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KENMERK CGM/151008-01
ONDERWERP Advies import van gg-katoen GHB614xLLCotton25xMON15985 en
LLCotton25xMON15985

Geachte mevrouw Mansveld,

Naar aanleiding van de adviesvraag over de milieurisico's van import en verwerking van de genetisch gemodificeerde katoen kruisingslijnen GHB614xLLCotton25xMON15985 en LLCotton25xMON15985 (EFSA/GMO/NL/2011/94) deelt de COGEM u het volgende mee.

Samenvatting:

De COGEM is gevraagd te adviseren over import en verwerking van de genetisch gemodificeerde (gg-) katoenlijnen GHB614xLLCotton25xMON15985 en LLCotton25xMON15985. LLCotton25xMON15985 brengt de *cryIAc*, *cry2Ab2*, *bar*, *nptII* en *uidA* genen tot expressie. GHB614xLLCotton25xMON15985 brengt daarnaast ook het *2m epsps* gen tot expressie. Hierdoor zijn LLCotton25xMON15985 en GHB614xLLCotton25xMON15985 resistent tegen bepaalde insecten uit de orde van de Lepidoptera en tolerant voor bepaalde herbiciden.

In Europa komen geen wilde verwanten van katoen voor. Katoen kan niet overleven in Noordwest-Europa vanwege het klimaat. De eigenschappen die in GHB614xLLCotton25xMON15985 en LLCotton25xMON15985 zijn ingebracht, veranderen dit niet. Daarom acht de COGEM de kans verwaarloosbaar klein dat het incidenteel morsen van de katoenzaden leidt tot verspreiding of vestiging van deze gg-katoenlijnen in Noordwest-Europa.

Omdat andere instanties een voedselveiligheidsbeoordeling uitvoeren heeft de COGEM bij deze vergunningaanvraag de risico's van incidentele consumptie niet beoordeeld.

Alle aspecten in overweging nemende, acht de COGEM de milieurisico's voor Nederland bij import en verwerking van gg-katoen GHB614xLLCotton25xMON15985 en LLCotton25xMON15985 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, appearing to be 'S. Schaap'. The signature is fluid and cursive, with a large loop at the end.

Prof. dr. ing. Sybe Schaap
Voorzitter COGEM

c.c. Drs. H.P. de Wijs, Hoofd Bureau ggo
 Mr. J.K.B.H. Kwisthout, Ministerie van IenM

Import and processing of genetically modified cotton GHB614xLLCotton25xMON15985 and LLCotton25xMON15985

COGEM advice CGM/151008-01

Summary

The present application EFSA/GMO/NL/2011/94 concerns import and processing for use in feed and food of genetically modified cotton GHB614xLLCotton25xMON15985 and LLCotton25xMON15985. Cultivation is not part of this application.

LLCotton25xMON15985 expresses the cry1Ac, cry2Ab2, bar, nptII and uidA genes. In addition to these genes, GHB614xLLCotton25xMON15985 expresses the 2m epsps gene. As a result, LLCotton25xMON15985 and GHB614xLLCotton25xMON15985 are resistant to certain lepidopteran insects and tolerant to certain herbicides.

GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 were produced by conventional breeding of the genetically modified parental cotton lines. Previously, COGEM issued positive opinions on import and processing of the parental lines GHB614, LLCotton25, MON15985 and GHB614xLLCotton25.

COGEM is of the opinion that the molecular characterisation of GHB614 and LLCotton25 is adequate. As stated before, COGEM notes that the molecular characterisation of MON15985 is presented in a disorderly manner and contains flaws.

In Northwestern Europe, no wild relatives of cotton are present. Modern cotton cultivars do not possess any of the attributes commonly associated with problematic weeds. Cotton cannot survive in Northwestern Europe due to the climatic conditions. The introduced traits will not enable GHB614xLLCotton25xMON15985 or LLCotton25xMON15985 to establish feral populations. Therefore, COGEM is of the opinion that incidental spillage of GHB614xLLCotton25xMON15985 or LLCotton25xMON15985 cotton seeds will not pose a risk to the environment in the Netherlands.

In view of the above, COGEM is of the opinion that import and processing of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 poses a negligible risk to the environment in the Netherlands. A food/feed safety assessment is carried out by other organisations. Therefore, COGEM abstains from advice on the potential risks of incidental consumption.

Introduction

The scope of the present application (EFSA/GMO/NL/2011/94), submitted by Bayer CropScience AG concerns import and processing of *Gossypium hirsutum* cotton GHB614xLLCotton25xMON15985 and LLCotton25xMON15985. The application was submitted in 2011, but was only recently declared valid after EFSA published opinions on all parental lines.

Import and processing of the parental lines and GHB614xLLCotton25 is authorised in the European Union.^{1,2,3,4}

COGEM has been asked to advice on the environmental risks of import and processing of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 cotton.

LLCotton25xMON15985 expresses the *cryIAc* and *cry2Ab2* genes conferring resistance to certain lepidopteran insects. It also expresses the *bar* gene, resulting in tolerance to glyphosate-ammonium based herbicides. In addition, LLCotton25xMON15985 expresses the *nptII* and *uidA* marker genes simplifying the selection of transformed cotton cells. LLCotton25xMON15985 also contains the *aad* marker gene, which is not expressed because it is under the control of a prokaryotic promoter.

In addition to the above listed genes, GHB614xLLCotton25xMON15985 expresses the *2m epsps* gene resulting in tolerance to herbicides containing glyphosate as the active ingredient. GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 were produced by conventional crossbreeding of the genetically modified parental lines.

Previous COGEM advices

COGEM has previously issued positive opinions on import and processing of GHB614,⁵ LLCotton25,⁶ MON15985^{7,8} and GHB614xLLCotton25.⁹ COGEM also advised positively on cultivation of GHB614.¹⁰

Aspects of the crop

Cotton is a member of the genus *Gossypium* and belongs to the *Malvaceae* family. The majority of cultivated cotton is *Gossypium hirsutum* (90%) and *Gossypium barbadense* (5%), while *Gossypium arboreum* and *Gossypium herbaceum* are cultivated as well.^{11,12,13} The only cultivated cotton species in Europe is *G. hirsutum*, which is grown in Greece, Spain and Bulgaria.¹⁴

Cotton plants reproduce sexually.¹³ Cotton is predominantly a self-pollinating species, but cross-pollination may occur. Dissemination of pollen by wind is (almost) absent.^{12,13} The pollen of cotton is large, heavy and somewhat sticky.^{12,13} Outcrossing rates for cotton are strongly influenced by the presence of insects. Pollinators of cotton flowers include bumblebees (*Bombus* spp.), honeybees (*Apis* spp.) and other bee species (*Anthophora* spp., *Melissodes* spp. and *Halictus* spp.).^{12,15} Hybridisation between *G. hirsutum* and *G. barbadense* may occur and can lead to viable progeny (F1). Hybrid F2 progeny contain either depauperate types or plants that closely resemble one of the parents.¹⁵ Wild relatives of cotton (*Gossypium* spp.) do not occur in Northwestern Europe. Therefore, hybridisation with wild relatives cannot occur in Northwestern Europe.¹²

Cotton is highly sensitive to temperature and susceptible to frost. Temperature is the main factor that determines the geographic range in which cotton can be grown. Plant development ceases below a temperature of 12 °C and delays when the temperature rises above 38 °C.^{12,13} *G. hirsutum* needs a period of 180 to 200 frost-free days for normal maturation, with an average of 150 days of suitable temperatures (averaging 21-22 °C). The optimal temperature for growth is between 30 and 35 °C.¹⁶ *G. barbadense* has a longer growing season. It needs 200 to 250 frost-free days and has a

lower optimum temperature for growth (25-30°C).^{12,17} In places where cotton is cultivated as a rain-fed crop, the average rainfall is 800-1200 mm.¹¹ In areas where the rainfall is less than 500 mm a year, irrigation is necessary.¹²

Cottonseed can be dispersed by wind, water, during transport or when feeding cattle.¹³ In addition, cottonseed can be transported by birds or rodents. Seeds from cotton cultivars do not possess dormancy and will germinate directly if conditions are favourable.^{12,13} Seeds usually do not survive in humid soil.¹³ In regions with mild and dry winters, cottonseeds may overwinter and germinate in spring. Seedlings are sensitive to competition from weeds.¹²

Modern cotton cultivars do not possess any of the attributes commonly associated with problematic weeds, such as dormancy, persistence in seed banks, germination under adverse environmental conditions, rapid vegetative growth, a short life cycle, very high seed output, high seed dispersal and long-distance dispersal of seeds. Cotton volunteers occur in cotton growing areas and may occur when cottonseed is used as livestock feed. The presence of volunteer cotton is limited by soil moisture content and frost.¹³ There are reports that *G. hirsutum* and *G. herbaceum* cotton are naturalised in some Southern European countries, e.g. Greece and Spain.^{18,19}

Properties of the introduced genes

Insect resistance

GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 express the *cry1Ac* and *cry2Ab2* genes. These proteins encode Cry1Ac and Cry2Ab2 proteins. When these proteins are ingested by susceptible insects they are proteolytically cleaved in the midgut of the insect. The resulting delta-endotoxins bind to specific receptors on the epithelial surface of the midgut, which causes the formation of pores. This leads to disruption of the movement of solutes across the gut epithelium and ultimately in death of the insect. As a result GHB614xLLCotton25xMON15985 is resistant to certain susceptible lepidopteran insects, such as the cotton bollworm (*Helicoverpa armigera*), the tobacco budworm (*Heliothis virescens*), the pink bollworm (*Pectinophora gossypiella*) and the beet armyworm (*Spodoptera exigua*).

Herbicide tolerance

GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 are tolerant to herbicides containing glufosinate ammonium. In non-transgenic plants, glufosinate ammonium inhibits the activity of glutamine synthetase, an enzyme necessary for the production of glutamine and for ammonia detoxification.²⁰ GHB614xLLCotton25xMON15985 expresses the *bar* gene which encodes phosphinothricin-N-acetyl transferase (PAT). This 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.²⁰

In addition to the *bar* gene, GHB614xLLCotton25xMON15985 expresses the *2m epsps* gene, which encodes a modified 5-enolpyruvylshikimate-3-phosphate synthase 2mEPSPS protein. The

modified 2mEPSPS protein differs from the wild type EPSPS enzyme by two amino acid substitutions. EPSPS is a naturally occurring enzyme involved in the biosynthesis of aromatic amino acids. Glyphosate inhibits EPSPS, resulting in a lack of amino acids essential for growth and development of plants. In contrast to EPSPS, the 2mEPSPS protein is not inhibited by glyphosate and therefore the plant is tolerant to glyphosate containing herbicides.²¹

Selection markers

GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 contain three different marker genes. One of these marker genes, the *aad* gene, is not expressed in cotton, since it is under the control of a prokaryotic promoter. The other introduced marker genes, i.e. *nptII* and *uidA*, are expressed, and allow an easy selection of transformed cotton cells. Expression of the *nptII* gene enables transformed cotton cells to survive in the presence of aminoglycosides (e.g. kanamycin). Aminoglycosides disrupt protein synthesis by binding to the 30S ribosomal subunit which causes misreading of mRNA and results in non-functional, misfolded proteins leading to cell death.²² The *nptII* gene encodes neomycin phosphotransferase type II which modifies the aminoglycoside molecule. The modified molecule cannot bind to the 30S ribosomal subunit, protein synthesis is no longer disrupted and the cotton cells can survive in the presence of aminoglycosides.²³

The *uidA* gene encodes β -D-glucuronidase (GUS), an exohydrolase which catalyzes cleavage of β -glucuronides. Expression of the *uidA* gene enables selection of transformed cotton cells because cotton cells that express the *uidA* gene turn blue in the presence of the substrate 5-bromo-4-chloro-3-indolyl β -D glucuronic acid (X-gluc).²⁴

Molecular characterisation

COGEM previously evaluated the molecular characterisation of the parental cotton lines of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985. The molecular characterisation of GHB614 and LLCotton25 was considered adequate.^{5,9,10} COGEM noted that the molecular characterisation of MON531, the GM cotton line that was used to produce MON15985, contained weaknesses. Consequently, also the molecular characterisation of MON15985 was flawed.^{7,8} Despite these weaknesses, COGEM concluded that import and processing of MON15985 poses a negligible risk to the environment because cotton cannot survive in the Netherlands and MON531 has a history of safe use.

Updated bioinformatic analyses of GHB614, LLCotton25 and MON15985 are included in the current application for import and processing of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985. The molecular characterisation of GHB614 and LLCotton25 meets the criteria of COGEM.

The molecular characterisation of MON15985 is presented in a disorderly manner. Not all studies which are referred to in the application (in particular those before 2008) are accessible by COGEM. In addition, the data in the current application seems to disagree with the data of the application filed in 2008. This unnecessarily complicates the risk assessment.

The applicant provided updated bioinformatic analyses of the DNA sequences flanking the inserts in MON15985 to assess whether endogenous genes were disrupted by the insertion of these

inserts. COGEM notes that there are discrepancies in the description of the current and the previous molecular characterisation of MON15985. In particular that of the insert containing the *uid-cry2Ab2* expression cassettes. In the current application it is mentioned that 1135 basepairs flanking the 5' end, and 323 basepairs flanking the 3' end of the inserted *uidA-cry2Ab2* expression cassettes cannot be identified, whereas in the application of 2008 it was described as 'cotton genomic DNA'. The applicant fails to mention and explain this discrepancy. Also, the origin of the unidentified DNA is not explained. It is unclear whether it co-integrated with the insert or whether it represents a regular endogenous sequence at the integration site.

The putative polypeptides at the junctions between the *uidA-cry2Ab2* insert and its flanking sequences were analysed for similarity to known toxins and allergens. However, no analyses were performed on the junctions between the 3' unidentified sequences and cotton genomic DNA, between the 5' unidentified sequences and the identified plastid DNA, and between the plastid DNA and the cotton genomic DNA. Strikingly, the applicant noticed mistakes in the bioinformatic analyses of 2008. Apparently, the *in silico* translations of sequences spanning the junctions between cotton genomic DNA and the *cry1Ac-nptII* and 242 bp inserts in MON15985 were incorrect. In the current application revised sequence data are used. The applicant states that no relevant sequence similarities were observed between the *in silico* translated putative polypeptides and allergens, toxins or biologically active proteins.

Despite the changes and improvements in the current molecular characterisation, not all weaknesses identified by COGEM in 2008, such as the potential presence of additional fragments, are addressed. Moreover, new ambiguities, i.e. the presence of unidentified sequences flanking the *uidA-cry2Ab2* insert, are introduced.

Environmental risk assessment

Cotton is predominantly a self-pollinating species, but cross-pollination may occur. Neither GHB614xLLCotton25xMON15985 nor LLCotton25xMON15985 can fertilise wild relatives because *G. hirsutum* and *G. barbadense* do not occur in North-western Europe.¹²

Cotton plants are susceptible to frost. A reasonably high temperature (optimally 25-30 °C for *G. barbadense* and 30-35 °C for *G. hirsutum*) is required in all stages of development. For normal maturation, a period of 200 to 250 frost-free days is needed for *G. barbadense* and 180 to 200 days for *G. hirsutum*. In addition, this period needs to have on average 150 days of suitable temperatures, averaging 21-22 °C. In the Netherlands, the summer months of May, June, July, August and September (in total 153 days) have average monthly temperatures above 12 °C, but below 18 °C.²⁵ In addition, in areas where rainfall is less than 500 mm a year, irrigation should be applied for cotton growth. In the months of May through September in the Netherlands, the average monthly precipitation does not exceed 100 mm.²⁵ Based on the above, the current Dutch climate is unsuited for cotton growth.

There is no reason to assume that the introduced traits (resistance to certain lepidopteran insects, tolerance to certain herbicides and easy selection of transformed cotton cells) will enable cotton to survive in the environment. The applicant carried out an agronomic assessment of GHB614xLLCotton25xMON15985. This assessment does not give any indication that under

natural conditions GHB614xLLCotton25xMON15985 or LLCotton25xMON15985 have an increased fitness compared to conventional cotton varieties.

The molecular characterisation of GHB614 and LLCotton25 meets the criteria of COGEM. As previously reported by COGEM, the molecular characterisation of MON15985 contains weaknesses. In addition to these weaknesses, COGEM notes discrepancies with the information previously provided as part of the application for import and processing of MON15985. COGEM considers the provided molecular characterisation inadequate. Despite the flawed molecular characterisation COGEM is of the opinion that import and processing of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985 poses a negligible risk to the environment because cotton cannot survive in the Netherlands.

Considering the above, there are no reasons to assume that in case of incidental spillage of cottonseed LLCotton25xMON15985 or GHB614xLLCotton25xMON15985 would be able to establish feral populations in the Netherlands.

Food/ feed assessment

COGEM abstains from giving advice on the potential risks of incidental consumption since a food/feed assessment is already carried out by other organisations.²⁶ This application is submitted under Regulation (EC) 1829/2003, therefore a food/feed assessment is carried out by EFSA and national organisations involved in the assessment of food safety. In the Netherlands, a food/feed assessment for Regulation (EC) 1829/2003 applications is carried out by RIKILT. The outcome of the assessment by these organisations (EFSA, RIKILT) was not known upon the completion of this advice.

Advice

The present application concerns import and processing for feed and food purposes of the genetically modified cotton GHB614xLLCotton25xMON15985 and LLCotton25xMON15985. Cultivation is not part of the application. Therefore, the risk assessment focuses on accidental spillage of cottonseeds.

The molecular characterisation of GHB614 and LLCotton25 meets the criteria of COGEM. As previously reported by COGEM, the molecular characterisation of MON15985 contains some weaknesses. In addition to these weaknesses, COGEM notes discrepancies with the information provided in 2008 as part of the application for import and processing of MON15985. COGEM considers the molecular characterisation of MON15985 inadequate. However, the molecular characterisation is one of the elements of the environmental risk assessment and has to be considered in connection with other elements such as the biological characteristics of the crop, the receiving environment etc.²⁷

Cotton plants are very sensitive to temperature. The Northwestern European climate is unsuited for cotton growth. There is no indication that the introduced traits, which confer resistance to certain lepidopteran insects, tolerance to certain herbicides, and allow easy selection of transformed cotton cells, will enable GHB614xLLCotton25xMON15985 or LLCotton25xMON15985 to

survive in the environment. Therefore, incidental spillage of cottonseeds will not lead to feral cotton populations in Northwestern Europe.

COGEM has published several recommendations for further improvement of the submitted general surveillance (GS) plan,^{28,29} but considers the current GS plan adequate for import and processing of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985.

COGEM notes that the molecular characterisation of MON15985 is flawed. However, considering all aspects, in particular the biological characteristics of GHB614xLLCotton25xMON15985 and LLCotton25xMON15985, COGEM is of the opinion that import and processing of these cotton events poses a negligible risk to the environment.

A food/feed safety assessment is carried out by other organisations. Therefore, COGEM abstains from advice on potential risks of incidental consumption.

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