Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on application EFSA-GMO-DE-2017-141 (cotton COT102) from Syngenta under Regulation (EC) No. 1829/2003

13 September 2023
Ref. SC/1510/BAC/2023_0891

Context

Application EFSA-GMO-DE-2017-141 was submitted by Syngenta for the authorisation for the marketing of genetically modified (GM) cotton COT102 (Unique Identifier SYN-IR1Ø2-7) for food and feed uses, import and processing (excluding cultivation) within the European Union, within the framework of Regulation (EC) No. 1829/2003[1].

Cotton COT102 contains a single insert consisting of one copy of the *vip3Aa19* and *aph4* expression cassettes, expressing the Vip3Aa19 protein for resistance against lepidopteran pest, and the APH4 protein as a marker.

The application was validated by EFSA on 24 July 2017 and a formal three-month consultation period of the Member States was started, 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). Six 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.

The opinion of the EFSA Scientific Panel on GMOs was published on 26 June 2023 (EFSA Journal 2023;21(6):8031[2]) together with the responses from the EFSA GMO Panel to comments submitted by the Member States during the three-month consultation period.

In delivering the present advice, the BAC considered in particular the comments formulated by the experts on application EFSA-GMO-DE-2017-141 and 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 https://www.efsa.europa.eu/en/efsajournal/pub/8031

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Scientific evaluation

1. 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.

2. Assessment of food/feed safety and nutritional value

2.1. Assessment of compositional analysis

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the compositional data of GM cotton COT102, in comparison with its conventional counterpart, does not raise safety concerns.

2.2. Assessment of toxicity

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the available data on the toxicity of GM cotton COT102, in comparison with its conventional counterpart, does not raise safety concerns.

2.3. Assessment of allergenicity

The Biosafety Advisory Council agrees with the GMO panel of EFSA that the available data on the allergenicity of the newly expressed Vip3Aa19 and APH4 proteins does not raise safety concerns, and that there are no indications of a potentially increased allergenicity of food and feed derived from cotton COT102 with respect to that derived from the non-GM comparator.

2.4. Nutritional value

The Biosafety Advisory Council is of the opinion that the information provided is sufficient to conclude that the nutritional characteristics of cotton COT102-derived food and feed are not expected to differ from those of conventional maize varieties.

3. Environmental risk assessment

The Biosafety Advisory Council is of the opinion that it is unlikely that the accidental release of cotton COT102 (i.e. during transport and/or processing) into the European environment[3] will lead to environmental harm.

4. Monitoring

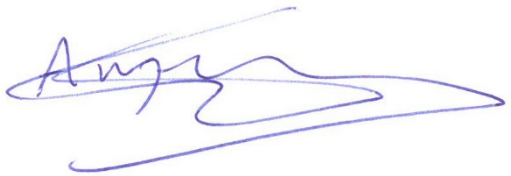
With regard to monitoring, the Biosafety Advisory Council is of the opinion that the information provided is sufficient.

[3] As the application doesn't imply cultivation of the GM crop in the EU, a full environmental assessment, as in the case of a cultivation dossier, is not warranted.

Conclusion

Based on the whole set of data on cotton COT102 provided by the applicant, the scientific assessment of the dossier done by the Belgian experts and the opinion of EFSA, the Biosafety Advisory Council:

1) Agrees with the GMO panel of EFSA that the accidental environmental release of viable cotton COT102 seeds would not raise safety concerns;
2) Agrees with the GMO panel of EFSA that in the context of its proposed uses, cotton COT102 is as safe as its non-GM comparator and the tested non-GM cotton reference varieties, with respect to potential effects on human and animal health;



Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex : Outcome of the assessment of the application

Annex : Outcome of the assessment of application EFSA-GMO-DE-2017-141 by the Biosafety Advisory Council during the formal consultation of the Member States (3-month commenting period in accordance with Articles 6.4 and 18.4 of Regulation (EC) No 1829/2003)

Coordinator: Philippe Baret
Experts: Eddy Decuypere (KUL), Leo Fiems (ILVO), André Huyghebaert (UGent), Peter Smet (Consultant), Frank Van Breusegem (UGent), Jan Van Doorsselaere (Vives).
SBB: Fanny Coppens

Application: EFSA-GMO-DE-2017-141
Applicant: Syngenta
GMO: cotton COT102
Validation of dossier by EFSA: 24 July 2017

Scope of the application:
☒ 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)

Given the characteristics of the GMO and its intended uses, experts were consulted to cover the following areas of expertise:
☒ Molecular characterization
☒ Environmental aspects
☒ Allergenicity
☒ Toxicology
☒ Food and Feed aspects

The experts were asked to evaluate whether 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.

No comments were selected to be sent to EFSA.

List of comments/questions received from the experts

PART I - GENERAL INFORMATION

Have evaluated this section and consider the information adequate: 3 experts

Comment
Based on the results of the compositional analysis and the weight of evidence with regard to the toxicological and the allergenicity assessment, it may be concluded that the chance that the new proteins of COT102 cotton (Vip3Aa19 and APH4) will pose safety risks is negligible, so that the import and processing of COT102 cotton may not exert adverse effects on human and animal health and the environment.

PART II - SCIENTIFIC INFORMATION

1. HAZARD IDENTIFICATION AND CHARACTERISATION

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

Have evaluated this section and consider the information adequate: 2 experts

1.2. MOLECULAR CHARACTERISATION

1.2.1. Information relating to the genetic modification

Have evaluated this section and consider the information adequate: 3 experts

1.2.2. Information relating to the genetically modified plant

Have evaluated this section and consider the information adequate: 3 experts

1.2.3. Additional information relating to the genetically modified plant required for the environmental safety aspects

Has evaluated this section and considers the information adequate: 1 expert

1.2.4. Conclusions of the molecular characterisation

Has evaluated this section and considers the information adequate: 1 expert

1.3. COMPARATIVE ANALYSIS

1.3.1. Choice of the conventional counterpart and additional comparators

Has evaluated this section and considers the information adequate: 1 expert

Comment
Choice of conventional counterpart with same genetic background as the test substance-line; and additional comparators: OK, no further comments.

1.3.2. Experimental design and statistical analysis of data from field trials for comparative analysis

Has evaluated this section and considers the information adequate: 1 expert

Comment
On p.51 it is stated that appropriate agronomic practices (i.e. insect weed and disease control) were implemented at each field testing site, but how was this treatment? Was the insecticide treatment identical for transgenic and isogenic comparator in spite of the GMO with insecticidal protein?

SBB comment: The full list of chemicals used at each site is available in Appendix 1.3.1, table 6.

1.3.3. Selection of material and compounds for analysis

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1.3.4. Comparative analysis of composition

Comment 1
The agronomic and phenotypic characteristics and the compositional characteristics of COT102 cotton are not different from those of conventional cotton, and are equivalent to the reference varieties.

Comment 2
P.71-82: figures in x-axis (fig 1.3.2) is expressed in what? Difference to comparator in g, or g/kg or % or what??
No further questions

SBB comment: The numeric x axis uses the analyte-specific transform scale, see Appendix 1.3.1 of this application and EFSA's Scientific opinion on statistical considerations for the safety evaluation of GMOs (https://www.efsa.europa.eu/en/efsajournal/pub/1250).

Comment 3
No remarks about the proximate analysis of cottonseed for human and animal nutrition. Dietary fiber is included.
Minerals: no remarks.
Amino acids: the range of relevant constituents is covered.
Fatty acids: no remarks.
Vitamins: the selection is motivated and is in agreement with the OECD documents.
Cottonseed is an unsaturated oil and is protected against oxidation by the presence of tocopherols and tocotrienols. There is only information about α-tocopherol but, in cottonseed oil, the level of γ-tocopherol is higher than α-tocopherol!
Relevant anti-nutrients are included particularly the important gossypol and cyclopropane acids. These constituents are very relevant for human and animal nutrition.
As a general remark: the selection of constituents according to the OECD guidelines is recommended but more attention has to be given to compounds important for the functional properties of food containing cottonseed oil. This is a general remark for all applications of GMO plants.
Results are schematically represented. In case any significant difference is observed, values are within the range for reference varieties. The biological relevance, taking into account the rather limited cottonseed consumption is the EU, is discussed.
I agree with the conclusion of the applicant that observed differences in composition are not expected to have a biological relevant impact on humans.

Comment 4
Dihydrosterculic acid, malvalic acid, sterculic acid and gossypol are examined.
Dihydrosterculic acid is different from the isoline but equivalent to the reference line. So this difference seems to be of no biological significance.

1.3.5. Comparative analysis of agronomic and phenotypic characteristics

Has evaluated this section and considers the information adequate: 1 expert

Comment
P.90: based on non-parametric analysis, COT102 cotton did not significantly differ from isoline for either disease incidence or insect damage; but why is this in view of the transgene cotton being modified with Vip3Aa gene for insecticidal activity against several lepidopteran pests? Is this related to the nature of insecticide treatment in the experimental protocol??

SBB comment: The evaluation of the efficacy of the newly expressed protein is not within the remit of the Council.

1.3.6. Effects of processing

Have evaluated this section and consider the information adequate: 2 experts

1.3.7. Conclusion

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1.4. TOXICOLOGY

1.4.1. Testing of newly expressed proteins

Comment 1
The chance that the new proteins (Vip3Aa19 and APH4) of COT102 will pose serious risks for toxicity is negligible. Vip3Aa19 protein is very similar to Vip3Aa20: isoleucine instead of methionine at position 129 (Raybould *et al.*, 2013). EPA (2007) reported that all mice, dosed with 3675 mg/kg body weight of Vip3Aa19 protein, survived the study, gained weight, and had no test material-related clinical signs, and had no test material-related findings at necropsy. Peng *et al.* (2007) proved that the NOAEL of VIP3Aa7 in a subacute test was greater than 5000 mg/kg body weight.
The protein APH4 was not acutely toxic in animal studies (Petersen *et al.*, 2005).

Comment 2
Vip3Aa19 is almost identical to Vip3Aa20, except in one amino acid, but with no impact on its insecticidal activity as stated, but is this also sufficiently verified??
Vip3A-proteins are cleaved by specific proteases under alkaline conditions of insect midgut leaving an active toxin core, but in mammalian digestion under acidic conditions the proteins are completely digested and not toxic. This is also the case in birds, and should be mentioned as such, also for APH4-protein on p.114, as cotton-seed products are used in poultry feed as well.

Comment 3
Both Vip3Aa19 and APH4 are readily degraded in SGF. In SIF only APH4 is rapidly degraded. For Vip3Aa19 two fragments resist degradation under alkaline conditions. In view of its mode of action, this is as expected.
For human and animal consumption this seems to be of no concern (passage through the acidic stomach and no binding possibility in the mammalian gut).
Acute oral toxicity tests were conducted for both proteins. No signs of toxicity were detected up to 3,675 mg VIP3A protein/kg and 779 mg APH4 protein/kg body weight.
No 28-day repeated dose toxicity studies were performed. No further testing is needed.
A repeated-dose 28-day oral toxicity study in rodents was conducted using Vip3Aa20 protein. Results showed that there were no adverse effects of Vip3Aa20 treatment at dose levels up to and including 500 mg/kg/day. Considering that Vip3Aa20 and Vip3Aa19 are 99.9% identical in primary structure and share the same insecticidal mechanism of action, no further testing is needed.

There were no alignments between any of the COT102 insert ORFs and any entry in the 2016 Syngenta toxin database that were below the reportable E-value threshold of 10 for both Vip3Aa19 and APH4.

1.4.2. Testing of new constituents other than proteins

Has evaluated this section and considers the information adequate: 1 expert

1.4.3. Information on natural food and feed constituents

Has evaluated this section and considers the information adequate: 1 expert

1.4.4. Testing of the whole genetically modified food or feed

Has evaluated this section and considers the information adequate: 1 expert

Comment
Dietary administration of COT102 CSM to rats for at least 91 consecutive days was well tolerated. There were no toxicological effects noted on body weight, food consumption, clinical condition (including neurotoxicity assessments), ophthalmoscopy, haematology, coagulation, chemical chemistry, organ weights, macroscopic or microscopic pathology at inclusion levels up to and including 10%.

1.4.5. Conclusion of the toxicological assessment

Have evaluated this section and consider the information adequate: 2 experts

1.5. ALLERGENICITY

1.5.1. Assessment of allergenicity of the newly expressed protein

Has evaluated this section and considers the information adequate: 1 expert

1.5.2. Assessment of allergenicity of the whole genetically modified plant

Has evaluated this section and considers the information adequate: 1 expert

Comment
Based on the weight of evidence, it is assumed that COT102 cotton has no greater allergenic potential compared to conventional cotton, and that it does not pose a serious allergenic risk.

1.5.3. Conclusion of the allergenicity assessment

Has evaluated this section and considers the information adequate: 1 expert

1.6. NUTRITIONAL ASSESSMENT

1.6.1. Nutritional assessment of the genetically modified food

Has evaluated this section and considers the information adequate: 1 expert

1.6.2. Nutritional assessment of the genetically modified feed

Has evaluated this section and considers the information adequate: 1 expert

Comment
There is no reason to assume that the genetic modification affects the nutritional value of the feed derived from COT102 cotton based on the compositional equivalence. Histidine, the only analyte found to be of Type 3, is an essential amino acid, but is rarely limiting or in diets for monogastric animals. So, the difference in composition between COT102 and isoline cotton are not expected to be biologically relevant.

1.6.3. Conclusion of the nutritional assessment

Has evaluated this section and considers the information adequate: 1 expert

2. EXPOSURE ASSESSMENT — ANTICIPATED INTAKE OR EXTENT OF USE

Has evaluated this section and considers the information adequate: 1 expert

Comment
The applicant refers to a zero intake of cottonseed hulls (Table 2.2 of the main text). However, cottonseed hulls are palatable, but its use is mostly limited because of the relatively low nutrient content (Rogers *et al.*, 2002). Due to the low crude protein content, the contribution of new proteins through cottonseed hulls will be small.

3. RISK CHARACTERISATION

Has evaluated this section and considers the information adequate: 1 expert

4. POST-MARKET MONITORING ON THE GENETICALLY MODIFIED FOOD OR FEED

Has evaluated this section and considers the information adequate: 1 expert

5. ENVIRONMENTAL RISK ASSESSMENT (ERA)

5.1. INTRODUCTION

Has evaluated this section and considers the information adequate: 1 expert

5.2. GENERAL APPROACH OF THE ERA

Has evaluated this section and considers the information adequate: 1 expert

5.3. SPECIFIC AREAS OF RISK

5.3.1. Persistence and invasiveness including plant-to-plant gene flow

Has evaluated this section and considers the information adequate: 1 expert

5.3.2. Plant to micro-organisms gene transfer

Has evaluated this section and considers the information adequate: 1 expert

5.3.3. Interactions of the GM plant with target organisms

Has evaluated this section and considers the information adequate: 1 expert

5.3.4. Interactions of the GM plant with non-target organisms (NTOs)

Has evaluated this section and considers the information adequate: 1 expert

Comment
Environmental risk assessments for cultivation of crops producing Vip3Aa have concluded that it is unlikely for there to be adverse effects to NTOs including threatened and endangered species (Raybould and Vlachos, 2011; CERA, 2012).

5.3.5. Impacts of the specific cultivation, management and harvesting techniques

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5.3.6. Effects on biogeochemical processes

Has evaluated this section and considers the information adequate: 1 expert

5.3.7. Effects on human and animal health

Has evaluated this section and considers the information adequate: 1 expert

Comment
The new proteins (Vip3Aa19 and APH4) in COT102 cotton are unlikely to be detrimental for human and animal health (Petersen *et al.*, 2005; EPA, 2007).

5.3.8. Overall risk evaluation and conclusions

Has evaluated this section and considers the information adequate: 1 expert

6. POST-MARKET ENVIRONMENTAL MONITORING PLAN (PMEM)

6.1. INTERPLAY BETWEEN ENVIRONMENTAL RISK ASSESSMENT, RISK MANAGEMENT AND PMEM

Has evaluated this section and considers the information adequate: 1 expert

6.2. CASE-SPECIFIC GM PLANT MONITORING (STRATEGY, METHOD AND ANALYSIS)

Has evaluated this section and considers the information adequate: 1 expert

6.3. GENERAL SURVEILLANCE FOR UNANTICIPATED ADVERSE EFFECTS (STRATEGY, METHOD)

Has evaluated this section and considers the information adequate: 1 expert

6.4. REPORTING THE RESULTS OF PMEM

Has evaluated this section and considers the information adequate: 1 expert

7. ADDITIONAL INFORMATION RELATED TO THE SAFETY OF THE GENETICALLY MODIFIED FOOD OR FEED

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