GenØk - Centre for Biosafety

Vår ref:2013/h68
Deres ref: 2013/7412

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 11.11.13

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på høringen av søknad EFSA/GMO/NL2009/68 som gjelder mat, fòr, import og prosessering av genmodifisert bomull linje 281-24-236x3006-210-23xMON88913 produsert av Agrigenetics, Inc. d/b/a Mycogen Seeds.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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

Bidragsytere:

Lise Nordgård
Forsker/Rådgiver
GenØk – Senter for Biosikkerhet

Marek Cuhra
Forsker
GenØk – Senter for Biosikkerhet

Marianne Iversen
Vit. Ass
GenØk – Senter for Biosikkerhet

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Assessment of the technical dossier submitted under EFSA/GMO/NL/2009/68 for approval of 281-24-236x3006-210-23xMON88913 Cotton from Agrigenetics, Inc. d/b/a Mycogen Seeds.

Sent to

Norwegian Environment Agency

by

Centre for Biosafety – GenØk
November 2013

KONKLUSJON PÅ NORSK

Vi trekker frem mangler i dossieret som ikke gir grunnlag for en konklusjon om sikker bruk, samfunnsnytte og bidrag til bærekraftighet av 281-24-236x3006-210-23xMON88913 bomull. Søker har ikke inkludert noe av den informasjonen omkring samfunnsnytten og bærekraftighet til 281-24-236x3006-210-23xMON88913 bomull som kreves i den norske genteknologiloven (Appendix 4) for godkjenning i Norge.

Hovedkonklusjon og anbefalinger

Søker konkluderer med at det ikke er behov for en overvåkningsplan på bakgrunn av tidligere godkjenning av 281-24-236x3006-210-23xMON88913 for mat og fór. Vår vurdering er at det er behov for en overvåkningsplan.

Søker gir ikke opplysninger som adresserer vurderingskriteriene bærekraft, samfunnsnytte og etiske aspekter som forutsettes anvendt i den norske genteknologiloven. I denne sammenheng er det viktig å få dokumentert erfaringer med hensyn på effekter på miljø, helse og samfunnsaspekter. Denne type dokumentasjon er ikke vedlagt søknaden om omsetting av mat produsert fra 281-24-236x3006-210-23xMON88913 bomull eller inneholdende ingredienser produsert fra 281-24-236x3006-210-23xMON88913 bomull.

Vår konklusjon er at norske myndigheter ikke godkjenner 281-24-236x3006-210-23xMON88913 bomull for bruk i mat, fôr og import som det søkes om.

SUMMARY OF THE ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/NL/2009/68

As a designated National Competence Center for Biosafety, our mission at GenØk in advice giving is to provide 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 following information is respectfully submitted for consideration in the evaluation of product safety and corresponding impact assessment of event 281-24-236x3006-210-23xMON88913, setting out the risk of adverse effects on the environment and health, including other consequences of proposed release under the pertinent Norwegian regulations.

This submission is structured to address specific provisions for an impact assessment required under the Norwegian Gene Technology Act of April 1993, focusing on the requirements in Appendix 2 - Principles for environmental risk assessment pursuant to sections 13-16 of the regulations, and Appendix 4 - Evaluation of ethical considerations, sustainability and benefit to society, cf section 17 of the "Regulations relating to impact assessment pursuant to the Gene Technology Act" of December 2005, pursuant to section 11 cf section 8. The information presented here may be applicable to more than one provision in different appendices.

Specific recommendations

Based on our findings, we propose a few specific recommendations, summarized here and detailed in the critique below.

- The regulator is encouraged to ask the Applicant the reason for the presence of the PAT gene as it has no tolerance effect in the field studies and studies are performed with exposure of glyphosate only.

- The regulator is encouraged to ask the Applicant to consider that we find that it would be ethically incongruous and a double standard of safety for Norway to ban the use of these herbicides domestically as a health concern, but support its use in other countries.

- The regulator is encouraged to ask the Applicant to provide a case-specific monitoring plan to monitor potential unintended but anticipated exposure routes and levels, and to verify the assessment of exposure routes and levels into the environment.

- The regulator is encouraged to ask the Applicant to provide a post-market monitoring plan as the risk analysis is based on single, microbial versions of the proteins in question, and not of the transgenic plant as a whole.

- The regulator is encouraged to ask the Applicant to consider the potential adverse effects of Cry proteins on non-target organisms based on recent per-reviewed literature.

- The regulator is encouraged to ask the Applicant to include long term exposure-/feeding studies before a GM plant product is released on the marked for food/feed consumption.

- The regulator is encouraged to ask the Applicant to demonstrate the lack of interactive effects between transgenic proteins through proper scientific testing and evidence gathering, rather than justify the lack of testing based on assumptions-based reasoning of no effects.

- The regulator is encouraged to ask the Applicant to provide full molecular characterization of the event.

- The regulator in encouraged to ask the Applicant to clarify why there is a low likelihood of molecular interaction and change in the molecular characteristics of the event.

- The limited scope of the analysis as presented does not allow a comprehensive and meaningful examination of the inserts present in 281-24-236x3006-210-23xMON88913 cotton.

- The regulator in encouraged to ask the Applicant to provide a more thorough discussion about unintended effects of the insertion of *Cry1F* event 281-24-236 in the 3' UTR of a putative GA 20-oxidase gene.

- The regulator is encouraged to ask the Applicant to consider potential effects of unprocessed transgenic Cry proteins in agricultural practice due to the evidenced immunogenicity of some of the proteins in this class. Combinatorial effects of these proteins are also not considered.

- The regulator is encouraged to ask the Applicant to submit required information on authorised, alternative and sustainable methods to control volunteers in Europe.

- The regulator is encouraged to ask the Applicant for to submit required information on the social utility of 281-24-236x3006-210-23xMON88913 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

Overall recommendation

From our analysis, we find that the deficiencies in the dossier do not support claims of safe use, social utility and contribution to sustainable development of **281-24-236x3006-210-23xMON88913. Critically, the Applicant has not included any of the required information to assess social utility and sustainability as required in Appendix 4 of the Norwegian Gene Technology Act, which would be necessary for consideration of approval in Norway.** Hence at minimum, the dossier is deficient in information required under Norwegian law. A new application or reapplication should only be reconsidered with the delivery of the information requests recommended here, including any additional information deemed significant by the Norwegian authorities.

Therefore, in our assessment of 281-24-236x3006-210-23xMON88913, we conclude that based on the available data supplied by the Applicant, the Applicant has not substantiated claims of environmental safety satisfactorily or provided the required information under Norwegian law to warrant approval in Norway at this time.

ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/ES/2012/104

About the event

The genetically modified 281-24-236x3006-210-23xMON88913 cotton was developed through *Agrobacterium*-mediated transformation. The genetic modification intended to be inserted was a *cry1F, cry1Ac, CS-cp4epsps* and *pat.* The presence of *cry1F* and *cry1Ac* confers resistance against certain *Lepidoptera* pests. The presence of *Cp4-epsps* confers tolerance to herbicides containing glyphosate and the presence of *pat* confers tolerance against glufosinate-ammonium.

The Applicant is requesting the authorization for food, feed, import and processing in the EU of glyphosate tolerant 281-24-236x3006-210-23xMON88913 cotton.

Assessment findings

Health and environment

General remarks

The genetically modified 281-24-236x3006-210-23xMON88913 cotton *express Cry1F, Cry1Ac, CP4-EPSPS and PAT proteins, conferring resistance to certain lepidopteran insect pests and tolerance to glyphosate herbicide under field conditions*" (Application part A. General Information). In this context, the PAT-gene can be expected to convey tolerance towards glufosinate-ammonium herbicides. The applicant states that the tolerance towards glufosinate ammonium herbicide is "not enough to be used in field conditions". It is unclear to us whether this is a deliberate construct quality of the inserted PAT-gene or an unintended effect, e.g. of hybridisation. We see that in the thorough and very detailed agronomical testing performed as supporting research for the application (Phillips 2008), test plots were sprayed only with glyphosate herbicides. If this glufosinate-ammonium-tolerant variety is intended to be cultivated with glufosinate-ammonium application, this should be clearly stated and test material representative of this practice should be produced and included in the assessment as a whole.

Potential risk from consumption

In chapter 7.8.4 (Testing of the whole GM food/feed) the basic assumption is that compositional equivalence is established (Phillips 2008). We acknowledge the detailed information on application rate of glyphosate herbicide (4 foliar applications, with representative rate of active ingredient application). Thus the information provided in the information about residual levels (well below current US EPA MRL (15 ppm)) is important as recent research into glyphosate herbicide residues in glyphosate tolerant GMO cultivars has demonstrated that plants such as glyphosate-tolerant soybean GTS40-3-2 has a

unanticipated ability to accumulate glyphosate residues in seed (TestBiotech 2013, Bøhn et al 2013). These results have been disclosed from samples taken from representative agriculture plots in South- and North America, indicating that other herbicide-tolerant GMO cultivars could represent the same issue. The relatively high levels of glyphosate residues have been hypothesized to be related to changing agriculture practice (Duke et al 2003) with applications even in the flowering season and higher than recommended application rates due to resistant species of weeds. Such issues might also affect the residue levels in cultivars such as 281-24-236x3006-210-23xMON88913 cotton and should be specifically monitored.

Post-market monitoring of GM food/feed
Based on the evaluation that there is no risk for human and animal health or environment, and that the use are not different from conventional cotton lines, a post marked monitoring is not regarded as needed by the applicant (Application section 7.11, page 40, Post-market monitoring of GM food/feed). The assumption of "no risk" is based on evaluation of the single proteins in question. Since they previously have been considered as safe, there is no need for a combinatorial effect study in general. We recommend the applicant rewrite the section on post-market monitoring, as the wording in general and specifically the use of the word "from" in the second line of first paragraph, implies that systematic testing of 281-24-236x3006-210-23xMON88913 cotton in food, feed and industrial products has been performed. Since no such testing has been performed, the section is misleading. Furthermore, the applicant has not prepared for adequate packaging, labelling, handling and storage systems, to ensure that potential adverse effects from use can be properly identified and rapidly remediated. This seems negligent when considering the fact that as of yet no feeding trials have been performed in neither human nor animal consumers.

Interactions with non-target organisms
The applicant states that *"Ecotoxicity studies have shown the lack of toxicity of the Cry1F and Cry1Ac proteins against non-target arthropods such as..."* and presents a list of studies in vertebrate and invertebrate organisms which are referenced as indications of Bt-toxin safety towards non-target organisms. This subject however is contested, as published findings have indicated that Cry-transgenes expressing Bt-toxins in plant tissues can induce other toxic properties than seen when expressed in donor organism (microbial Bt-toxin) (Bøhn et al 2008). This is yet another argument supporting the demand for representative testing, ie that effects of in-plantae Bt-toxins induced by transgenes be assessed from material representative of what will be consumed, not from models based on feeding trials with microbially produced analogs.

Environmental Monitoring Plan
The applicant states that it has been confirmed that there is no selective advantage or disadvantage to the transgenic cotton plants outside agricultural environments (Phillips 2008). However, the documentation provided in Phillips 2008 does not mention the specific question of selective advantage or –disadvantage. Also, since the application does not concern cultivation within the EU/EEC area, this question is of minor importance. We acknowledge the application referring to OECD 2003 consensus document on cotton (which subsequently has been revised, OECD 2008) and which establishes sufficient evidence on ecological and biological characteristics of cotton to warrant the conclusion

that establishment of volunteers/wild populations from accidental spillage of 281-24-236x3006-210-23xMON88913 cotton seed material, is not a relevant issue within the EU/EEC area.

Glyphosate tolerance
The genetically modified cotton expresses CS-cp4*EPSPS* that confers tolerance to herbicides products containing glyphosate.

In recent years glyphosate has received more risk-related attention due to negative effects on both aquatic and terrestrial ecosystems (Blackburn and Boutin 2003, Ono et al 2002, Solomon and Thompson 2003), and also because of constantly increasing number of glyphosate herbicide applications since the introduction of this chemicals in 1971 (Dill et al 2010, Cuhra et al 2012).

Studies in animals and cell cultures indicate possible health effects in rodents, fish and humans. Glyphosate given in the feed to pregnant female rats resulted in higher embryonic mortality and aberrations in the skeleton (Dallegrave et al 2003). Nile-tilapia (Oreochromis niloticus) fed sublethal concentration of Roundup (active ingredient: glyphosate) resulted in a number of different histopathological changes in organs (Jiraungkoorskul et al 2003). Experiments with sea urchins exposed to Roundup influenced early cell divisions (Marc et al 2002), effects that have relevance to potential health effects in many eukaryotic organisms, including domestic animals and humans. Exposure to Roundup affected the CDK1/CyclinB regulator which is nearly identical in sea urchins and humans.

Glyphosate has also been shown to negatively affect the differentiation of nerve cells (Axelrad et al 2003). In human placenta cells, Roundup is more toxic than the active ingredient glyphosate (Richard et al 2005). The authors concluded that additional components of Roundup increase the biological availability and accumulation in organisms.

In a recently published study by Seralini et al (Seralini et al 2012) the authors concludes that long term exposure of lower levels of complete agricultural glyphosate herbicide formulations, at concentrations well below officially set safety limits, induce severe hormone-dependent mammary, hepatic and kidney disturbances in rats.

Recommendation: The regulator is encouraged to ask the Applicant to include long term exposure-/feeding studies before a GM plant product is released on the marked for food/feed consumption.

Glufosinate-ammonium
The Applicant states that the *pat* gene in this transgenic cotton stack is not enough to give tolerance towards gluphosinate ammonium under field conditions, the gene is still present and the issue of glufosinate ammonium use is thus present. The *pat* gene derived from *Streptomyces viridochromogenes* confers tolerance to herbicides containing glufosinate-ammonium, a class of herbicides that are banned in Norway and in EU (except a 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, swallowing and by skin contact and serious health risks may result from exposure over time. Effects on humans and

mammals include potential damage to brain, reproduction including effects on embryos, and negative effects on biodiversity in environments where glufosinate ammonium is used (Hung 2007, Matsumura et al 2001, Schulte-Hermann et al 2006, Watanabe and Sano 1998). According to EFSA, the use of glufosinate ammonium will lead to exposures that exceed acceptable exposure levels during application.

Recommendation:

- The regulator is encouraged to ask the Applicant to consider that we find that it would be ethically incongruous and a double standard of safety for Norway to ban the use of these herbicides domestically as a health concern, but support its use in other countries.

Stacked events

Until recently, the dossiers submitted for marked authorization almost only covered single GM events. Today there is a clear trend to combine two or more transgenic traits present in single events through traditional breeding. However, information on how these GM stacked events should be assessed is limited and in some cases assessment data for each single GM events has been taken into account to prove the safety of the whole food/feed.

Stacked events are in general more complex and it has been an increased interest in the possible combinatorial and/or synergistic effects that may produce unintended and undesirable changes in the plant – like the potential for up- and down regulation of the plants own genes. Interactions with stacked traits cannot be excluded that the group of expressed toxins in the plant can give specific immunological effects or adjuvant effects in mammals (Halpin 2005, Schrijver et al 2006). Then (2009) reviews and discusses the evidence for changes in activity and specificity of Bt proteins dependent on synergistic interactions with extrinsic features. Such changes may critically influence the bioactivity and hence the potential for unintended effects.

This is why combinatorial, synergistic effects must be carefully considered in the development and risk assessments of stacked events and robust data are necessary to identify whether the combined presence of transgenes influences expression levels, e.g. by silencing effects.

Most of the information submitted in this safety assessment is derived from previous finding with the single lines. In general the applicant describes most of the traits and characteristics of the "stacked event" as being the same as those of the parental GM events used in production of GM maize. That applicant has not demonstrated that interactions among the different transgenic proteins, particularly for allergenic or toxic effects, are not taking place in this event, despite evidence of the potential (Mesnage et al 2012). Assumptions-based reasoning with single events should not replace scientific testing of hypotheses regarding interactions. GenØk means that stacked events cannot be approved based on the information on the single events.

Recommendation: The regulator is encouraged to ask the Applicant to demonstrate the lack of interactive effects between transgenic proteins through proper scientific testing and evidence gathering, rather than justify the lack of testing based on assumptions-based

reasoning of no effects.

Molecular characterization

Information relating to the GM plant

281-24-236x3006-210-23xMON88913 cotton is a GM plant containing stacked transformation events. There is no scientific literature available on the full genetic construct, the genetic stability, transgene expression products or immune-toxicological effects, or cross resistance effects unique to the stacked event in question in order to make an appropriate scientific evaluation.

Information on the sequences actually inserted or deleted (p. 10)

The Applicant claims that there is low likelihood of molecular interactions between the different inserts, and therefore, low likelihood of any changes in the molecular characteristics of the inherited insert in 281-24-236x3006-210-23xMON88913 cotton (e.g. insert number, copy number, absence of backbone DNA and integrity of the individual inserts) and consider event-specific fingerprint Southern blot analysis as sufficient. The Applicant does not explain why there is a low likelihood of molecular interaction and change in the molecular characteristics of the insert.

The data submitted by the applicant to conclude molecular equivalence of 281-24-236x3006-210-23xMON88913 cotton with the parental GM lines consist of *Southern Blot Analysis* of the introduced traits to confirm the maintenance of the transgenic insert of the GM parental lines, comprising their copy number and the structure. Critical here is the size of the probes > 500bp, which means that point mutations, small deletions and rearrangements that might occur during breeding will possible not be detected (Fagard&Vauvheret 2000, de Schrijver et al 2006).

The Applicant claims that "According to the sequence data on the flanking border regions and their alignments with the parental locus, the cDNA and genomic sequences of the cotton GA 20- oxidase gene, the insert in *Cry1F* event 281-24-236 apparently landed in the 3' UTR of a putative GA 20-oxidase gene. However, the detail structure of this putative gene cannot be defined with currently available information (Song 2010c, Appendix)."
However, there are studies that show that GA 20-oxidase in cotton (Xiao et al 2010) and other plants is connected to regulation of growth and development (Carrerra et al 2000, Niki et al 2001, Yamaguchi 2008). Thus the insertion of *Cry1F* event 281-24-236 in the 3' UTR of a putative GA 20-oxidase gene could have implications for cotton growth and development if the putative gene is a true gene. This is an uncertainty, and may have implications for the concept of substantial equivalence.

Recommendation:

- The regulator in encouraged to ask the Applicant to provide a full molecular characterization of for this event.
- The regulator in encouraged to ask the Applicant to clarify why there is a low likelihood of molecular interaction and change in the molecular characteristics of the event.

- The limited scope of the analysis as presented does not allow a comprehensive and meaningful examination of the inserts present in 281-24-236x3006-210-23xMON88913 cotton.
- The regulator in encouraged to ask the Applicant to provide a more thorough discussion about unintended effects of the insertion of *Cry1F* event 281-24-236 in the 3' UTR of a putative GA 20-oxidase gene.

Information on the expression of the insert
The results from the expression of Cry1F, Cry1Ac, CP4-EPSPS and PAT proteins are given for cottonseeds as the aim of this application is for food and feed only. Both the stacked event and its parental lines are tested for level of expression by ELISA. All proteins levels are considered as low and there seem to be no significant differences between comparable cotton events analyzed (stack is both sprayed and unsprayed with herbicide).
Fusion proteins have not been looked for as they are not expected.

Toxicology and Allergy
Based on the history of safe us of all the transgenic proteins in question (Cry1F, Cry1Ac, CP4-EPSPS and PAT) the transgenic cotton is considered not harmful.
Toxicological assessments are performed for newly expressed proteins in the context of animal health and not for humans as the Applicant states that humans not will be exposed to these proteins. However, the Applicant has not considered that during agricultural practice, humans will be handling cotton, and thus be exposed to these proteins that not will be digested or processed in any way.
The safety aspects given by the Applicant are based on assessments given for the parental lines 281-24-236x3006-210-23 (EFSA GMO NL 2005) and MON88913 (EFSA GMO UK 2007) separately. The proteins used in these assessments were of bacterial origin. It is recommended to use the plant version of the proteins due to potential post translational differences between species. The combined effect of these proteins (all transgenic proteins in the stack) is not investigated for toxicological purposes besides an acute toxicity study performed in 2001 (Brooks and Yano) for analysis of Cry1F and Cry1Ac. In this study, these two proteins are mixed to a ratio of 50:50 and there was no observed mortality, clinical signs or pathology observed. In the stacked cotton 281-24-236x 3006-210-23xMON88913 the ratio between Cry1F and Cry1Ac is not 50:50, but more close to 3:1. Thus, the mixture used in the old study is not relevant for this stack. A new study with all the transgenic proteins in question should have been performed.
All transgenic proteins in this application (Cry1F, Cry1Ac, CP4-EPSPS and PAT) have no sequence similarity to known toxins or allergens (single proteins analyzed. Not from stack). They are rapidly digested in simulated gastric fluid (SGF), have histories of safe use, high specificity, no toxicology data and are considered safe as single proteins. Again, the stack itself (and the mixture of transgenic proteins there) is not considered to influence this. The sources of these proteins are also not known to be allergenic and no glycosylation patterns have been found of the proteins. Again, it is the microbial version that has been tested. Also, Cry1F and Cry1Ac are found to have low immunoreactivity after heating.
The potential adjuvancy effect of Cry-proteins is not considered. Already back in 2000 and 2003 (Vasquez et al 2000, Moreno-Fierros et al 2003) Cry1Ac was found to have such an effect. Other Cry proteins have also been shown to have immunological effects. This should

have been mentioned and considered, given the fact that this stack contains to Cry-proteins. No published data on adjuvance effects of Cry1F is available.
The whole GM plant or crop is not tested due to the assumption of compositional equivalence between conventional and transgenic cotton.
However, as this transgenic stacked plant contains several inserted proteins, testing in an animal model would provide some conformation of this hypothesis.

Recommendation:

- The regulator is encouraged to ask the Applicant to consider potential effects of unprocessed transgenic Cry proteins in agricultural practice due to the evidenced immunogenicity of some of the proteins in this class. Combinatorial effects of these proteins are also not considered.

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. In accordance with the aim of the Norwegian Gene Technology Act, 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 detailed in the regulation on consequence assessment section 17 and its annex 4. The Norwegian Gene Technology Act, with its clauses on societal utility and sustainable development, comes into play with a view also to health and environmental effects in other countries, such as where GMOs are grown. Although the literature concerning the socio-economic aspects related to the cultivation (and to a much lesser extend the use) of GM cotton is extense, the Applicant does not mention any these references, nor there is an attempt to identify how 281-24-236x3006-210-23xMON88913 cotton might contribute to sustainability and social utility (neither in the producing countries nor in Norway or Europe).

Therefore, the Applicant has not provided relevant information that allows an evaluation of the issues laid down in the aim of the Act, regarding ethical values, social justification of the GMO within a sustainable development. 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 281-24-236x3006-210-23xMON88913 cotton.

Further, published reviews on aspects related to societal utility (e.g. impacts among poor, 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 (Glover 2010). 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. Hence it cannot be expected that the same effects will apply between different environments and across continents.

On the sustainability of the product, 281-24-236x3006-210-23xMON88913 cotton confers tolerance to herbicides containing glufosinate-ammonium and glyphosate. Glufosinate-amonium is a class of herbicides that are banned in Norway and in EU (except a limited use on apples) due to both acute and chronic effects on mammals including humans.

As this application excludes the cultivation of 281-24-236x3006-210-23xMON88913 cotton in the European Unión, in page 21, II Part, the Applicant states that "*This application is to market in the EU of 281-24-236x3006-210-23xMON88913 cotton and derived products and not for cultivation. Exposure to the environment from the import of 281-24-236x3006-210-23xMON88913 cotton will be limited to unintended release of 281-24-236x3006-210-23xMON88913 cotton e.g. via spillage during transportation of cottonseeds, therefore the impact on the specific cultivation, management and harvesting techniques will be negligible*". However, the Gene Technology Act applies not only for Norway but also for cultivating countries, and therefore, information for the risk assessment on the cultivation, management and harvesting stages as well as the post market environmental monitoring is required in order to assess the sustainability criteria laid down in the Act. The Applicant has not provided information on how long (e.g. number of planting seasons) it will take before the 81-24-236x3006-210-23xMON88913 cotton containing plants develop sensitivity to the combined glufosinate-ammonim and glyphosate herbicides. Therefore, it would be incongruent with the principle of sustainable development. Weed resistance to glycines in cotton cultivation has been vastly documented[1].

The Applicant should thereby provide the necessary data in order to conduct a thorough assessment on these issues. It is also important to evaluate whether alternative options (e.g. the parental non-GM version of this 281-24-236x3006-210-23xMON88913 cotton) may achieve the same outcomes in a safer and ethically justified way.

In page 6 of the part II document, paragraph 3.b of the B section (Specific factors affecting survivability), it is stated that "*In most cotton growing areas in Europe, seeds which may remain in the soil may germinate in the autumn if conditions are right, otherwise, they are likely to rot and die. Cotton volunteers, can be easily controlled by current agronomic practices such as cultivation, and use of selective herbicides (atrazine, bromoxynil, paraquat and glyphosate).*"

At this respect, it is important to highlight that both atrazine and paraquat are banned herbicides in the European Union (see EU pesticides database[2]). In the case of atrazine, it was banned in Europe since 2004 because of persistant groundwater contamination. Paraquat use is forbidden in Europe since 2007 for protecting human health and the environment[3]. It has

[1]http://www.weedscience.org/Summary/Crop.aspx?SituationID=8
[2] http://ec.europa.eu/sanco_pesticides/
[3]Press Release No° 45/07. 11 July 2007. Judgment of the Court of First Instance in Case T – 229/04. Kingdom of Sweden v Commission of the European Communities. THE COURT OF FIRST INSTANCE ANNULS THE DIRECTIVE AUTHORISING PARAQUAT AS AN ACTIVE PLANT

also been linked to Parkinson' disease (Tanner et al 2011). On its turn, although broxomoxynil is allowed in the European Union, it was also banned in Norway in 2000 for reasons pertaining to the environment and human health. The following is a summary from the Rotterdam Convention database describing the reasons for the Norwegian ban: "*Bromoxynil is labeled with many risk phrases, including may cause cancer, and possible risk of harm to the unborn child . The risks to the applicator are judged to be too high to be found acceptable. In addition, an important reason to not accept bromoxynil is that there are already alternatives on the market that pose a lower risk to human health"*. Moreover, it is also considered extremely toxic to aquatic organisms[4]. Therefore, it would be incongruent to support the use of 281-24-236x3006-210-23xMON88913 cotton if control of volunteers require products that are banned in Norway. Finally, 281-24-236x3006-210-23xMON88913 cotton is modified to tolerate glyphosate (as well as glufosinate ammonium), which does not make it suitable to control volunteers, as in fact it is stated in page 51 of the part I of the technical dossier.

Ethical considerations

The evaluation of coproducts, that is, secondary products that are specifically designed and intended to be used in conjunction with the GMO, is considered important in the risk assessment of a GMO (Dolezel et al 2009). Therefore, considerations of the co-products also warrant an evaluation of safe use.

The event contain the phosphinothricin acetyl transferase (PAT) gene that confers tolerance to herbicides containing glufosinate ammonium, a class of herbicides that are banned in Norway. In fact, it is not clear how glufosinate ammonium will be used, as it is stated by the Applicant that tolerance for this herbicide is not enough to be used under field conditions. While it is understood that the Applicant has not applied for deliberate release of 281-24-236x3006-210-23xMON88913 cotton in Norway, the acceptance of a product in which the intended use includes the use of a product banned in Norway would violate basic ethical and social utility criteria, as laid out in the Act. That is, we find that it would be ethically incongruous to support a double standard of safety for Norway on one hand, and safety for countries from which Norway may import its food and feed on the other. This line of reasoning is consistent with the provisions under the Act to assess ethical, social utility and sustain able development criteria not only for Norway, but for countries from which Norway imports food and feed. Specifically, this issue is relevant particularly in revised regulations 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.

Besides, information provided by the Applicant regarding the control of volunteers (see social utility and sustainability aspects) should also be evaluated from an ethical perspective. Again, it would be a double standard to accept a product that might require the use of banned herbicides to control volunteers.

PROTECTION
SUBSTANCE. http://curia.europa.eu/en/actu/communiques/cp07/aff/cp070045en.pdf
[4]http://www.pic.int/Countries/CountryProfile/tabid/1087/language/en-US/Default.aspx

Recommendation:

- The regulator is encouraged to ask the Applicant to submit required information on the social utility of 281-24-236x3006-210-23xMON88913 cotton and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.
- The regulator is encouraged to ask the Applicant to submit required information on authorised, alternative and sustainable methods to control volunteers in Europe.

Conclusion

Available information for risk assessment evaluation

This evaluation is based on the Applicant's own submitted information, along with our own expertise in related fields. The relevant scientific literature is very limited in some cases, yet we have tried to extract information from the peer-reviewed literature that may inform the scientific validity of the information under consideration. In situations where lack of knowledge, complexity and uncertainty are high, particularly in relation to unknown adverse effects that may arise as a result of approval for release of a living modified organism into the environment or food supply, the available information may not be sufficient to warrant approval. Further information may address some of these issues; however an accurate description of uncertainties provided by the applicant would provide a more useful basis for assessing the level of risk that may come with regulatory approval of the GMO, taken on a case-by-case basis.

In all cases, product-related safety testing should have an independent and unbiased character. This goes both for the production of data for risk assessment, and for the evaluation of the data.

The lack of compelling or complete scientific information to support the claims of the Applicant documented here highlights the need for independent evaluation of the dossier as performed here, including the raw data produced by the Applicant. We therefore support better transparency and independent review of information to ensure high standards within the regulatory process. This would include any information provided by the Applicant used to justify confidentiality claims on any scientific data. We encourage the authorities to insist on this level of transparency and accessibility to all scientific data (including raw data) to ensure the scientific validity of the information presented.

Overall recommendation

Above we highlight a number of issues in relation to the questionable safe use of 281-24-236x3006-210-23xMON88913 that do not justify a conclusion of safe use, social utility and contribution to sustainable development. Critically, the Applicant's environmental monitoring plan lacks sufficient details and descriptions to support the required monitoring activities, and has not included any of the required information to assess social utility and sustainability as required in Appendix 4 of the Norwegian Gene Technology Act, which would be necessary for consideration of approval in Norway. Taken together, these deficiencies fail to address the necessary safety regulations under Norwegian Law, and thus the application is incomplete and should not be approved. A new application or reapplication should only be reconsidered with the delivery of the information requests recommended here, including any additional information deemed significant by the Norwegian authorities.

Therefore, in our assessment of 281-24-236x3006-210-23xMON88913 we conclude that based on the available data, the Applicant has not substantiated claims of safety satisfactorily to warrant approval in Norway at this time.

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