Vår ref:2015/H_124
Deres ref: 2015/11039

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 12.11.15

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring under EU forordning 1829/2003 av oppsummert søknad for **EFSA/GMO/NL/2015/124**, mais **MON87411** fra Monsanto Company som gjelder mat, fòr, import og prosessering av genmodifisert mais **MON87411.**

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Vår ref:2015/H_124
Deres ref: 2015/11039

Assessment of the summary of the dossier under 1829/2003/EU of EFSA/GMO/NL/2015/124 maize.

Sent to

Norwegian Environment Agency

By

GenØk- Centre for Biosafety
November 2015

KONKLUSJON PÅ NORSK

Vi trekker frem mangler i oppsummert søknad og data som ikke gir grunnlag for en konklusjon om sikker bruk, samfunnsnytte og bidrag til bærekraft av **MON87411 mais**. Søker har ikke inkludert noe av den informasjonen omkring samfunnsnytte og bærekraft av **MON87411 mais** som kreves i den norske genteknologiloven (Appendix 4) for godkjenning i Norge.

Hovedkonklusjon og anbefalinger:
Genøk–Senter for Biosikkerhet viser til brev fra Miljødirektoratet angående offentlig høring for **MON87411 mais** i bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra **MON87411 mais.**

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 tilstrekkelig i oppsummert søknad om omsetting av **MON87411 mais** til import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra **MON87411 mais.**

Basert på den informasjonen vi har tilgjengelig er vår konklusjon at norske myndigheter ikke godkjenner bruk av **MON87411 mais** til import og prosessering og til bruk i fòr og mat som det søkes godkjenning for.

ASSESSMENT OF THE SUMMARY OF THE TECHNICAL DOSSIER UNDER 1829/2003 OF EFSA/GMO/NL/2015/124 MAIZE.

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 event **MON87411 maize**, setting out the risk of adverse effects on the environment and health, including other consequences of proposed release under the pertinent Norwegian regulations.

*As we do not have access to the full technical dossier of **MON87411 maize** we can not give a full assessment of this event.*

Specific recommendations

Based on our findings, we propose some specific recommendations, summarized here and detailed in the go-through below.

- We strongly encourage the Applicant to investigate the 118 bp deletion in the plants genome further with thorough analysis of the ORFs and potential polypeptides resulting thereof.
- We also encourage the Applicant to implicate the potential interruptions of expression/ regulation of expression in the plant and the potential implications this might have.
- We encourage the applicant to verify if the 35S promoter used, contain ORFs and if there are are any phenotypical changes resulting from that (as in unintended protein expression).
- We ask the Applicant to reflect on the issue of potential non-target effects of the RNAi used.
- The regulator is encouraged to ask the applicant to address the potential of non-target effects of Bt toxins.
- The regulator is further encouraged to investigate the potential role of Cry3Bb1 as a protein having adjuvance effects.
- The regulator is encouraged to also ask the applicant to consider the evolution of resistance and cross-resistance towards Bt-proteins in target organisms.
- The applicant should include a full evaluation of the co-technology intended to be used with MON87411 maize, namely the use of glyphosate containing herbicides. Particular focus should be given to the accumulation of this herbicide inside the plants, particularly the parts used in food and feed production, and whether or not these levels of exposure could cause acute and/or chronic health issues. This needs to be tested in animal and feeding studies, separating the effects of the plant and the herbicide(s) by using both sprayed and unsprayed plant samples.
- We strongly encourage the Applicant to use plant-derived proteins for analysis of allergy and toxicology due to the potential translational differences between prokaryotic and eukaryotic cells.
- 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 the MON 87411 maize and its contribution to sustainable development. The information provided by the Applicant must be relevant for the agricultural context in the producing country(ies). The information should include issues such as: development of resistance in target pest populations, impacts on non-target organisms, changes in pesticide use, emergence of herbicide resistant weeds, potential for gene flow and possible impacts among farmers practicing different production forms for maize cultivation in the producing country(ies), possible impacts among poor and/or small-scale farmers in producing countries and share of the benefits among sectors of the society.

Overall recommendation

From our analysis, we find that the information provided in the summary of the technical dossier have deficiencies that do not support claims of safe use, social utility and contribution to sustainable development of MON87411 maize**. 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.** A new application 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 **MON87411 maize**, we conclude that based on the available data, the Applicant has not provided the required information under Norwegian law to warrant approval in Norway at this time.

ASSESSMENT OF THE SUMMARY OF THE TECHNICAL DOSSIER UNDER 1829/2003 OF EFSA/GMO/NL/2015/124 MAIZE.

About the event

The event **MON87411** maize was made by *Agrobacterium tumefaciens* transformation of maize using a transformation plasmid vector.

The application for maize event MON87411 is for food, feed, import and processing.

MON87411 maize is not approved in Norway for any of these applications.

Maize event MON87411 is not approved for food, feed, import or processing in EU.

Application for approval of maize event MON87411 has been sent to Canada, Japan, Korea, Taiwan and Australia for all applications.

Maize event MON87411 is not approved for any applications in a third country.

Assessment findings

We do not have access to the full technical dossier for maize event MON87411.

The event MON87411 maize has a *DvSnf7*^{p} insert from *Diabrotica virgifera virgifera* encoding a double stranded RNA transcript with a 240 bp fragment of the WCR Snf7 gene. The *DvSnf7*^{p} insert provides RNA interference resulting in downregulation of the target gene Snf7 leading to Western corn worm mortality.

It also contains a *CS*^{6}*-cry3Bb1* gene from *Bacillus thuringiensis* sp. *Kumamotoensis* that provides resistance to certain coleopteran insects and *CS-cp4-epsps* from *Agrobacterium* sp. strain CP4 which provides tolerance to herbicides containing glyphosate.

Molecular characterization

Transformation process and genetic elements inserted in the MON 87411 maize genome

The maize event MON 87411 was developed through *Agrobacterium*-mediated transformation using the transformation plasmid vector PV-ZMIR10871. Transformed embryos were selected through growth on medium containing glyphosate, as the vector contains the *cp4 epsps* expression cassette that confers resistance to this herbicide.

Three new genetic elements has been inserted into the MON 87411 genome:

- DvSnf7 suppression cassette: The cassette consists of two partial sequences of the Snf7 gene, which upon expression forms a dsRNA. The dsRNA is toxic upon digestion by the CRW larvae through the RNAi pathway.
- The *cp4 epsps* expression cassette that confers resistance to the herbicide glyphosate
- The cry3Bb1 expression cassette, which encodes the Cry toxin against larval damage.

The backbone vector consist of genes that maintains the plasmid in the bacteria, and an antibiotic resistance marker (ARM) gene, *aadA*, that confers resistance to certain antibiotics. The backbone is not inserted in the plant genome.

Place of insertion and number of insertions.

The applicant has performed “Next Generation sequencing” (NGS) and “Junction Sequence Analysis” (JSA) together with bioinformatics to investigate the number of inserts and the insertion site. The results indicate that the MON 87411 maize contains a single DNA insert (Food Standards Assessment Australia New Zealand (FSANZ) Safety Assessment report on MON87411).

The integrity of the inserted sequence was further analyzed through PCR of eight overlapping regions of the MON87411 genomic DNA (insert and flanking regions). A consensus sequence was generated through compiling sequences from the multiple sequencing reactions performed by the overlapping PCR products. This resulted in an 11248 nt long insert, with identical sequence to the T-DNA of the plasmid PV-ZMIR109. The analysis further confirmed that there was no plasmid backbone incorporated in the plant genome (FSANZ Safety Assessment report on MON87411).

An investigation of the insertion site and genomic changes as a result of the insertion event was done through primers specific to the 5' flanking sequence of MON87411 and one specific to the 3' sequence for PCR of genomic DNA isolated from the untransformed parent (LH244). This product was then sequenced and compared to the sequence of the 5' and 3' flanking regions of the MON87411 maize. This showed a **118 bp deletion** of the genomic DNA at the insertion site in MON87411.
The applicant provides evidence that this is quite common in *Agrobacterium* mediated transformation. An Open reading frame (ORF) analysis was performed of the sequence spanning the 5' and 3' junctions of the MON87411 insert using DNAStar software. This analysis showed the presence of **eight potential ORFs**, which might encode putative polypeptides. The assessment done by FSANZ states that no further investigation was made into whether any potential regulatory elements were associated with these ORFs.

The Expression of the dsRNA from the DvSnf7 suppression cassette was investigated and validated through Northern blot analysis.

Conclusion
The applicant has provided comprehensive molecular characterization of the transformation event. Three cassettes has been inserted in the MON87411; the DvSnf7 suppression cassette, the cry3Bb1 expression cassette and the cp4 epsps expression cassette.

Thorough molecular analysis indicates one insertion site and no evidence of presence of the vector backbone.

Genetic and phenotypic stability of insert has been analyzed together with investigation of dsRNA formation.

Analysis of the insertion site showed a 118 bp deletion in the plants genome in the transformation process, accordingly occurring during integration of the T-DNA.

The applicant analyzed these regions and found ORFs and putative genes for polypeptides. However, the function and putative regulatory effects of these were not investigated further.

Recommendation

- We strongly encourage the Applicant to investigate the 118 bp deletion in the plants genome further with thorough analysis of the ORFs and potential polypeptides resulting thereof.
- We also encourage the Applicant to implicate the potential interruptions of expression/ regulation of expression in the plant and the potential implications this might have.

P⁴-e35S promoter

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 (2012). In the article, the authors state that some P35S variants contain open reading frames that when expressed could lead to "unintended phenotypic changes. Gene VI encodes the multifunctional P6 protein that can be divided into four domains (Li and Leiser, 2002). Functions of P6 include nuclear targeting (Haas et al. 2008), viral particle binding and assembly (Himmelbach et al. 1996), si- and ds-RNA interference and interference suppression (Shivaprasad et al. 2008) and transcriptional transactivation (Kobayashi et al 2004, Palanichelvam et al. 2002).

Recommendation

- We encourage the applicant to verify if the 35S promoter used, contain ORFs and if there are are any phenotypics changes resulting from that (as in unintended protein expression).

RNA interference

As a technique, RNAi has developed quickly. How specific these RNAi`s will be in a potential effect on non-target organisms, is still not fully known. As the RNAi technique in itself is specifically targeting sequences of homology, it will be important to look at sequence homologies between target and non-target organisms. In the maize event MON87411, the RNAi technique used is targeting a sequence in a pest organism, namely the *Diabrotica virgifeira virgiferia*. If the RNAi sequence used here only is present in this species, the chance of non-target effects is lower than if the sequence it is meant to target, also is present in other species that could be affected.

Recommendation

- We ask the Applicant to reflect on the issue of potential non-target effects of the RNAi used.

Protein expression

Protein expression of inserted transgenes were analysed in both glyphosate sprayed and unsprayed MON87411 maize.

Cry toxins

Maize event **MON87411** contains a Bt protein, a Cry toxin, namely CS[6]-cry3Bb1.
The cry3Bb1 expression has been investigated in different parts of the plant and at different growth stages. Mean levels of Cry3Bb1 was lowest in grain, while leaf and root had the highest levels where the *Diabrotica* species it is intended to kill, most presumably will feed (FSANZ Safety Assessment report on MON87411).

Cry toxins are claimed to be safe, however the potential of non-target effects of Bt toxins, including alternative modes of action have been addressed previously (Bøhn et al 2008, Gilliand et al 2002, Crickmore 2005, Hilbeck and Schmidt 2006).

Negative effects of Bt- protein producing transgenic plants on non-target organisms are documented. A meta-analysis of published studies on non-target effects of Bt-proteins in natural enemies, (Lövei and Arpaia 2005) documented that 30% of studies on predators and 57% of studies on parasitoids display negative effects to Cry1Ab transgenic insecticidal proteins. Further, Cry toxins and proteinase inhibitors have often non-neutral effects on natural enemies, and more often negative than positive effects (Lövei et al 2009). A review by Hilbeck and Schmidt (2006) on Bt-plants, found 50% of the studies documenting negative effects on tested invertebrates.

Another issue is that many Cry proteins only have been tested with a very limited number of organisms: thus, activity outside of the target organisms of many Cry proteins may lack documentation simply because testing has not included sensitive organisms (van Frankenhuyzen, 2013).

A quantitative review analysis based on 42 field experiments showed that unsprayed fields of Bt-transgenic maize plants have significantly higher abundance of terrestrial non-target invertebrates than sprayed conventional fields (Marvier et al. 2007). 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 (Marvier et al. 2007).

Research on aquatic environments has sparked intense interest in the impact of Bt-crops on aquatic invertebrates including *Daphnia magna* (Bøhn et al. 2008) and caddisflies (Rosi-Marshall et al. 2007). Given the potential load of Cry toxins (also in combination with herbicides) that may end up in aquatic environments, further studies are warranted. Douville et al. (2007) presented evidence of the persistence of the *cry1Ab* transgene in aquatic environments: 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 (Douville et al. 2009).

Impacts on soil microflora and fauna, including earthworms (Zwahlen et al. 2003), mychorizzal fungi (Castaldini et al. 2005) and microarthropods in response to Cry endotoxins have also been reported (Wandeler et al. 2002, Griffiths et al. 2006, Cortet et al. 2007). The significance of tri-trophic effects of accumulation, particularly of insecticidal Cry toxins (Harwood et al. 2006, O`brist et al. 2006) is not clear. It has been demonstrated that sub-chronic dosages of Cry proteins may affect both foraging behavior and learning ability in non-target bees (Ramirez-Romero et al. 2008), with potential indirect effects on recipient populations. Given the important role of bees as pollinators, such effects may have consequences for both primary production and on entire food webs.

In relation to health impacts, a publication by (Dona and Arvanitoyannis 2009) reviewed the potential health implications of GM foods for humans and animals, including incidences and effects of increased immunogenicity, amounts of anti-nutrients, possible pleiotropic and epigenetic effects, including possible reproductive and developmental toxicity. They conclude that while there is strong evidence for health concerns, testing and exposure duration may have not been long enough to uncover important effects.

The potential adjuvancy of Cry proteins has previously been assessed by the GMO Panel of the Norwegian Scientific Committee for Food Safety (VKM 2012) where they state that:

"the Panel concludes on the basis of current knowledge that it is very unlikely that the Cry proteins in food pose an increased health risk in the amounts that would be ingested by eating processed GM maize or soya, compared with eating food based on isogenic non-modified plants".

However, they also refer to studies showing that:

"*Animal studies have shown that the Cry1Ac protein binds to the surface of the mouse gut and induces immunological reactions against itself and against proteins administered simultaneously".*

And:

"One element of uncertainty in exposure assessment is the lack of knowledge concerning exposure via the respiratory tract and the skin, and also the lack of quantitative understanding of the relationship between the extent of exposure to an adjuvant and its effects in terms of development of allergies".

The MON 87411 maize confers resistance to certain coleopteran pests (*Diabrotica spp*.). Gassmann et al., (2011, 2012, 2014) have reported on field-evolved resistance to Cry3Bb1 by the western corn rootworm (Diabrotica virgifera virgifera).

Recommendations

- The regulator is encouraged to ask the applicant to address the potential of non-target effects of Bt toxins.
- The regulator is further encouraged to investigate the potential role of Cry3Bb1 as a protein having adjuvance effects.
- The regulator is encouraged to also ask the applicant to consider the evolution of resistance and cross-resistance towards Bt-proteins in target organisms.

EPSPS

This MON87411 maize event contains one herbicidal tolerance gene, namely ***CS-CP4-epsps***, providing tolerance to herbicides containing glyphosate. The EPSPS protein is expressed in different parts of the plant with the lowest level in the grain (FSANZ Safety Assessment report on MON87411). Expression levels were measured in both glyphosate sprayed and unsprayed samples.

Antibiotic resistance marker genes (ARMs)

In the summary of the application for MON87411, the *aadA* gene is present in the vector backbone used for transformation (see table 1). This is a gene encoding an antibiotic resistance marker (ARM) gene providing resistance to the antibiotics spectinomycin and streptomycin. The AadA gene is ranked by the EFSA GMO Panel (2004) as a class II antibiotic resistance, hence only recommended for use in restricted field trials with a view to the theoretical transfer of this gene to micro-organisms.The summary of the technical dossier do not give an overview of the analysis for the presence or absence of this gene.

However, in the safety assessment made by FSANZ (Safety Assessment Report on MON87411), where they have been able to see the full construct and dossier, they say that no ARM gene is present in corn line MON87411 and that:

> "the insert sequence analysis…showed no plasmid backbone has been integrated into the MON87411 during transformation , i.e. the aadA gene which was used as a bacterial selectable marker…".

Thus, it seems like the ARM gene is not present.

Herbicide tolerance traits

Herbicide tolerant (HT) plants

Herbicide tolerant (HT) plants are specifically designed to be used in combination with herbicides, and will always be sprayed with the intended herbicide. Without spraying the introduction of HT plants would be useless. Surprisingly, these herbicides are often not tested as part of the assessment and risk evaluation of HT plants. In feeding studies with HT GM plants for quality assessment the herbicide is systematically overlooked, which represents a serious knowledge gap in the testing and risk evaluation.

Glyphosate containing herbicides

Since the purpose of the *cp4 epsps* (infers glyphosate tolerance) is to treat the maize crop with glyphosate based herbicides, we find it disconcerting that the presence of the herbicide has not been considered in the comparative assessment nor the toxicological assessment.

A recent study found that glyphosate and AMPA accumulated in soybeans (Bøhn et al., 2014), highlighting the importance of including the herbicides in the comparative and toxicological assessment of GM crops with herbicidal co-technology.

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 (Dill et al., 2010, Cuhra et al., 2013). There have been reports on negative effects in terrestrial and aquatic ecosystems (Blackburn and Boutin, 2003, Solomon and Thompson, 2003). Studies in animals and cell cultures have indicated that there could be health implications from exposure to glyphosate (Axelrad et al., 2003, Benachour et al., 2007, Cuhra et al., 2013). 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.
The best-known glyphosate-based herbicides (GBH) products are the Roundup products that contains additional chemicals (surfactants, adjuvants). The phenomenon of higher toxicity in formulated herbicides, as compared to the active ingredient only, is documented for glyphosate-based herbicides as well as for a number of other herbicide active ingredients (Mesnage et al., 2014).

Glyphosate-based herbicides (Roundup) leads to oxidative stress, endocrine disruption and neurotoxicity in rats (Cattani et al., 2014), justifying claims of being a neurotoxic hazard also for humans (Grandjean and Landrigan, 2014, Malhotra et al., 2010). Some evidence of arrhythmic and cardiac electrophysiological changes mediated by GBH also indicate cardiovascular risk to animals and humans (Gress et al., 2015).

A recent study investigated gene expression changes in rats after long-term exposure to Roundup at very low concentrations (0.1 ppb) in the drinking water. The results showed that 263 genes from kidney and liver had a fold-change > 2, indicating liver and kidney damage and potential health implications also in other animals including humans (Mesnage et al., 2015b). A review study summarizes further evidence that Roundup at or below regulatory limits may be toxic or cause teratogenic, tumorigenic and hepatorenal effects (Mesnage et al., 2015a). Such effects can be linked to endocrine disruption and oxidative stress (Gasnier et al., 2009).

Additionally, the International Agency for Research on Cancer (IARC) recently released a report concluding that glyphosate is “probably carcinogenic to humans” (Fritschi et al., 2015).

Recommendations

- The applicant should include a full evaluation of the co-technology intended to be used with MON87411 maize, namely the use of glyphosate containing herbicides. Particular focus should be given to the accumulation of this herbicide inside the plants, particularly the parts used in food and feed production, and whether or not these levels of exposure could cause acute and/or chronic health issues. This needs to be tested in animal and feeding studies, separating the effects of the plant and the herbicide(s) by using both sprayed and unsprayed plant samples.

Toxicology and allergy of expressed proteins
From the summary of the applicaton on MON87411, the *cry3Bb1* and *cp4 epsps* proteins are tested for toxicological and allergical abilities.

Toxicology assessment is based on data on history of safe use, structural similarity to known toxins and speed of digestibility in gastrointestinal systems of mammals.
It is not clear from the summary if it is the plant version or a bacterial version of the proteins that are tested.

Allergy assessment is based on evaluations on the allergenicity of the source of the protein, structural similarities to known allergens based on amino acid sequence, and rapidity of digestion by pepsin.

Here, it is also no clear if it is the plant or a bacterial version of the proteins that are tested.

However, in the safety assessment made by FSANZ (Safety Assessment of MON87411 p.27), they claim that the *cry3Bb1* is purified from *E.coli* and subjected to testing. We have no access to the full technical dossier and can not verify this.

From our point of view, the plant version should be used for such purposes even though the concept of equivalence is proven by structure analysis (sequencing). This means that the protein that actually is expressed in the gene modified species, and derived from it, should be used due to the potential differences that can arise because of post translational differences between species, tissues and stages of development (Gomord et al 2005, Küster et al 2001).

Recommendation

- We strongly encourage the Applicant to use plant-derived proteins for analysis of allergy and toxicology due to the potential translational differences between prokaryotic and eukaryotic cells.

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). 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. The NGTA, with its clauses on societal utility and sustainable development, comes into play with a view also to health, environmental and socio-economic impacts in other countries, such as where the GMOs are grown. In the following we identify areas that are relevant to consider in order to assess social utility and sustainability aspects, and highlight information needed to properly assess these issues.

Socio-economic impacts

Very few studies take a comprehensive view of social impacts associated with GM crops in agriculture (Fisher et al. 2015). Reviews on social and economic impacts from GM crop cultivation (e.g. economic gains, distribution of benefits, access to seeds and improved wellbeing) relevant for a sustainability assessment 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). Fisher et al. (2015) point to factors such as different political and regulatory contexts when explaining differences reported in distribution of economic gains and farmers' access to seeds. This underlines that it cannot be expected that the same effects will apply between different social and environmental contexts.

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. The MON 87411 maize has not yet been approved for cultivation in a third country. A proper evaluation of potential social impacts of relevance to sustainability can therefore not be completed until this event has been approved for cultivation in a third country, so that information relevant for the socio economic impacts assessment in the producing country(ies) can be provided (e.g. impacts among poor and/or small-scale farmers in developing countries and share of the benefits among sectors of the society).

Resistance development towards the Bt-toxin in target pest population
Widespread cultivation of Bt plants places intense selection pressure on target pest populations to evolve resistance, and this is recognized as an important factor that may cut short benefits of Bt maize. The MON 87411 maize confers resistance to certain coleopteran pests (*Diabrotica spp*.). Gassmann et al. (2011, 2012, 2014) have reported on field-evolved resistance to Cry3Bb1 by the western corn rootworm (Diabrotica virgifera virgifera). It seems likely that the SNF7-subunit is inserted in the MON 87411 maize to strengthen its resistance to *Diabrotica spp*. Still, evaluation of the efficiency of this RNAi-based control method and how it affects target pest larval development is very important in order to understand to what extent this approach will strengthen the durability of the MON 87411 maize resistance to *Diabrotica spp*. Additionally, evaluation of resistance development within the target pest population and strategies suggested to halt this development, is crucial in a sustainability assessment.

Impacts of the Bt-toxin on non-target organisms
Larva of *Diabrotica spp.* feeds on the roots of the maize plants, and the Cry3Bb1gene is therefore expressed in the roots of the maize plant. Hence, it is particularly important to investigate impacts on non-target soil-living organisms. A study performed by Neher et al. (2014) investigated impacts of coleopteran-active Bt corn on non-target nematode communities in soil and decomposing corn. Their results support the hypothesis that Bt corn does not affect adversely non-target soil nematodes in the rhizosphere and decaying roots. Similarly, Svobodová et al. (2015) did not detect any detrimental environmental effects when investigating impacts on above-ground arthropods in fields with GM maize resistant to *Diabrotica spp*. in the Chez republic. There are however a growing number of studies and reviews that indicate potential harm from Bt toxins to a range of non-target organisms (Holderbaum et al., 2015; Marvier et al. 2007; Rosi-Marshall et al. 2007; Bøhn et al. 2008; Bøhn et al. 2010). Further studies on impacts on non- target organisms present in producing country(ies), particularly soil living organism, is therefore needed.

Environmental and health impacts of the co-technology: glyphosate
The evaluation of the co-technology, that is, secondary products that are intended to be used in conjunction with the GMO, is also 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 MON 87411 maize confers tolerance to herbicides containing glyphosate. Recent studies have shown negative effects from glyphosate, both on species present in terrestrial and aquatic ecosystems and on animals and cell cultures. Consequently, glyphosate is now increasing recognized as more toxic to the environment and human health than what it

was initially considered to be (for further elaboration and references on these issue see section on p.13).

Glyphosate resistant weeds in maize is vastly documented globally[1], and it is documented that the introduction of glyphosate tolerant GM plants has led to an increase in the use of glyphosate (Dill et al. 2010). Moreover, studies has shown increased levels of glyphosate residues in glyphosate tolerant GM crops (Bøhn et al. 2014). This could have health impacts on humans and animals consuming food/feed based on ingredients from this type of GM plants.

The Applicant should provide information on the contribution of the MON 87411 maize to the emergence of glyphosate resistance in weeds, management strategies to prevent herbicide resistance development in weeds, and if there are already cases of this in the areas intended for cultivation of the variety. In order to evaluate changes in the use of glyphosate, after the introduction of MON 87411 maize, more information about the use of these herbicides in the producing country(ies) are 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. For instance, Binimelis (2008) have investigated consequences on co-existence of Bt maize in Spain among small-scale farmer and has found that co-existence is very difficult and that farmers in some areas has given up growing non-GM maize. Information about the strategies adopted to ensure co-existence with conventional and organic maize production and potential consequences for these production forms in the producing country(ies) is required for an assessment of social and economic impacts in the producer country. Additionally, an evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies is important for a sustainability assessment.

Assessment of alternatives

It is also important to evaluate whether alternative options (e.g. the parental non-GM version of the MON 87411 maize) may achieve the same outcomes in a safer and ethically justified way. Furthermore, in order to evaluate whether the MON 87411 maize contributes to social utility, it is important to consider current and future demand for this GM maize product for food, feed and processing purposes in Norway and to what extent this demand is/can be satisfied by existing sources. GM maize accounts for approximately 30% of the current global maize production (www.GMO-compass.org). Non-GM maize is therefore abundant for importation to the Norwegian market and the MON 87411 maize can therefore not be considered to meet a societal need or demand.

[1] http://weedscience.org/summary/crop.aspx

Recommendation

- 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 the MON 87411 maize and its contribution to sustainable development. The information provided by the Applicant must be relevant for the agricultural context in the producing country(ies). The information should include issues such as: development of resistance in target pest populations, impacts on non-target organisms, changes in pesticide use, emergence of herbicide resistant weeds, potential for gene flow and possible impacts among farmers practicing different production forms for maize cultivation in the producing country(ies), possible impacts among poor and/or small-scale farmers in producing countries and share of the benefits among sectors of the society.

Conclusion

The applicant does not attempt to identify socio-economic implications, nor demonstrate a benefit to the community and a contribution to sustainable development from the use of the MON 87411 maize and does therefore not provide sufficient information as required by the NGTA.

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