Vår ref:2016/H_122
Deres ref: 2016/9712

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 07.12.16

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring under EU forordning 1829/2003 av søknad **EFSA/GMO/NL/2014/122**, genmodifisert bomull GHB614xT304-40xGHB119, fra Bayer CropScience LP som gjelder mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

Idun Merete Grønsberg
Forsker II
GenØk – Senter for Biosikkerhet
idun.gronsberg@genok.no

Bidragsytere:

Lise Nordgård
Forsker II
GenØk-Senter for Biosikkerhet

Lilian van Hove
Forsker III
GenØk – Senter for Biosikkerhet

Vår ref:2016/H_122
Deres ref: 2016/9712

Vurdering av søknad EFSA/GMO/NL/2014/122 under EU-forordning 1829/2003/EC som gjelder mat, fôr, import og prosessering av genmodifisert bomull GHB614 x T304-40 x GHB119.

Sendt til

Miljødirektoratet

av

GenØk-Senter for Biosikkerhet
Desember 2016

Vår ref:2016/H_122
Deres ref: 2016/9712

Assessment of the technical dossier of EFSA/GMO/NL/2014/122 under 1829/2003/EU.

Sent to

Norwegian Environment Agency

by

GenØk- Centre for Biosafety
December 2016

OPPSUMMERING

GenØk–Senter for Biosikkerhet, viser til høring av søknad EFSA/GMO/NL/2014/122, genmodifisert bomull **GHB614 x T304-40 x GHB119,** som omfatter bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra denne.

Vi har gjennomgått de dokumenter som vi har fått tilgjengelig, og fremhever punkter med mangelfull informasjon i søknaden:

- Adjuvans effekt av multiple Cry proteiner i stablede planter; selv om bomull stort sett brukes i tekstil så vil feks frø brukes i olje og i fôr.
- Helse og miljøfare ved bruk av glufosinat ammonium og glyfosat i land som bomullen skal produseres i.
- Samfunnsnytte og bærekraft aspekter ved dyrkning og bruk av bomullen.

SUMMARY

We have assessed the documents available, and highlights in particular the following points for the current application for GHB614 x T304-40 x GHB119:

- Adjuvancy effects of multiple Cry proteins used in stacked plants; even if cotton mainly is used for fabrics, seed is used in oil and in feed.
- Health and environment related issues upon use of glufosinate ammonium and glyphosate in countries were the cotton is agricultured.
- Issues on social utility and sustainability by cultivation and use of the cotton.

ASSESSMENT OF THE TECHNICAL DOSSIER UNDER 1829/2003 OF EFSA/GMO/NL/2014/122 GENEMODIFIED COTTON.

GenØk, as a National Competence Center for Biosafety, aims at providing independent, holistic and useful analysis of technical and scientific information/reasoning in order to assist authorities in the safety evaluation of biotechnologies proposed for use in the public sphere.

The information in this assessment is respectfully submitted for consideration in the evaluation of product safety and corresponding impact assessment of event GHB614 x T304-40 x GHB119 cotton, setting out the risk of adverse effects on the environment and health, including other consequences of proposed release under the pertinent Norwegian regulations.

MAIN SUMMARY:

In our assessment of the stacked cotton event GHB614 x T304-40 x GHB119 we find that data provided in the application on social utility and sustainability is lacking. There is also a need for further investigation of whether Cry toxins Cry1Ab and Cry2Ae might have potential for non-target and adjuvant effects.

We therefore comment that the applicant has not provided the information required to perform an assessment of social utility and sustainability as required by the Norwegian Gene Technology Act (NGTA, Appendix 4) (1).

ASSESSMENT OF THE TECHNICAL DOSSIER UNDER 1829/2003 OF EFSA/GMO/NL/2014/122 COTTON.

About the event

The event **GHB614 x T304-40 x GHB119** cotton was made by conventional crossing of the three gene modified, single parental cotton lines GHB614, T304-40 and GHB119.
Each of the single parental lines were developed using *Agrobacterium tumefaciens* mediated transformation.

The application of cotton event GHB614 x T304-40 x GHB119 is for food, feed, import and processing.

Neither GHB614 x T304-40 x GHB119 nor its parental lines are approved in Norway for any of the applications.

Cotton event GHB119 is under assessment in EU, while parental lines GHB614 and T304-40 are approved in EU for food, feed and processing.

The cotton event GHB614 x T304-40 x GHB119 is cultivated in US, Mexico and Brazil.

ASSESSMENT FINDINGS

The event GHB614 x T304-40 x GHB119 (also called GLT or GlyTol x TwinLink) cotton is a stacked event that has tolerance to the herbicides glyphosate through the *2mEPSPS* gene and increased resistance to gluphosinate-ammonium through the *bar* gene from two parental lines. It also has resistance to certain lepidopteran insect pests through the Bt-toxins Cry1Ab and Cry2Ae.

GHB614xT304-40XGHB119 cotton has its traits from the following single events:

- GHB614 cotton confers tolerance to the herbicide glyphosate (contains the **2mEPSPS** protein)
- T304-40 cotton confers resistance to certain lepidopteran cotton pest and tolerance to the herbicide glyfosinate (contains **cry1Ab** and **bar** genes)
- GHB119 cotton confers resistance to certain lepidopteran cotton pest and tolerance to the herbicide glyfosinate (contains the **cry2Ae** and **bar** genes)

The dual herbicide tolerance offers growers additional weed control. The combination of cry proteins provide enhanced insect control and offers an additional insect-resistance management tool for growers.

The assessment is based on the documentation that is available on EFSAs webpage GMO EFSAnet

Molecular characterization

Evaluation of the molecular characteristics of the GHB614 x T304-40 x GHB119 cotton

- Bayer crop Science has developed the stacked herbicide tolerant and insect resistant cotton by conventional breeding - cross hybridization and selection involving transgenic donor(s).
- The applicant claims that the inserted genes and respective protein products have a history of safe use and have been reviewed and approved globally by regulatory agencies. No interactions or negative synergistic effects have been shown or are expected in the stacked trait product. The Applicant is also referring to the technical dossier of each single event to confirm the safety.
- In this stacked event application, Southern blot hybridization have been used in the molecular characterization to:
    - confirm the structure of the inserts after the breeding process
    - confirm size and copy number of all detectable inserts

  The size of the probes used in the 1.2.2.2 section on information on the sequences actually deleted or inserted is unclear. Size of probes used will be critical, depending on aim: if they are to unspecific due to size (too large), point mutations, small deletions or even rearrangements will not be possible to detect. If they are small (olignonucleotide probes), even slight differences within genes can be detected (2).

  The quality of the southern blot hybridization pictures are good, but a detailed molecular weight marker on the left side of the gel picture is not included.

- The bar gene constructs and the cry2Ae construct contains the CaMV 35S promoter from cauliflower mosaic virus. The 35S cauliflower mosaic virus (CaMV) promoter is commonly used to drive transgene expression in the genetically engineered (GE) crop plants that have been commercialized so far (3-5).

Previous comments on GHB614.
http://genok.no/wp-content/uploads/2013/03/h96_genokinspill_forweb.pdf

1. The Applicant should undertake safety assessments using versions of the target proteins derived from the plant variety/event under assessment.
2. The Applicant should submit required information on the social utility of GHB119 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.
3. The Applicant should undertake safety assessments using versions of the target proteins derived from the plant variety/event under assessment.
4. The applicant should follow up short-term acute studies with longer term toxicity studies commensurate with the life cycle of the tested organism.
5. The Applicant should submit required information on the social utility of GHB119 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act

Horizontal gene transfer (HGT)
The issue on HGT has been evaluated for the single parental cotton event GHB614 by the EFSA GMO Panel (EFSA-GMO-NL-2008-51). They concluded that it is very unlikely that HGT will occur with the 2mEPSPS gene due to lack of selective pressure, and it will not provide microorganisms with increased fitness.
The potential for HGT has also been evaluated for the other parental lines, cotton event T304-40 and GHB119. HGT is considered unlikely to occur here as well, and if such "recombination events" should occur "they would replace only natural variants".

Information on the expression of the inserts
Various cotton tissues (root, leaf, squares, pollen, bolls, whole plant, seeds) were analysed for expression of the inserted proteins in event GHB614 x T304-40 X GHB119 at different growth stages.

All proteins (2mEPSPS, bar/PAT, Cry1A and Cry2Ae) were detected in analysed tissues at levels within expected ranges. Here, levels of bar/PAT were higher than for the single parental lines as there are two copies of these genes in the stack GHB614xT304-40xGHB119.

Summary:

- Size and structure of inserts are verified using southern blot
- CaMV promoter is present in the gene modified cotton
- HGT is unlikely to occur according to Applicant.

Toxicology
According to the applicant, the expressed proteins Cry1A, Cry2Ae, PAT/bar and 2mEPSPS have very specific activities with different pathways in the stacked GHB614xT304-40xGHB119 cotton. Based on data from assessment of the proteins, they are not expected to have adverse effects on humans or animals.

The four proteins are assessed separately (not in combination) and no data for potential interactions between the proteins are present from these assessments. It is unclear from the dossier if they are checked for that. However, the applicant conclude that there is no change in effect when the proteins are assessed in combination due to their distinct specificities.

The stack is also not tested in feeding experiments due to no indications of interactions between the proteins expressed from the transgenes.

Each of the single parental lines have previously been considered as safe by EFSA (http://www.efsa.europa.eu/en/efsajournal/pub/985, http://www.efsa.europa.eu/en/efsajournal/pub/3251), except GHB 119 which still is under evaluation in EU, and where a scientific opinion came 21st. October 2016 (https://www.efsa.europa.eu/en/efsajournal/pub/4586).

Testing of newly expressed proteins
Testing of the newly expressed proteins is not considered necessary due to previous assessments of each protein in previous applications where they are considered as safe.

It is not clear from the technical dossier if it is the bacterial or the plant variety of the proteins that were analysed in the previous applications. But, based on previous assessments it indicates that all testing is done with bacterial versions.

Acute toxicity assays are also not found necessary due to the previous assessments of the single proteins and the history of safe use and mode of action.

Allergenicity
According to applicant, no data indicate interactions between Cry1Ab, Cry2Ae, bar/Pat or 2mEPSPS.

Based on previous assessments on parental, single events GHB614 and T304-40 cotton, data indicate that it is unlikely that the proteins expressed in these are allergenic. This is based on the available information on the proteins (biochemical characteristics, glycosylation pattern, digestion in simulated gastric fluids, sequence homology to known allergens etc).
For the parental line GHB119 which is under assessment in EU, the applicant conclude on the safety of the proteins Cry2Ae and pat/bar based on the same criteria.

The molecular analysis of the cotton stack GHB614xT304-40xGHB119 demonstrate integrity of the inserts as data presented by the applicant. Thus, they assume that crossing of the parental lines results in no new interactions. However, no data are presented on that.

Cottoseed oil for human consumtion is processed and are considered to contain very low levels of toxins or anti-nutrients. The applicant base their assumption from available literature on

presence of proteins in cottonseed oil and other edible oils for human consumption. Level of transgenic proteins in GHB614xT304-40xGHB119 are thus not checked due to this.

Potential for Cry2Ae as adjuvant was considered as neglible in EFSA-GMO-NL-2011-96 (Additional Information submitted on 3rd Dec 2013).

The proteins expressed from cotton GHB614xT304-40xGHB119 are thus assumed to be non allergenic.

For the issue on adjuvancy: see page: 12.

Cry proteins

The stacked event **GHB614xT304-40xGHB119 cotton** combines two Bt-proteins named Cry1Ab and Cry2Ae. These proteins, also called Bt-toxins work by giving the gene modified cotton plants protection against certain Coleoptera insects. However, Bt-toxins also have the potential of non-target effects, and alternative modes of action for Cry toxins have been addressed previously (6-9).

Studies performed on non-target insects of Bt-proteins have documented that 30% of studies on predators and 57% of studies on parasitoids display negative effects to Cry1Ab transgenic insecticidal proteins (10). Further, Cry toxins and proteinase inhibitors have shown non-neutral effects on natural enemies, and seemingly more often negative than positive effects (11). A review by Hilbeck and Schmidt (9) on Bt-plants, found that half of the studies documented negative effects on tested invertebrates.

In addition, a review by van Frankenhuyzen (12) indicated that several Cry proteins exhibit activity outside of their target orders. This study also found that many Cry proteins had been tested with a very limited number of organisms: thus, activity outside of the target organisms of many Cry proteins may be undocumented because testing has not included sensitive organisms.

A quantitative review analysis based on 42 field experiments with GM plants showed that unsprayed fields of Bt-maize plants have significantly higher abundance of terrestrial non-target invertebrates than sprayed conventional fields (13). Thus, Bt-plants with a single Bt-gene inserted may represent an improvement for non-target organisms in the environment. However, an indication of some negative effects of the Cry1Ab toxin itself, or the Cry1Ab maize plant, on non-target abundance was shown in the same meta-analysis: when conventional (non-GM) fields were not sprayed, the non-target abundance was significantly higher than in the Bt-fields (13).

Research on aquatic environments investigating potential impact of Bt-crops on aquatic invertebrates including *Daphnia magna* (6) and caddisflies (14) has also been performed. Douville et al. (15) presented data of the persistence of the *cry1Ab* transgene in aquatic environments: it persisted more than 21 days in surface waters, and 40 days in sediments. A follow-up on this study in 2009 indicated possible horizontal gene transfer of transgenic DNA fragments to aquatic bacteria (16). Impacts on soil microflora and fauna, including earthworms

(17) , mychorizzal fungi (18) and microarthropods in response to Cry endotoxins have also been reported (19-21). The significance of tri-trophic effects of accumulation, particularly of insecticidal Cry toxins (22, 23) is, however, yet to be firmly established.

In an experiment using broccoli plants containing Cry1Ac, Cry1C or both to investigate resistance development in a population of diamondback moths (*Plutella xylostella*), they found that when using stacked, similar Cry proteins, the resistance development in this population increased to both traits (24). Another group (25) later commented this on; suggesting that gene stacking might not be a solution to the development of resistance towards Cry proteins.

It has also been shown that the combination of two (or maybe more) insecticidal proteins against the same pest as target, is a tactic used to delay the resistance development towards either protein in the combination (26).

A study in mice showed that exposure to purified Cry1Ab resulted in specific anti-Cry1Ab IgG1 and IgE production, indicating inherent immunogenicity and allergenicity. Further, mice exposed to leaf extracts from both MON810 and unmodified maize demonstrated influx of lymphocytes and eosinophils in the broncho-alveolar lavage, and increased cytokine release in mediastinal lymph node cells (27). We suggest that further studies should also include animals with immune-deficiencies and/or animals exposed to other stress agents simultaneously.

Adjuvancy effects
The potential adjuvancy of Cry proteins has previously been addressed by the GMO Panel of the Norwegian Scientific Committee for Food Safety (28). Scientific studies have shown that the Cry1Ac protein is highly immunogenic and has systemic and mucosal adjuvant effects (29). In the evaluation of a GM maize event, MIR604 x GA21, the panel found that it was difficult to evaluate if kernels from this stack would cause more allergenic reactions than kernels from unmodified maize. The Panel continues:

"As the different Cry proteins are closely related, and in view of the experimental studies in mice, the GMO Panel finds that the likelihood of an increase in allergenic activity due to Cry1Ab and mCry3A proteins in food and feed from maize Bt11 x MIR604 x GA21 cannot be excluded. Thus, the Panel's view is that as long as the putative adjuvant effect of Cry1Ab and mCry3A with reasonable certainty cannot be excluded, the applicant must comment upon the mouse studies showing humoral antibody response of Cry1A proteins and relate this to a possible adjuvant effect of the Cry1Ab and mCry3A proteins expressed. Furthermore, although Cry1Ab and mCry3A proteins are rapidly degraded in gastric fluid after oral uptake, there is also the possibility that the protein can enter the respiratory tract after exposure to e.g. mill dust. Finally, rapid degradation is no absolute guarantee against allergenicity or adjuvanticity" (30).

The GMO Panel of the Norwegian Scientific Committee for Food Safety (28) also writes that:

"There are many knowledge gaps related to assessment of adjuvants. Most of the immunologic adjuvant experiments have been performed using Cry1Ac. Whether the other Cry proteins have similar adjuvant properties is unknown".

And;

"The possibility that Cry proteins might increase the permeability of the intestinal epithelium and thereby lead to "bystander" sensitization to strong allergens in the diet of genetically susceptible individuals cannot be completely excluded."

We also agree with these concerns and highlight them for the stacked cotton event GHB614xT304-40xGHB119 although cotton as a food source is consumed at low levels as compared to many other food sources.

Summary:

- Cry proteins might have potential for non-target effects.
- Pyramiding of Cry genes can delay resistance development of either of the proteins in the pyramide.
- As some Cry proteins have adjuvant effects, it can not be excluded that other Cry proteins have that also. This should be investigated.

As some Cry proteins have adjuvant effects, it can not be excluded that other Cry proteins have that also. This should be further investigated.

Herbicide tolerance and use on GM plants

This **GHB614 x T304-40 x GHB119** cotton event contains two herbicidal tolerance genes, namely *2mepsps* and *bar* providing tolerance to the herbicides glyphosate and glufosinate-ammonium.

The combination of Bt-protein and herbicide tolerance (HT) gene is the most used combination of inserted genes when it comes to GM plants. In this case, the stacked cotton event GHB614xT304-40xGHB119 is tolerant to the herbicides glufosinate ammonium and glyphosate, as well as expressing two Bt-proteins.

HT plants are sprayed with the actual herbicide (s), leaving the weed to die whereas the plant with the inserted gene(s) will survive. However, the accumulation of herbicides inside plants is often not tested as part of the risk assessment of the HT plants.

In some cases, data presented from feeding studies using HT plants have presented data where the HT plant material used, is not sprayed with the intended co-technology herbicide (31). In the application for GHB614xT304-40xGHB119 plots used for field trials were sprayed with glyohosate and glufosinate ammonium in addition to the conventional herbicide management scheme (p.60).The material used for expression analysis is expected to be sprayed also.

Another issue is the potential for accumulation of herbicides in the HT plants, including metabolic pathways and metabolites of these. Recently, Bøhn et al. (32) documented high levels of glyphosate residues in HT GM soybeans grown in the USA, and the same research group have published papers showing that such residues have the potential for negatively to affect the feed quality of HT GM soybeans (33, 34). It is important to look at the potential metabolites of

the herbicides in use and if these are documented to have a negative effect on health and environment.

Glyphosate tolerance
In the recent years, glyphosate has received a lot of risk-related attention partly due to its increased use since the introduction of glyphosate-tolerant GM-plants (35, 36). There have also been reports on negative effects in terrestrial and aquatic ecosystems (37, 38). Studies in animals and cell cultures have indicated that there could be health implications from exposure to glyphosate (36, 39-45). Among the health effects observed in animal models are histopathological changes in organs such as the liver, cell-division dysfunction in early embryos, negative impact on nerve-cell differentiation, increased fetal mortality, growth reduction, and skeletal malformation. Additionally, the International Agency for Research on Cancer (IARC) recently released a report concluding that glyphosate is "probably carcinogenic to humans" (46).

Glufosinate ammonioum tolerance
Glufosinate-ammonium belongs to a class of herbicides that is banned in Norway and has limited use in EU (limited use on apples) due to both acute and chronic effects on mammals including humans. Studies have shown that glufosinate-ammonium is harmful by inhalation, ingestion and skin contact and that serious health risks may result from exposure over time. Observations of patients poisoned by glufosinate-ammonium have found that acute exposure causes convulsions, circulatory and respiratory problems, amnesia and damages to the central nervous system (CNS) (47). Chronic exposure in mice has been shown to cause spatial memory loss, changes to certain brain regions, and autism-like traits in offspring (48, 49). According to EFSA, the use of glufosinate-ammonium will lead to farm workers being exposed to herbicide levels that exceed acceptable exposure levels during application.

A "Pesticide Residue Intake Model (PRIMo) (PRIMo; http://www.efsa.europa.eu/en/mrls/mrlteam.htm, accessed on July 23, 2014) has been developed by EFSA for national food consumption figures regarding acute chronic dietary consumer exposure to pesticide residues in member states (data provided by member states).
Here, cottonseed (categorized as oilseeds and fruits, code 401090 according to applicant) has no listed figures for consumption/acute or chronic intake by Europeans as no consumption of cottonseed derived products were reported, thus it is believed to be levels of the newly expressed proteins from the cotton stack GHB614xT304-40xGHB119 at neglible levels (technical dossier p111).

CaMV Promoter
The 35S cauliflower mosaic virus (CaMV) promoter is commonly used to drive transgene expression in the genetically engineered (GE) crop plants that have been commercialized so far (3-5). Safety questions related to the use of the Cauliflower Mosaic Virus 35S promoter (P35S) in GM plants has recently been discussed in an article from Podevin and Du Jardin (50). In the article, the authors state that some P35S variants contain open reading frames (ORFs) that when expressed could lead to "unintended phenotypic changes". Gene VI encodes the multifunctional P6 protein that can be divided into four domains (51). Functions of P6 include nuclear targeting (52), viral particle binding and assembly (53), si- and ds-RNA interference and interference suppression (54) and transcriptional transactivation (55, 56). The main debate when it comes to

the use of this promoter is that it may not only be active in plants, but may confer activity with respect to gene expression in lower and higher vertebrates such as mammals and fish. Today there are reports that conclude that the 35S CaMV promoter is active in several eukaryotic cell lines after transfection (3, 5), as well as that the promoter is able to drive expression of a transgene in fish as demonstrated recently by Seternes et al (4). The potential risk when it comes to GM food/feed that contains the CaMV promoter may be unlikely but cannot be excluded.

Summary:

- GHB614xT304-40xGHB119 is tolerant to glufosinate ammonium and glyphosate. These herbicides are damaging to health and environment.
- Potential of accumulation of glufosinate ammonium and glyphosate should be considered for GM plants used in food and feed.
- Cotton GHB614xT304-40xGHB119 has a 35S CaMV promoter driving expression of one of the transgenes. This promoter is shown active in plant as well as mammalian cells and that some variants have ORFs.

SOCIAL UTILITY AND SUSTAINABILITY ASPECTS

In addition to the EU regulatory framework for GMO assessment, an impact assessment in Norway follows the Norwegian Gene Technology Act (NGTA) (1). In accordance with the aim of the NGTA, production and use of the GMO shall take place in an ethically and socially justifiable way, under the principle of sustainable development. This is further elaborated in section 10 of the Act (approval), where it is stated that: "*significant emphasis shall also be placed on whether the deliberate release represent a benefit to the community and a contribution to sustainable development*". These issues are further elaborated in the regulations relating to impact assessment pursuant to the NGTA, section 17 and its annex 4. Moreover, new European legislation on GMOs allows Member States to restrict the cultivation of GMOs on their own territory based on socio-economic impacts, environmental or agricultural policy objectives, or with the aim to avoid the unintended presence of GMOs in other products (57). Discussions around a similar amendment for imports are also taking place within Europe. Additionally, in recent years there has been an increase in attention within academic as well as policy spheres to include broader aspects in the assessment of new and emerging (bio)technologies beyond human and environmental health, such as sustainability, benefit for society and ethical considerations (58-63).

The Applicant has not provided relevant information that allows an evaluation of the issues laid down in the aim of the Act, regarding ethical justification, social utility or the contribution to sustainable development of the GMO. Given this lack of necessary information for such an evaluation, the Applicant has not demonstrated a benefit to the community and a contribution to sustainable development from the use of GHB614 x T304-40 x GHB119 cotton.

In the following, we identify areas that are relevant to consider in order to assess the criteria of social utility, ethical justifiability and the contribution to sustainability and highlight information that is missing from the Applicant.

Impacts in producer countries

As already stated, the Applicant does not provide data relevant for an environmental risk assessment of GHB614 x T304-40 x GHB119, as it is not intended to be cultivated in the EU/Norway. However, this information is necessary in order to assess the sustainability criteria as laid down in the NGTA. Importantly, it is difficult to extrapolate on hazards or risks taken from data generated under different ecological, biological, genetic and socio-economic contexts as regional growing environments, scales of farm fields, crop management practices, genetic background, interactions between cultivated crops, and surrounding biodiversity are all likely to affect the outcomes. It can therefore not be expected that the same effects will apply between different environments and across continents. Hence, a proper evaluation of potential impacts that are relevant for sustainability is lacking, and sufficient information relevant for the ERA and socio economic impacts assessment in these agricultural contexts needs to be provided. This should include information from an ERA concerning impacts on cultivation, management and harvesting stages, as well as the post-market environmental monitoring in the producing country. With regard to potential socio-economic impacts in the producer country or countries, published reviews on sustainability-relevant aspects (e.g. impacts among poor and/or small-scale farmers in developing countries, share of the benefits among sectors of the society) indicate that these effects have been very complex, mixed and dependent on the agronomic, socio-economic and institutional settings where the technology has been introduced (64). Similarly, Fisher et al. (65) point to factors such as different political and regulatory contexts when explaining differences reported in distribution of economic gains and farmers' access to seeds in studies included in the review. This underlines that it cannot be expected that the same effects will apply between different social and environmental contexts. In order to meet the requirements in the NGTA, further investigations of social and economic implications from cultivating insect resistant and herbicide tolerant GM cotton is needed.

Social and economic impacts from gene flow and co-existence management

The cultivation of GM plants in general is causing problems with regard to co-existence. An evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies are important for a sustainability assessment. Information about the strategies adopted to ensure co-existence with conventional and organic cotton production and potential consequences for these production forms in the producing countries is required for an assessment of social and economic impacts in the producer country.

Assessment of alternatives

It is also important to evaluate whether alternative options may achieve the same outcomes in a safer and ethically justified way. This relates to the increased trend to anticipate impacts and reflect on underlying values, assumptions, norms and beliefs within research and policy of science and innovation (61, 66) to reflect on what kind of society we want, and assess how certain (biotechnological) developments may or may not contribute to shaping a desired future. Indeed, in order to evaluate whether GHB614 x T304-40 x GHB119 contributes to social utility, it is important to consider current and future demand for this GM product for food, feed and processing purposes in Norway and to what extent this can be satisfied by existing sources.

About the use of glufosinate-ammonium

T304-40, an event in GHB614 x T304-40 x GHB119, is tolerant to glufosinate-ammonium that is banned for use in Norway. While it is understood that the Applicant has not applied for

deliberate release of GHB614 x T304-40 x GHB119 in Norway, the acceptance of a product in which the intended use involves the use of a product banned in Norway, raises questions to the criteria of sustainability as laid out in the NGTA. Indeed, within the NGTA, the aim to assess the contribution to sustainable development is not limited to Norway, but there is significant emphasis to consider the impacts and consequences for producing countries from which Norway imports food and feed as well. Specifically, this issue is relevant particularly in the revised guidelines for impact assessment pursuant to the Act of 2005 Section 17, "*Other consequences of the production and use of genetically modified organisms"* points 2 and 3, "*ethical considerations that may arise in connection with the use of the genetically modified organism(s)*», and "*any favorable or unfavorable social consequences that may arise from the use of the genetically modified organism(s)*", respectively.

Final summary

In order to meet the requirements for the NGTA, the regulator is encouraged to ask the Applicant to submit information relevant for the assessment of the social utility of GHB614 x T304-40 x GHB119 and its contribution to sustainable development. The information provided by the Applicant must be relevant for the agricultural context in the producing country/countries, and for Norway as a potential importing country. The information should include issues such as:

- changes in pesticide use,
- development of pest resistance in target populations,
- impacts on non-target organisms,
- potential for adjuvancy effects
- potential for gene flow
- possible impacts among poor and/or small-scale farmers in producing countries,
- share of the benefits among sectors of the society, and
- meeting a need among consumers or industry.

Furthermore, due to the event T303-40, GHB614 x T304-40 x GHB119 is tolerant to glufosinate-ammonium which is banned for use in Norway due to health and environmental concerns. How the use of this herbicide contribute to sustainable development in the producing country needs therefore to be demonstrated by the applicant. Moreover, the applicant does not attempt to identify ethical implications, nor demonstrate a benefit to the community in Norway or in the producing country from the use GHB614 x T304-40 x GHB119 and does therefore not provide sufficient information as required by the NGTA.

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