Bioveiligheidsraad
Conseil de Biosécurité

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Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2014_0591

Title: Advice of the Belgian Biosafety Advisory Council on application EFSA/GMO/NL/2010/77 from Bayer CropScience under Regulation (EC) No. 1829/2003

Context

The application EFSA/GMO/NL/2010/77 was submitted by Bayer CropScience on 4 February 2010 within the framework of Regulation (EC) No. 1829/2003[1] for authorisation of genetically modified (GM) cotton GHB614 x LLCotton25 for import and processing, and for food and feed uses.

Cotton GHB614 x LLCotton25 was obtained by conventional crossing (no new genetic modification involved) of two transgenic lines containing the following single events:
- Line GHB614 expressing the 2mEPSPS protein conferring tolerance to glyphosate-based herbicides, and
- Line LLCotton25 expressing the PAT protein conferring tolerance to glufosinate ammonium-based herbicides.

The application was officially acknowledged by EFSA on 26 January 2011. On the same date EFSA started the formal three-month consultation period of the Member States, 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 GM 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 Biosafety and Biotechnology Unit (SBB). Three experts answered positively to this request, and formulated a number of comments to the dossier, which were edited by the coordinator. See Annex I for an overview of all the comments and the list of comments actually placed on the EFSAnet on 26 April 2011.

The opinion of the EFSA GMO Panel was adopted on 11 April 2014 and published on 16 May 2014 (EFSA Journal 2014; 12(5):3680[2]). The responses from the Panel to comments submitted by the experts during the three-month consultation period were made available on 21 May 2014.

On 04 June 2014 the EFSA opinion and the responses from the EFSA GMO Panel were forwarded to the Belgian experts. They were invited to give comments and to react if needed to the answers given by the Panel, in particular in case the comments formulated in their initial assessment of the dossier were not taken into account in the opinion of EFSA.

[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 http://www.efsa.europa.eu/fr/efsajournal/pub/3680.htm

The comments formulated by the experts together with the EFSA opinion including the answers of the EFSA GMO Panel, form the basis of the advice of the Biosafety Advisory Council given below.

The two advices already published by the BAC on the single events GHB614[3] and LLCotton25[4] have also been considered. In this regards, the conclusions of the BAC were as follows:
- For GM cotton GHB614, the BAC supported the conclusion of the GMO panel of EFSA that (i) No major risks concerning the environment were identified, and that (ii) No major risks for human and animal health were identified.
- For GM cotton LLCotton25, the BAC agreed with the conclusion of the GMO panel of EFSA that "it is unlikely that LLCotton 25 will have adverse effects on human and animal health or the environment in the context of its proposed uses".

Scientific evaluation

1. Environmental risk assessment

According to the Biosafety Advisory Council no major risks were identified concerning the European environment[5]. For the sake of consistency, the statement of the notifier that "Cultivated cotton does not produce seeds which can persist in the environment for long periods of time, furthermore cotton seed lacks the ability to develop dormancy" should be scientifically substantiated.

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

Statistically significant differences between GM cotton GHB614 × LLCotton25 and its conventional counterpart were observed for crude fat, ash, calcium, potassium, magnesium, iron, zinc, phytic acid, dihydrosterculic acid and free and total gossypol among a total 49 parameters. With the exception of magnesium,17 these endpoints were also statistically significantly different between cotton GHB614 × LLCotton25 and its parental lines.

These differences raise two types of issues :
1. GM cotton GHB614 x LLCotton25 is not equivalent to its conventional counterpart and, in consequence, should be subject to further nutritional and toxicological assessment to exclude any potential risk for human and animal health;
2. Since gossypol is considered to be an undesirable substance in feed and to be toxic to non-ruminants, the Biosafety Advisory Council welcomes the further toxicological and nutritional assessment of the observed difference in gossypol levels carried out by EFSA.

[3] Advice of the Belgian Biosafety Advisory Council of 21 April 2009 on the application EFSA/GMO/NL/2008/51 from Bayer CropScience under Regulation (EC) No. 1829/2003 (ref WIV-ISP/BAC/2009_924)
[4] Advice of the Belgian Biosafety Advisory Council of 12 March 2007 on the application EFSA/GMO/NL/2005/13 from Bayer CropScience under Regulation (EC) No. 1829/2003 (ref WIV-ISP/BAC/2007_SC_461)
[5] Since this application does not imply a cultivation of the GM crop in the EU, a full environmental assessment is not required in EFSA procedure and was not achieved.

3.2. Assessment of toxicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed 2mEPSPS and PAT proteins in the context of previous applications, and no concerns were identified. Taking into account the updated information provided by the applicant, the Council is of the opinion that this conclusion remains valid.
The Biosafety Advisory Council is also of the opinion that the combined expression of these two proteins in the stacked event should not raise toxicological concerns.
However, the Biosafety Advisory Council is of the opinion that the unexplained higher content of gossypol and the significant differences for 8 other parameters in the whole cottonseed from GHB614 × LLCotton25 is a matter of concern and raises uncertainties as regards the toxicity of this GM cotton.

3.3. Assessment of allergenicity

The Biosafety Advisory Council has evaluated the safety of the newly expressed 2mEPSPS and PAT proteins in the context of previous applications, and no concerns were identified.
The Biosafety Advisory Council is also of the opinion that the combined expression of these two proteins in the stacked event does not raise concerns regarding the allergenicity.
Since the allergenicity of the whole GM cotton has not been assessed, it is recommended to take up monitoring of allergenicity as part of the general surveillance.

3.4. Nutritional value

The Biosafety Advisory Council is of the opinion that the unexplained higher content of gossypol in the whole cottonseed from GHB614 × LLCotton25 is a matter of concern and raises uncertainties as regards the nutritional equivalence of this GM cotton with its non-GM counterpart and conventional cotton varieties.

4. Monitoring

With regard to monitoring, the Biosafety Advisory Council is of the opinion that the information provided is sufficient.

Conclusion

Based on the scientific assessment of the dossier done by the Belgian experts, taking into account the EFSA opinion, the answers of the EFSA GMO Panel to the questions raised by the Belgian experts, the answers of the applicant to the questions of the EFSA GMO Panel and considering the data presently available, the Biosafety Advisory Council:

- Did not identify any risk that the import and processing of GM cotton GHB614 x LLCotton25 could pose to the European environment.

- Despite the fact that the compositional analysis of GM cotton GHB614 x LLCotton25 does not take away all concerns with regard the equivalence between the comparators used and the stacked event, the majority of the members are of the opinion that in this case the differences do not present a safety issue because the differences are within the range reported for non-GM varieties. Based on these considerations, the Biosafety Advisory Council gives a positive advice regarding the health safety of this event.

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

Prof. Maurice De Proft
President of the Belgian Biosafety Advisory Council

Annex1: Minority Declaration
Annex 2: Compilation of comments of experts in charge of evaluating application EFSA/GMO/NL/2010/77 and comments submitted on the EFSAnet (ref. BAC_2011_0372)

Minority Declaration of P. Baret, M. Lateur and D. Perreaux

Considering that the compositional analysis of GM cotton GHB614 x LLCotton25 does not take away all concerns with regard the equivalence between the comparators used and the stacked event and in absence of toxicological complementary studies, the Biosafety Advisory Council should give a negative advice regarding the health safety of this crop.

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N./réf. : WIV-ISP/41/BAC_2011_0372
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26-04-2011

Compilation of comments of experts in charge of evaluating the application EFSA/GMO/NL/2010/77 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 25 February 2011
Coordinator: Prof. Philippe Baret
Experts: Eddy Decuypere (KUL), Johan Van Waes (ILVO), Jan Van Doorsselaere (KH Zuid-West Vlaanderen)
Domains of expertise of experts involved: Molecular characterisation, breeding techniques, human & animal nutrition, agronomy, ecology, herbicide tolerance, impact on bio-diversity, cotton
Secretariat (SBB): Didier Breyer, Adinda De Schrijver, Martine Goossens, Philippe Herman, Katia Pauwels

INTRODUCTION

Dossier **EFSA/GMO/NL/2010/77** concerns an application of the company **Bayer CropScience** for the marketing of the genetically modified **Cotton GHB614 x LLCotton25** for food and feed applications under Regulation (EC) 1829/2003.
The application has been officially acknowledged by EFSA on 26 January 2011.

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 received from the experts

GENERAL COMMENTS

Comments/Questions of the expert(s)

Comment 1

According to the dossier the scope of application does not include the authorization for the cultivation of GHB614 x LLCotton25 cotton seed products in the EU. It can however be worthwhile to give some remarks on the different topics, dealing with cultivation and survivability of seeds, in the case that the applicant should ask in the near future for an extension for the scope of cultivation, especially for cultivation in some southern European countries.
So as agronomical expert I will also give some comments in this questionnaire, related to cultivation and the environmental aspect.

Comment 2

GT and LL cotton is glyphosate and glufosinate ammonium tolerant. The glyphosate tolerance is inherited from GHB614 cotton which expresses a modified 2mEPSPS heading to tolerance to glyphosate.
The tolerance to glufosinate ammonium herbicides is inherited from LL Cotton25 which expresses the specific enzyme phosphinothricin acetyl-transferase (PAT) that acetylates glufosinate ammonium and in its way inactivates the herbicide.

A. GENERAL INFORMATION

Comments/Questions of the expert(s)

B. INFORMATION RELATING TO THE RECIPIENT OR (WHERE APPROPRIATE) PARENTAL PLANTS

Comments/Questions of the expert(s)

Comment 1

Under “3. Survivability – Ability to form structures for survival or dormancy” it is mentioned that “Cultivated cotton does not produce seeds which can persist in the environment for long periods of time, furthermore cotton seed lacks the ability to develop dormancy. The question is : Are there data available to prove this?

Remark SBB and coordinator : This comment was sent many times to EFSA in the frame of previous Cotton dossiers. It led in particular to a general statement of the BAC in its advices on 2 dossiers, stating that the "Biosafety Advisory Council fully shares the EFSA's recommendation that the general surveillance should include specific measures to actively monitor the occurrence of feral cotton plants

in areas where seed spillage and plant establishment are likely to occur where climatically appropriate (such as harbours, transit road-sides and vicinity of processing plants)".
Given the fact that EFSA never gave an answer to this comment, it was sent once again.

Comment 2

No questions

C. INFORMATION RELATING TO THE GENETIC MODIFICATION

Comments/Questions of the expert(s)

Comment 1

No comments

D. INFORMATION RELATING TO THE GM PLANT

D.1 DESCRIPTION OF THE TRAITS AND CHARACTERISTICS WHICH HAVE BEEN INTRODUCED OR MODIFIED

Comments/Questions of the expert(s)

Comment 1

No questions

Comment 2

No comments

D.2. INFORMATION ON THE SEQUENCES ACTUALLY INSERTED OR DELETED

Comments/Questions of the expert(s)

Comment 1

No questions

Comment 2

No comments

D.3. INFORMATION ON THE EXPRESSION OF THE INSERT

Comments/Questions of the expert(s)

Comment 1

No questions

Comment 2

No comments

D.4. INFORMATION ON HOW THE GM PLANT DIFFERS FROM THE RECIPIENT PLANT IN: REPRODUCTION, DISSEMINATION, SURVIVABILITY

Comments/Questions of the expert(s)

Comment 1

No questions

D5. GENETIC STABILITY OF THE INSERT AND PHENOTYPIC STABILITY OF THE GM PLANT

Comments/Questions of the expert(s)

Comment 1

No questions

Comment 2

No comments

D.6. ANY CHANGE TO THE ABILITY OF THE GM PLANT TO TRANSFERR GENETIC MATERIAL TO OTHER ORGANISMS

Comments/Questions of the expert(s)

Comment 1

No questions

D.7. INFORMATION ON ANY TOXIC, ALLERGENIC OR OTHER HARMFUL EFFECTS ON HUMAN OR ANIMAL HEALTH ARISING FROM THE GM FOOD/FEED

D.7.1 Comparative assessment

Comments/Questions of the expert(s)

Comment 1

In general for D.7 : Why in the study with mice and the purified proteins, 2mEPSPS was administered by oral gavage, while for the PAT protein it was administered via intravenous injection in mice ?
For D.7.1.: no questions.

D.7.2 Production of material for comparative assessment

Comments/Questions of the expert(s)

Comment 1

This is a randomized complete block design with 3 replicates (and 5 treatments) and in 7 different geographical areas. The statistical model used is ok.

D.7.3 Selection of material and compounds for analysis

Comments/Questions of the expert(s)

Comment 1

- No differences found in the 3 amino acids from the shikimic pathway, the aromatic a.a. tyrosine, phenylalanine and tryptophane.

- Why the higher gossypol values in GTxLL (table 15) compared with the conventional treated FM958?
- GT x LL compared with the parental events GHB614 and LL cotton25 also showed higher gossypol values.
Of course these are all within the reference range from literature values of gossypol, but this reference range may be due to a biological range of differences between varieties of cotton, or to a methodological range of differences in measurements.

Remark coordinator : The 2 following questions were sent to EFSA
1) Why GHB614 x LLCotton25 (table 15) showed higher gossypol values when compared with the conventional treated FM958 ?
2) Why GHB614 x LLCotton25 showed higher gossypol values when compared with the parental events GHB614 and LL cotton25 ?

- P. 81: if anti-nutritional cyclopropenoid fatty acids are less found, doesn't it then has the potential to be nutritionally better (in animal feed e.g.)?

D.7.4 Agronomic traits

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.5 Product specification

Comments/Questions of the expert(s)

Comment 1

If cottonseed meal is processed by direct solvent extraction, free gossypol is higher than with other processing methods, but protein quality would be better.
However, if more gossypol is present in GTxLL, would this not affect the quality of the meal for monogastrics? Or perhaps the percentage of this meal that can or may be incorporated in chicken or pig feed?
Remark coordinator : not relevant / don't send to EFSA.

D.7.6 Effect of processing

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.7 Anticipated intake/extent of use

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.8 Toxicology

Comments/Questions of the expert(s)

Comment 1

No questions

D. 7.8.1 Safety assessment of newly expressed proteins

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.8.2 Testing of new constituents other than proteins

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.8.3 Information on natural food and feed constituents

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.8.4 Testing of the whole GM food/feed

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.9 Allergenicity

Comments/Questions of the expert(s)

Comment 1

No questions

D.7.10 Nutritional assessment of GM food/feed

Comments/Questions of the expert(s)

Comment 1

It is noted that the introduced trait is of agronomic interest and is not intended to change any nutritional aspects of this cotton. Can this be proved by data?
Remark SBB and coordinator : Introduced traits encode glyphosate and glufosinate.
This comment was not sent to EFSA. For application RX-MON15985xMON1445 and application MON1445, same comment was not forwarded to EFSA.

Comment 2

Is this not too straightforward to state that cottonseed meal can be included and has no nutritional impact in animal feed use in the light of what is discussed above? Has this been tested in animal experiments? These are not included in the document anyway.
Remark coordinator : The following comment must be sent to EFSA :
The notifier states (7.7) that "GTxLL varieties would represent at maturity only 6% of the total area of cultivation, so the exposure to proteins expressed in cottonseed products derived from GTxLL will be very limited, especially as the processing steps (Section D.7.5) will denature these proteins." Where is the 6 % coming from ? On the long term, this kind of proportion may change. What is the relevance of this type of information in a risk oriented assessment ?

D.7.11 Post-market monitoring of GM food/feed

Comments/Questions of the expert(s)

Comment 1

No questions

D.8. MECHANISM OF INTERACTION BETWEEN THE GM PLANT AND TARGET ORGANISMS (IF APPLICABLE)

Comments/Questions of the expert(s)

Comment 1

No questions

D.9. POTENTIAL CHANGES IN THE INTERACTIONS BETWEEN THE GM PLANT WITH THE BIOTIC ENVIRONMENT RESULTING FROM THE GENETIC MODIFICATION

D.9.1. Persistence and invasiveness

Comments/Questions of the expert(s)

Comment 1

No questions

D.9.2 Selective advantage or disadvantage

Comments/Questions of the expert(s)

Comment 1

In this chapter it is mentioned that the agronomic performance of GHB614 x LLCotton25 shows no disadvantage. Furthermore we note that “the likelihood that some escaped seed would germinate is very low because most of the imported seed is non-viable. My question is: Is the germination power of the imported seed analysed?

Comment 1

No questions

D.9.3 Potential for gene transfer

Comments/Questions of the expert(s)

Comment 1

No questions

D.9.4 Interactions between the GM plant and target organism

Comments/Questions of the expert(s)

Comment 1

No questions

D.9.5 Interactions of the GM plant with non-target organism

Comments/Questions of the expert(s)

Comment 1

No questions

D.9.6 Effects on human health

Comments/Questions of the expert(s)

Comment 1

No questions

D.9.7 Effects on animal health

Comments/Questions of the expert(s)

Comment 1

Referring to section D. 7.3. : "It is as safe and as nutritious as any other cotton in commerce" but in view of the discussion about difference in one way or another for the antinutritional substances (gossypol and cyclopropenoid fatty acid) this may be questioned or should at least be carefully tested in monogastrics.

Remark coordinator : Has been sent to EFSA as follows :

Referring to section D. 7.3. : "It is as safe and as nutritious as any other cotton in commerce" but in view of the discussion about difference in one way or another for the antinutritional substances (gossypol and cyclopropenoid fatty acid) this may be questioned ? Were this safety and nutrition properties thoroughly tested in monogastrics ?

D.9.8 Effects on biogeochemical processes

Comments/Questions of the expert(s)

Comment 1

No question

D.9.9 Impacts of the specific cultivation, management and harvesting techniques

Comments/Questions of the expert(s)

Comment 1

In this paragraph it is mentioned that the scope of the present application does not include cultivation of cotton plants in the EU and is limited to import and processing. Nevertheless I give here some remarks in the case that the applicant should ask in the near future for an extension for the scope of cultivation. In the framework of the EU regulation 2002/53 a new variety has to be submitted to DUS (Distinctness, Uniformity, Stability) and VCU (Value for Cultivation and Use) tests before the variety can be commercialised. The new variety has to be compared with the best existing standard varieties. So my question here is : can the GM cotton be incorporated in normal VCU trials, for example treated with specific herbicides for cotton and will the agronomical value be the same as tested in trials, where the herbicides glyphosate and glufosinate ammonium, for which the variety is tolerant, is used ?
Remark coordinator : Not relevant at this stage.

Comment 2

No question

D.10. POTENTIAL INTERACTIONS WITH THE ABIOTIC ENVIRONMENT

Comments/Questions of the expert(s)

Comment 1

No question

D.11. ENVIRONMENTAL MONITORING PLAN

D.11.1 General

Comments/Questions of the expert(s)

Comment 1

No question

D.11.2 Interplay between environmental risk assessment and monitoring

Comments/Questions of the expert(s)

Comment 1

Based on the scope of application (no cultivation) I can agree with the remark that the overall environmental risk posed by this genetically modified plant is negligible in the context of the intended uses of GHB 614 x LLCotton25.

Comment 1

No question

D.11.3 Case-specific GM plant monitoring

Comments/Questions of the expert(s)

Comment 1

No question

D.11.4 General surveillance of the impact of the GM plant

Comments/Questions of the expert(s)

Comment 1

No question

D.11.5 Reporting the results of monitoring

Comments/Questions of the expert(s)

Comment 1

No question

References

None