GenØk - Centre for Biosafety

Vår ref:2014/h116
Deres ref: 2014/3727

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 05.05.14

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på høringen av søknad **EFSA/GMO/NL/2013/116** som gjelder mat, fòr, import og prosessering av genmodifisert soya **DAS-81419-2** produsert av Dow AgroSciences LLC.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Vår ref:2014/h116
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Assessment of the technical dossier submitted under EFSA/GMO/NL/2013/116 for approval of DAS-81419-2 soybean grain

Sent to

Norwegian Environment Agency

by

GenØk- Centre for Biosafety
May 2014

KONKLUSJON PÅ NORSK

Vi trekker frem mangler i dossieret som ikke gir grunnlag for en konklusjon om sikker bruk, samfunnsnytten og bidrag til bærekraftighet av **DAS-81419-2 soya.** Søker har ikke inkludert noe av den informasjonen omkring samfunnsnytten og bærekraftighet til **DAS-81419-2 soya** 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 høring som omfatter **DAS-81419-2 soya** for bruksområdet dyrkning.

Søker gir ikke opplysninger som adresserer vurderingskriteriene bærekraft, samfunnsnytten 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 søknaden om omsetting **DAS-81419-2 soya** til import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra **DAS-81419-2 soya**.

Vår konklusjon er at norske myndigheter ikke godkjenner bruk av **DAS-81419-2 soya** for mat for import og prosessering som det søkes om.

SUMMARY OF THE ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/NL/2013/116

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 **DAS-81419-2 soybean**, 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 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 address the potential of non-target effects of Bt toxins

- 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 state the minimum level above which the expressed proteins are undesirable and what comparators are used.

- The regulator is encouraged to ask the Applicant to explain the implications of the *Cry1Ac* partial fragments and the deletion of parental locus in the light of the assumed substantial equivalence to the parental comparator.

- The regulator is encouraged to ask the Applicant to use the real plant versions of the proteins for the safety assessments as plants and bacteria differ in their post-translational processing of proteins. This should be considered and further analysed.

- The regulator is encouraged to ask the Applicant to analyze for other meaningful post-translational modifications. If glycosylation is the only PTM relevant for risk assessment, it should be clearly stated in the dossier.

- The regulator is encouraged to ask the Applicant to also analyze the entire soybean proteome for PTMs.

- The regulator is encouraged to ask the Applicant to also include molecular weight markers on gels for size determination.

- The regulator is encouraged to ask the Applicant to provide more recent/updated data for the proteolytic cleavage of synpro *Cry1Ac* and *Cry1F* proteins.

- The regulator is encouraged to ask the Applicant to perform repeated dose toxicity studies with the exact versions of the synpro proteins applied for in this application and not refer to data from old and sequencence wise potentially different Cry proteins.

- The regulator is encouraged to ask the Applicant to perform acute oral toxicity studies with the actual synpro proteins in combination and also a whole GM plant feeding study as these proteins are expressed in a new context.

- The regulator is encouraged to ask the Applicant to be clear on whether the homology to known allergens are checked for the Cry protein parts derived from the subspecies of *Bacillus Thuringiensis*.

- The regulator is encouraged to ask the Applicant to submit required information on the social utility of **DAS-81419-2 soybean** 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 DAS-81419-2 soybean**. 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 **DAS-81419-2 soybean**, we conclude that based on the available data supplied by the Applicant, the Applicant has not substantiated claims of environmental safety satisfactorily or provide the required information under Norwegian law to warrant approval in Norway at this time.

ASSESSMENT OF THE TECHNICAL DOSSIER RELATED TO EFSA/GMO/NL/2013/116

About the event

The genetically modified **DAS-81419-2 soybean** was developed through *Agrobacterium*-mediated transformation of soybean cotyledonary explants.

The genetic modification intended to be inserted was a *cry1F, cry1Ac, and pat.* The *cry1AFv3* expression cassette is designed to express a synthetic version of the *cry1AF* protein. The *cry1Ac*(synpro) expression cassette is designed to express a synthetic version of the *Cry1Ac* protein. Both the presence of *cry1F* and *cry1Ac* confers resistance against certain *Lepidoptera* pests. The presence of *pat* confers tolerance against glufosinat-ammonium.

The Applicant is requesting the authorization for food, feed, import and processing in the EU of glyphosate tolerant **DAS-81419-2 soybean**.

Assessment findings

Glufosinate-ammonium

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 glufosinat 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.

The soybean DAS-81419-2 is tolerant to the active herbicide ingredient glufosinate-ammonium through the insertion of the *pat* gene, but it is not portrayed as such in the dossier. The tolerance to a herbicide in general is connected to heavier use, and in most cases biotransformation of the herbicides active ingredient to another compound which should also be evaluated for toxicity. Though the mechanism of PAT is described in the dossier, the food and feed safety and toxicology testing, of the references to such tests in other transgene plants has been done without considering the effects of applying glufosinate to the plants.

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.

Safety of Cry genes

DAS-81419-2 soybean combines two different classes of Bt proteins named Cry toxins (*Cry1F and Cry1Ac*). These toxins are claimed and believed to be safe, however the potential of non-target effects of Bt toxins concerning mode of action have been addressed (Gilliand et al 2002, Crickmore 2005, Hilbeck and Schmidt 2006, Mesnage et al, 2012). A review by (Hilbeck and Schmidt 2006) on all Bt-plants found 50% of studies documenting negative effects on tested invertebrates.

In relation to non-target and environmental effects, in two meta-analyses of published studies on non-target effects of Bt proteins in insects, (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. A review by (Hilbeck and Schmidt 2006) on all Bt-plants found 50% of studies documenting negative effects on tested invertebrates.
Another quantitative review by (Marvier et al. 2007) suggested a reduction in non-target biodiversity in some classes of invertebrates for GM (Bt) cotton fields vs. non-pesticide controls, yet found little reductions in biodiversity in others. More recent research on aquatic environments has sparked intense interest in the impact of Bt-crops on aquatic invertebrates *Daphnia magna* (Bøhn et al. 2008), and caddisflies (Rosi-Marshall et al. 2007). These publications warrant future study, given the potential load of novel target proteins that may end up in agricultural runoff and end up in aquatic environments. Further, (Douville et al. 2007) present evidence of the persistence of the transgenic insecticidal protein *Cry1Ab* in aquatic environments and suggest that that sustained release of this potently bioactive compound from Bt maize production could result in negative impact on aquatic biodiversity.
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, Obrist et al. 2006) is, however, yet to be firmly established. 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), and may have indirect effects on recipient populations, and, given the key-stone role of bees as pollinators, on both primary production and on entire food-webs.
In relation to health impacts, a publication by (Dona and Arvanitoyannis 2009) reviews 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 on many fronts, exposure duration many have not been long enough to uncover important effects. Studies should also include subjects with immunodeficiency or exposed to other stress agents.
Indications of harm to non-target organisms in the environment, and possible impacts to human and animal health prompted the Austrian Authorities to invoke a safeguard clause to ban the use of Cry1Ab-containing maize even MON810 (Umweltbundesamt, 2007). We refer to this report as a detailed analysis of potential adverse effects from a *Cry1Ab*-producing GMO.

Recommendation: The regulator is encouraged to address the potential of non-target effects of Bt toxins

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, deSchrijver et al, 2007). 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 soybeans. 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 effects? (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

2.2.3 Information on the expression of the inserted/modified sequence
Expression levels of inserted sequences of *Cry1Ac*, *Cry1Fv3* and *PAT* were analyzed in soy grain using ELISA. The applicant is not stating whether the level of expression is good / sufficient for the different proteins.

Applicant states "In addition, expression levels of the newly expressed proteins, *Cry1Ac*, *Cry1F* and *PAT*, were characterized and presented a relatively low SD across sites" (page 76), but did not state level of the insert gene product that is undesirable or the standard used as a comparator.

Recommendation: For meaningful risk assessment the Applicant should state the minimum level above which the expressed proteins of are undesirable; the Applicant should also state what comparators are used.

2.3: Conclusions (Page 76) and Table 5 (Page 70)

(1) The conclusion on the bioinformatics analysis of the flanking boarder sequences is limited to linear sequence comparisons. This will not reveal all possible potential similarity in structure and function known allergenic or toxic proteins because only sequence identity and not similarity was reported.

(2) The conclusion that "Based on the above, no unintended changes were identified" (second paragraph, Page 76), overlooks that inserted partial fragments of cry1Ac as well as the deletion of 57 bp of parental locus (see Page 69), can constitute unintended effects.

Recommendation:

- Sequence similarity data should also be reported alongside sequence identity data
- Applicant should explain the implications of the Cry1Ac partial fragments and the deletion of parental locus in the light of the assumed substantial equivalence to the parental comparator.

4. Toxicological assessment
The toxicological assessment of proteins *Cry1Ac*, *Cry1Fv3* and *PAT* are based on the biochemical characterizations (mode of action, heat lability, equivalence to microbially derived protein used in toxicity studies) and toxicology (history of safe use, amino acid sequence comparisons, bioinformatics and toxicity to mammals).
The applicant refers to prior risk assessment of these proteins expressed in a GM cotton called WideStrike (EFSA, 2010d in the dossier).

The Cry1Ac (synpro) protein is composed of residues from *Cry1Ac1* (synthetic version of insect active part from *Bacillus thuringiensis* subsp.*kurstaki* HD73, residues 1-612) and C-

terminal domains from Cry1Ca3 (residues 613-648 from *Bacillus thuringiensis* subsp.*aizawai* PS81I) and Cry1Ab1 (residues 649-1156 from from *Bacillus thuringiensis* subsp.*berliner* 1715). The protein consists of different parts from different Cry proteins, but is referred to as *Cry1Ac* only, as the other parts are "approximately those removed by alkaline proteases in the lepidopteran midgut during formation of the active *Cry1ac* core toxin "and is the primary determinant against insect activity.
The Cry1F protein is also a synthetic version of the *Cry1F*, consisting of different parts from different subspecies of *Bacillus thuringiensis*.
The PAT protein was derived from *Streptomyces viridichromogenes*.
For the toxicological assessments, the microbial version of these proteins is used and not the plant derived ones.

Recommendation: It is recommended that the Applicant should use the real plant versions of the proteins for the safety assessments as plants and bacteria differ in their post-translational processing of proteins. This should be considered and further analysed.

4.2 Equivalence of microbially-derived proteins to DAS-81419-2 Soybean expressed proteins.

The statement in the 2nd paragraph, line 6 "There was no evidence of any post-translational modifications (PTMs) (i.e. glycosylation) of the DAS-81419-2 Soybean-derived Cry1F protein" is misleading because only glycosylation was determined. Applicant did not analyze for other post-translational modifications. In addition, only the expressed protein was checked for PTMs. The entire proteome of the plant was not analyzed for potential PTMs.
This also applies to the Cry1Ac and PAT proteins also .

The SDS-PAGE gel on p.161 in the dossier with microbial and plant version of the *Cry1F* protein lack molecular weight marker for the glycoprotein stained gel. This is also the case for the SDS-PAGE gel with the different versions of *Cry1Ac* (p.179). It is thus difficult to interpret sizes of proteins.

Also, the Applicant refers to Gao et al 2006 for the data on Western blot analysis. It is unacceptable that data generated in 2006 with a near obsolete mass spectrometry would be presented in 2013 to support risk assessment of a transgenic plant meant for human consumption.

The unidentified peptides found in the MS spectra for *Cry1F* and *Cry1Ac* protein should have been discussed for potential biological relevance. The Applicant states that these peptides do not indicate that the protein is different from the predicted amino acid sequence: however, no data are provided to support this statement.

The *PAT* protein has been assessed at several occasions previously. The figure text of figure 56 in the dossier (p.194) states that the molecular weight markers used in the western blot with microbial and plant version of the protein was applied AFTER the development of the film. This can cause mistakes and it is recommended to use pre-stained/labeled markers that

are following the whole development process. The bands with nonspecific binding should have been further analyzed by MS for protein identification.

Recommendation:

- The Applicant should analyze for other meaningful post-translational modifications. If glycosylation is the only PTM relevant for risk assessment, it should be clearly stated in the dossier.
- The Applicant should also analyze the entire soybean proteome for PTMs.
- The Applicant should also include molecular weight markers on gels for size determination.
- The Applicant should use plant version of the protein for the risk assessments.

The proteins are subjected to heat and pH treatment and proteolytical cleavage. For the proteolytical cleavage data the Applicant refer to data from 2001. Newer data should have been provided with the synpro proteins used in this event of soy. It cannot be assumed from the text whether this is the case.

Synergistic effect of microbial version of *Cry1Ac* and *Cry1F* was not found by the analysis performed.

No repeated dose toxicity studies were performed due to the data provided on equivalence, history of safe use, no additive/synergistic/antagonistic effects or structural similarities to proteins with adverse effect on health. However, this should have been done due to the old references used on other versions of these proteins (seemingly) and the fact that the Cry proteins are made with sequences from different subspecies *of Bacillus Thuringiesis*.
Acute oral toxicity data lacks the combination of the transgenic proteins for evaluation of acute oral toxicity and a whole food/feed study with the whole GM plant is not provided as the Applicant does not find it necessary. This should have been performed as this stacked soy event with the synpro Cry proteins are meant for human as well as animal consumption.

Recommendation:

- The Applicant should provide more recent/updated data for the proteolytic cleavage of synpro *Cry1Ac* and *Cry1F* proteins.
- The Applicant should perform repeated dose toxicity studies with the exact versions of the synpro proteins applied for in this application and not refer to data from old and sequencence wise potentially different Cry proteins.
- The Applicant is encouraged to perform acute oral toxicity studies with the actual synpro proteins in combination and also a whole GM plant feeding study as these proteins are expressed in a new context.

5. Allergenicity assessment

Biochemical characteristics of the potential allergens were analyzed and the safety of donor organisms, homology to known allergens and simulated gastric fluid analysis were performed.

B. Thuringiensis is not considered allergenic. As the Cry proteins in this soy stack is made of sequences from different subspecies of *B. Thuringiensis*, the statement from the Applicant is thought to cover all subspecies involved. This is however not stated clearly in the dossier.
The *PAT* protein (with gene derived from *S. viridochromogenes*) is also not considered as an allergenic source.
No amino acid sequence homology was found between these proteins (*Cry1Ac*, *Cry1Fv3*, *PAT*) and allergenic proteins. The proteins were rapidly digested in simulated gastric fluid at pH 1.2. No other pHs were tested.

Recommendation: The Applicant should be clear on whether the homology to known allergens are checked for the Cry protein parts derived from the subspecies of *Bacillus Thuringiensis*.

5.2 2-D SDS-PAGE and Western Analyses

Images of the 2-D gels prior to being probed with sera were not presented so it was difficult to compare the separation pattern with the cross-referenced (Natarajan et al 2005). Nonetheless in the present gels of Figure 57, the following issues need to be addressed:

The 2D-Gels should be interpreted both in terms of pattern and intensity. Applicant interpreted gels only in the context of pattern. Additionally, specific issues observed in the gels are presented below:

1. Gels of Serum 20770-MH
   Pattern and intensity of protein spots are variable: some spots that are present in the transgenic plants are absent in the non-transgenic plants
2. Gels of Serum 22734-JL
   Some spots are present in the transgenic plants that are absent in the control
3. Gels of Serum 23736-M
   Intensity of spots are variable between transgenic and control plants. Spot intensity is weak in transgenic compared to control
4. Gels of Serum 23508-JK
   Some spots that are present in transgenic are absent in control plants. Also intensity of spots is variable
5. Gels of Serum 23450-SM
   There are clear higher spot intensity between the control non-transgenic and the transgenic plants

Recommendation: Variability in gel patterns and protein spots intensity indicate differential reaction to allergenic sera. In the light of the different patterns and protein spots intensity highlighted above, the Applicant should, using LC-MS/MS, identify the spots that are present in one but absent in the other gel. Spots of different intensities should also be identified using LC-MS/MS. Identified proteins should be checked in the database to rule out that they are not allergens or toxins. In addition, peptides of identified proteins should be analyzed for post-translational modifications.

5.3 Adjuvanicity

It is stated by the Applicant that the low levels of *Cry1F, Cry1Ac and PAT* and rapid digestibility etc is considered to be evidence for no potential as adjuvants. From the literature, various concentrations of adjuvant proteins show different effects. 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 two Cry-proteins. No published data on adjuvance effects of *Cry1F* is available.

In a report from the Norwegian Scientific Committee for Food Safety (VKM) on health risk assessment related to the adjuvant effects of Cry proteins from GM food, plants and fodder (VKM Doc no 11-313-4, 2012) they comment on the adjuvant effects seen by some Cry proteins. These studies are 10-15 years old. Nevertheless, the awareness of these potential effects are emphasized. The new, combined synpro proteins have seemingly not been analyzed for their adjuvance potentials. Thus, this must be taken into consideration and new experiments with the synpro Cry proteins should be performed in order to verify whether the adjuvant effects of *Cry1Ac* has changed as a result of the sequence changes.

Recommendation: The Applicant should consider the potential adjuvant effects of the Cry proteins involved due to previous literature on especially Cry1Ac and the changes made in the sequences of the synpro Cry proteins through experimental approaches.

Persistence and invasiveness

Although current experience and circumstances can lead to the conclusions that the conventional and domesticated soybean has little or no potential to persist in the agricultural environment or natural habitats of Europe it is important to consider the impact that insect tolerance could have on the survival of accidentally spilled grain and possible hybrids. Insect tolerance is a competitive advantage, as long as the cost to other important traits is not too negatively affected (fecundity, growth). Both insect tolerant sunflower and rapeseed hybrids have been shown to have a selective advantage in competition with their wild counterparts, particularly under high insect pressure (Vacher, 2004, Snow, 2003). Although there are no current relatives in Europe with which the DAS-81419-2 soybean could interact, global warming is affecting the distribution of plant species and it is possible that in the future wild relatives could establish in Europe, through natural migration from Asia or human activites (Walther, 2002). From Asia it is known that domesticated and wild soybean hybridize easily if given the opportunity (Nakayama, 2002).

Recommendation: The Applicant should submit information regarding the potential of wild relatives of the domesticated soybean to establish themselves in Europe in the future, considering the impact of climate change and possible pathways of introduction. Also, the selective advantage of insect tolerance has been studied in other genetically modified crops, but not in soybean. A study should be performed evaluating if there is a selective advantage (and possibly under what circumstances) when outside agricultural context.

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 represents 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 Applicant has not provided relevant information that allows an evaluation of the issues laid down in the aim of the Act, regarding ethical values and social justification of the GMO within a sustainable development. The applicant only states: "*Commercialisation of DAS-81419-2 will therefore provide substantial benefits to growers by limiting yield losses from insect pressure*" (Part VII of the dossier, Summary, p. 10). However, there is no data supporting this potential benefit for producers. Given this lack of necessary information for a socio-economic evaluation, the Applicant has not demonstrated a benefit to the community nor a contribution to sustainable development from the use of **DAS-81419-2 soybean**. The Applicant should thereby provide the necessary data in order to conduct a thorough assessment on these issues, or the application should be refused.

Further, 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. In this case, the Applicant states that applications for the full range of uses (including cultivation) have been send to USA, Canada and Argentina, and that additional applications for commercialization are being prepared for Brazil, Mexico, Colombia, South Africa, Japan, Republic of Korea, Taiwan and Philippines. Although the literature concerning the socio-economic aspects related to the cultivation of GM soybeans in these producing countries is extense, the Applicant does not mention any of these references, nor there is an attempt to identify how **DAS-81419-2 soybean** might contribute to sustainability and social utility (neither in the producing countries nor in Norway or Europe).

A recent article by Leguizamón (2013) analysing the contribution of GM soy in Argentina from the socio-economic (i.e. labour and rural depopulation, agricultural deskilling, distribution of land, protection of indigenous and small peasant communities, increase of violence related to landgrabs, herbicide-sprays over rural populations or food sovereignty) and environmental perspectives (i.e. expansion of the agrocultural frontier, deforestation, biodiversity, nutrient depletion and soil structure degradation), concludes that although the massive adoption of GM soy has provided important economic revenues, "*the GM soy-based agro-export model as currently configured in Argentina is a socially and ecologically unsustainable model of national development*". Although there is an important controversy, similar conclusions have been also reached by other authors for the case of Argentina or

Brazil (see e.g. Austin, 2010; Binimelis et al., 2009; Catacora-Vargas, 2012; Catacora-Vargas et al., 2012; Nepstad et al., 2006; Ortega et al., 2005; Pengue, 2005; Richards, 2010).

On the sustainability of the product and co-technology, **DAS-81419-2 soybean** confers soybeans tolerance to herbicides containing glufosinate ammonium. Glufosinate-amonium is a class of herbicides that is banned in Norway and in EU (except a limited use on apples) due to both acute and chronic effects on mammals including humans (see section «herbicides»). Moreover, weed resistance to glycines in soybean cultivation has been vastly documented, including multiple resistance to glufosinate-ammomium and glyphosate in United States[1].

As this application excludes the cultivation of **DAS-81419-2 soybean** in the EU, the risk assessment is only focused on the import, processing and all other uses but does not assess the cultivation phases, and the potential impacts in the producing countries (Part VII of the dossier, Summary, p. 16). 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 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 **DAS-81419-2 soybean**) may achieve the same outcomes in a safer and ethically justified way.

Recommendation: The applicant should submit required information on the social utility of **DAS-81419-2 soybean** and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act.

[1] http://www.weedscience.org/Summary/Crop.aspx?SituationID=8

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 **DAS-81419-2** soybean 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 **DAS-81419-2 soybean** 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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