteins could interact to cause a synergistic effect, e.g. on non-target organisms. Synergistic effects are a point of attention in case of applications for cultivation. The current application concerns import and processing. In the Netherlands, establishment of maize plants in the wild has never been observed. Therefore, COGEM does not consider potential synergistic effects a point of concern for the current import application.

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