Vår ref:2017/H_115
Deres ref: 2017/3534

Høringsuttalelse av søknad om markedsføring av genmodifisert soya DAS-68416-4 x MON89788

EFSA/GMO/NL/2013/115

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Mai 2017

Vår ref:2017/H_115
Deres ref: 2017/3534

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 08.05.2017

Vedlagt er innspill fra GenØk – Senter for biosikkerhet på offentlig høring av søknad **EFSA/GMO/NL/2013/115**, genmodifisert, stablet soya DAS-68416-4 x MON89788, fra Dow AgroSciences Europe, under EU forordning 1829/2003. Søknaden gjelder bruksområdene mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Innhold/Content

Vår ref:2017/H_115
Deres ref: 2017/3534

Høringsuttalelse – genmodifisert, stablet soya DAS-68416-4 x MON89788 (EFSA/GMO/NL/2013/115) under EU forordning 1829/2003.

Søknad EFSA/GMO/NL/2013/115 omhandler genmodifisert, stablet soyalinje til bruksområdene mat, for, import og prosessering.

Den genmodifiserte soyaen har toleranse mot herbicider som inneholder glyfosat via det innsatte genet *cp4 epsps* , mot glufosinat ammonium via det innsatte genet *pat*, og mot 2,4-D via det innsatte genet *aad-12*.

Hverken den stablete soya linjen eller dens foreldrelingjer er godkjent for noen av bruksområdene i Norge.

I EU er samtlige foreldrelinjer godkjente for de omsøkte bruksområder, men ikke den stablete soyalinjen denne søknaden omhandler.

Oppsummering

GenØk–Senter for biosikkerhet, viser til høring av søknad EFSA/GMO/NL/2013/115 om DAS-68416-4 x MON89788 soya som omfatter bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra denne soyaen.

Vi har gjennomgått de dokumenter som vi har fått tilgjengelig, og nevner spesielt følgende punkter vedrørende søknaden:

- Genmodifisert soya DAS-68416-4 x MON89788 er ikke godkjent i Norge eller EU for noen av de omsøkte bruksområdene.
- Foreldrelinje MON89788 er godkjent for de omsøkte bruksområdene i EU.
- Genmodifisert soya DAS-68416-4 x MON89788 er tolerant mot sprøytemidler som inneholder glyfosat, glufosinat - ammonium og 2, 4-D som har ulike grader av helse- og-miljø fare ved bruk.
- Glufosinat ammonium er ikke tillatt brukt i Norge.
- Søknaden om soya linje DAS-68416-4 x MON89788 mangler data og informasjon som er relevant for å kunne vurdere kriterier rundt etisk forsvarlighet, samfunnsnytte og bærekraft.

Summary

GenØk-Centre for biosafety refers to the application EFSA/GMO/NL/2013/115 on DAS-68416-4 x MON89788 soy for import, processing, food and feed or ingredients thereof.

We have assessed the documents available, and highlights in particular the following points for the current application:

- The gene modified soy event DAS-68416-4 x MON89788 is not approved for any application in Norway or the EU.
- Parental event MON89788 is approved for food, feed, import and processing in EU.
- Soy event DAS-68416-4 x MON89788 is tolerant to herbicides containing glyphosate, gluphosinate ammonium and 2, 4-D that has distinct health and environmental dangers upon use.
- It is not allowed to use gluphosinate ammonium in Norway.
- The application on soy event DAS-68416-4 x MON89788 lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.

Application on EFSA/GMO/NL/2013/115

The stacked event DAS-68416-4 x MON89788 soy contains genes providing herbicide tolerance *(cp4 epsps*, *pat and aad-12*).

Previous evaluations

The Norwegian Scientific Committee for Food Safety (VKM) has commented on the application for the parental, single event soy DAS-68416-4 (EFSA/GMO/NL/2011/91) (1) with a preliminary risk assessment related to health and environment with the following issues:

- Due to limitations in the feeding experiments performed by the Applicant and their quality, it is not possible to perform a complete risk assessment related to health and environment according to the intended use in EU, health and environmental regulations in the Food Act (https://lovdata.no/dokument/NL/lov/2003-12-19-124) (Lov om matproduksjon og mattrygghet,(Matloven)) and the Norwegian gene technology act ((NGTA), (Genteknologiloven)) (2) or demands in EUs directives 1829/2003 or 2001/EU.
- The feeding experiment performed (on broiler) is with soy that is not sprayed with the actual herbicides intended for use on this event.
- It is asked for analysis of herbicide residues, and their metabolites, in the soy.
- A 90 day subchronic analysis is asked for, as well as feeding studies on relevant fish (salmon) to perform analysis of toxicity on farmed fish.

VKM has evaluated the parental, single event MON89788 (EFSA/GMO/NL/2006/36) (3) in 2015 in a final health and environmental risk assessment where they commented on the following issues:

- The molecular characterization did not reveal any safety concerns.
- The soy event MON89788 is equivalent to its conventional counterpart, with the exception of the introduced trait.
- There is no increased likelihood of establishment of this event in Norway and do not represent any environmental risk.

GenØK has previously commented the parental, single events DAS-68461-4 and MON89788 alone and in combinations (stack) in previous hearings (http://genok.no/radgiving/horingsuttalelser/).

In the assessment EFSA/GMO/NL/2016/135 on MON87708 x MON89788 x A5547-127 (2017) soy, the following comments were made to the application that also accounts for the present application:

- *Soy event MON87708 x MON89788 x A5547-127 is tolerant to herbicides that has distinct health and environmental dangers upon use.*

- *It is not allowed to use gluphosinate ammonium in Norway.*
- *The application on soy event MON87708 x MON89788 x A5547-127 lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.*

In the assessment EFSA/GMO/NL/2015/126 (2016) soy, the following comments were made, that also accounts for the present application:

- *The Applicant should include a full evaluation of the co-technology intended to be used with MON87705 x MON87708 x MON89788. Particular focus should be given to the level of accumulation of herbicides in 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.*
- *The Applicant should look into and compare the levels of herbicide residues in the plants in order to provide an improved comparative assessment. The health implications (if any) of the herbicide residue exposure to humans and animals should subsequently be discussed in the toxicological assessment. The toxicological assessment should also include a section on farm worker exposure to the herbicide.*
- *The Applicant should use herbicide treated, as well as untreated plant material in long-term chronic exposure feeding studies.*
- *The environmental risk assessment should include a section on the potential environmental effects of the herbicide (monitoring changes in use, potential drift into surrounding areas and ecosystems, leaching to aquatic environments, potential effects on wildlife).*
- *We encourage the Applicant to investigate the deletions and insertions in the transgenic stacks insertion sites, to verify potential changes by using sequence alignment analysis.*
- *We encourage the Applicant to specify the source of DMO and EPSPS proteins used for safety analysis, also in the summary of the technical dossiers.*
- *We encourage the Applicant to perform allergenicity analysis of proteins isolated from the whole stack.*
- *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 MON87705 x MON87708 x MON89788 soy and its contribution to sustainable development. The information provided by the Applicant must be relevant for the agricultural context in the producing country/countries. The information should include issues such as: herbicide resistance in weed populations, co-existence consequences and possible impacts among poor and/or small-scale farmers in producing countries and share of the benefits among sectors of the society.*

In the assessment EFSA/GMO/NL/2011/100, MON87705 x MON89788 (2013) soy, we had the following comments that can account for the present application:

- *The Applicant should demonstrate the lack of interactive effects between transgenic proteins through proper scientific testing and evidence gathering.*

- *Most of the information submitted in this safety assessment is derived from previous finding with the single lines. Stacked events should not be approved based on the information on the single events but on the actual event.*
- *The Applicant should submit required information on the social utility of MON87705xMON89788 and its contribution to sustainable development, in accordance with the Norwegian Gene Technology Act*

In the assessment EFSA/GMO/NL/2012/108 on MON87708 x MON89788 (2013), we had these comments to the Application that also will account for the present application:

- *Data should be provided for evidence of lack of combinatorial effects arising from the expression of stacked proteins.*
- *Evaluate the environmental consequences from the use of multiple herbicides in the same plant.*
- *Long term feeding studies of the whole plant before release on the market.*
- *What is the fate of the herbicide residues?*
- *The antibodies used should be specified in order to detect all in-planta forms.*
- *Microbial versions of the proteins were used for the safety assessments.*
- *Toxic potential should be analyzed by repeated dose toxicity studies.*
- *Data from the stack itself should be the basis of identification of the transgenic proteins, rather than conclusions made in the single, parental lines.*
- *Data on glycosylation status of the transgenic proteins should be provided for the allergenic risk assessment.*

In the assessment EFSA/GMO/NL/2009/73 on MON87701 x MON89788 (2010) soy, we had these comments that can account for the present application:

- *Based on data available there are knowledge gaps related to the risk for the health and environment by MON87701 x MON89788. These knowledge gaps are related to potential effects by the combinations or synergistic effects by the inserted transgenes.*

Social utility and sustainability issues on the stacked soy event DAS-68416-4 x MON89788, EFSA/GMO/NL/2013/115

In Norway, an impact assessment follows the Norwegian Gene Technology Act (NGTA) (2) in addition to the EU regulatory framework for GMO assessment. In accordance with the aim of the NGTA, the development, introduction and/or use of a GMO needs to be *ethically justifiable*, demonstrate a *benefit to society* and contribute to *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*" (See section 17 and annex 4 for more detail on the regulation on impact assessment). Recent developments within European legislation on GMOs allow Member States to restrict the cultivation of GMOs on their own territory based on socio-economic impacts, environmental or agricultural policy objectives, or with the aim to avoid the unintended presence of GMOs in other products (Directive 2015/412) (4). Additionally, attention within academic and policy spheres increased in recent years on broadening the scope of the assessment of new and emerging (bio) technologies to include issues that reach beyond human and environmental health (5-10).

To assess the criteria of *ethically justifiable*, *benefit to society* and *sustainability* as in the NGTA, significant dedication is demanded as it covers a wide range of aspects that need to be investigated (e.g. Annex 4 within the NGTA, or 11). Nevertheless, the Applicant has currently not provided any information relevant to enable an assessment of these criteria. Therefore, this section will highlight some areas that are particularly relevant to consider with soy DAS-68416-4 x MON 89788 and where the Applicant should provide data for in order to conduct a thorough assessment according to the NGTA. Table 1 offers specific questions connected to the sections below.

It should be noted that the information provided by the Applicant on page 5 is outdated. The Applicant specifies that *"Notification of intent to commercialize DAS-68416-4 × MON-89788-1 has been sent to Canada (Canadian Food Inspection Agency), with approval expected by April 1, 2013. Additional applications for food and feed use are being prepared for Mexico, Columbia, South Africa, Japan, Korea, Taiwan, Philippines, and will be submitted throughout 2013 and 2014."* This information is not updated nor consistent with chapter 14 (page 25). It is worrying that the Applicant has made such a mistake and makes us doubt the adequacy and care taken to perform and document its assessment and evaluation of soy DAS-68416-4 x MON 89788.

Sustainability

The soy DAS-68416-4 x MON 89788 contains a modified *cp4 epsps* gene that confers increased tolerance to herbicides that contain glyphosate. Recent studies have shown negative effects from glyphosate, both on species present in terrestrial and aquatic ecosystems and on animals and cell cultures (for further elaboration and references on this issue see p. 18-19) as well as in villages in areas where glyphosate is systematically used as part of the GM crops tolerance to glyphosate (12). Consequently, glyphosate is now increasingly recognized as more toxic to the environment and human health than what it was initially considered to be. This is particularly a concern as the introduction of glyphosate tolerant GM crops has led to an increase in the use of glyphosate (13-16). As soy DAS-68416-4 x MON89788 is genetically modified to possess a gene that provides glyphosate tolerance, this crop could potentially further increase the use of glyphosate as a higher amount of glyphosate will not affect soy DAS-68416-4 x MON89788. An increase in the resistance and use of glyphosate is in contrast to a contribution to sustainable development and therefore an important aspect the Applicant should provide information on, for example by mentioning the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate.

Herbicide-resistant genes

When an herbicide - such as glyphosate – is used in agriculture, it is important to minimize the potential of weeds becoming resistant. Indeed, when crops are engineered to be herbicide tolerant in order to maintain an agricultural practice that uses herbicide, it is essential to remain attentive to the amount of herbicide used, the potential increase of use and the consequences of this for the area in which the crop is cultivated. The development of management strategies to make sure that this does not create (more) resistant weed is warranted to be able to respond to a potential increase in weed-resistance. Moreover, studies have shown increased levels of herbicide residues in herbicide tolerant GM crops (e.g. 17), which could have health impacts on humans and animals consuming food/feed based on ingredients from this type of GM plants.

The Applicant has not provided information on whether the cultivation of soy DAS-68416-4 x MON89788 could affect the emergence of glyphosate resistance in weeds, nor if there are cases of this in the areas intended for cultivation of the variety, which are also important aspect to evaluate the ethical justifiability. Furthermore, this soy is cultivated in Canada and Japan, where glyphosate resistant weeds have increased significantly, especially in Canada[1]. However, the field trials of this soy have mainly taken place in the USA, and some in Argentina and Chile. This means that none of the field trials have taken place in the countries that are cultivating soy event DAS-68416-4 x MON 89788. Although the Applicant claims that the location of these field trials provide a variety of environmental conditions, no argumentation or justification is documented how this may suffice, differ and / or relate to the sites of cultivation. Additionally, no information is currently provided by the Applicant that demonstrates reflection on how the monitoring, assessment or evaluation of the GM crop in countries where the crop will potentially be cultivated in the future is assessed, as the Applicant considers information on this not relevant because soy DAS-68416-4 x MON 89788 will not be cultivated in Europe. However, it remains an important aspect for a sustainability evaluation and thus necessary if the application is to be evaluated according to this criteria in the NGTA.

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 (18). Therefore, considerations of the co-products also warrant an evaluation of safe use and data required for such an assessment is not provided by the Applicant.

1 http://weedscience.org/Summary/Country.aspx Status of Herbicide Resistance in Canada and Japan, accessed on May the 4th 2017.

Impacts in producer countries

As already stated, the Applicant does not provide data relevant for an environmental risk assessment of soy DAS-68416-4 x MON89788 as it is not intended to be cultivated in the EU/Norway. However, this information is necessary in order to assess the sustainability criteria as laid down in the NGTA. This criteria is referring to a global context, including the contribution to sustainable development in the producing countries with a view to the health, environmental and socio-economic effects in other countries, in this case where the soy DAS-68416-4 x MON89788 is cultivated.

In addition to a lack of information, there can also be ambiguity about how scientific conclusions may be achieved. For example, it is difficult to extrapolate on hazards or risks taken from data generated under different ecological, biological, genetic and socio-economic contexts as regional growing environments, scales of farm fields, crop management practices, genetic background, interactions between cultivated crops, and surrounding biodiversity are all likely to affect the outcomes. It can therefore not be expected that the same effects will apply between different environments and across continents. This is particularly relevant to consider as field trials of the soy are not in country as its planned cultivation.

The Applicant highlights that the appearance of "volunteer" soy in rotational fields following the soy crop from the previous year is rare under European conditions. Still, an evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies is important for a sustainability assessment. Information about the occurrence of volunteers and which herbicides that will potentially be used for killing volunteers is required to evaluate potential health and environmental impacts of these.

Benefit to society

The criteria of 'benefit to society' in the NGTA should be interpreted on a national level. That means that the import of soy DAS-68416-4 x MON89788 needs to demonstrate how it will benefit Norway. However, the Applicant provides no information on this part. It is important to evaluate how GM crops in general, GM soy in particular, and Norwegian consumers value the use of GM soy in food and feed. This information will contribute to anticipate impacts at an early stage, as well as that it may demonstrate a need to assess the alternative options for import of soy. A report published in 2017 on the perceptions among Norwegian citizens on GMOs describes how about half of the respondents expressed that they were negative for sale of GMO-products in Norwegian grocery stores in the future, whereas only 15 percent were positive (19). Nevertheless, the empirical data available on the attitude of Norwegian citizens towards GM remains limited (e.g. 20, 21) and more empirical research on this is warranted to investigate consumers' attitude, demand and acceptance on different aspects such the cultivation, import and or processing of GM crops within and outside of Norway, as the perspectives on GM food and feed.

Assessing alternatives

When a new (bio-) technology is developed, it is important to reflect on what problem it aims to solve and to investigate whether alternative options may achieve the same outcomes in a safer and / or a more ethically justifiable way. After all, when a crop is genetically modified to tolerate a particular herbicide, it means that the crop is developed for a particular cultivation practice in which these herbicides are to be used. What is meant with alternatives, and what would benefit from being assessed could include alternative varieties (e.g. conventional or organic soy) for import, alternative sources to satisfy the demand, alternative ways of agriculture, or even explore alternative life visions. In fact, this corresponds with the increased trend within research and policy of science and innovation to anticipate impacts, assess alternatives, reveal underlying values, assumptions, norms and beliefs (8, 22) as a way to reflect on what kind of society we want, and assess how certain (biotechnological) developments may or may not contribute to shaping a desired future. Thus, in order to evaluate whether soy DAS-68416-4 x MON89788 contributes to social utility, it is important to investigate current and future demands and acceptance of this in Norway and if there are alternatives sources for soy that could be cultivated elsewhere that may satisfy this demand, or are more desirable.

Ethical considerations: socio-economic impacts

As known, GM crops have been, and still are, a hot topic for debate. A significant amount of this debate focuses on the safety of GMOs and currently no scientific consensus on this topic has been achieved (23). Nevertheless, another substantial part of the debate is around the socio-economic impacts of GM productions and many questions for evaluating the above mentioned criteria in the NGTA are based on an assessment of the socio-economic impacts. These impacts can vary and range from seed choice for farmers, co-existence of different agricultural practices, impacts among poor and/or small-scale farmers in developing countries, share of the benefits among sectors of the society, changing power dynamics among stakeholders, autonomy of farmers, intellectual property right on seeds, benefit sharing, the decreasing space for regional and local policy, and more organisational work and higher costs for non-GM farmers (e.g. for cleaning of sowing machines or transport equipment to avoid contamination). Although the examples of socio-economic impacts clearly indicate the complexity and extensive list of concerns beyond safety aspects, little empirical investigation on these kind of aspects has been done. For example a study performed by Fischer et al. (24) concerning social implications from cultivating GM crops found that from 2004 – 2015 there has only been 15 studies corning socio-economic implications of cultivating Bt-maize. The study demonstrates that published literature is dominated by studies of economic impact and conclude that very few studies take a comprehensive view of social impacts associated with GM crops in agriculture. Although this study focused on Bt-maize, the amount of research performed in this case and the minimal focus on social impacts strongly indicate a high need for further investigation on how the cultivation of GM crops affects different parties involved. It is therefore striking that no information on any of the above mentioned points is discussed by the Applicant.

Co-existence

The cultivation of GM plants in general is causing problems with regard to co-existence, an important socio-economic impact. For instance, Binimelis (25) has 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 have given up growing non-GM maize. Even though the cultivation of soy DAS-68416-4 x MON89788 is not planned in Europe/Norway, it is important to obtain information about the strategies adopted to ensure co-existence with conventional and organic soy production and information about consequences for co-existence in the countries intended for cultivation of soy DAS-68416-4 x MON89788 and minimize the likelihood for gene flow to wild relatives, or contamination during transport or processing. Legal information and clarity could provide evaluators a more comprehensive understanding of governance strategies and possibilities to ensure co-existence, although it has been noted that this may not suffice as co-existence has become an arena of opposed values and future vision of agriculture, including the role of GM crops within these visions (26). Indeed, although a framework for maintaining co-existence in Europe was established in 2003 (27) this effectively meant technical measurements and recommendations (e.g. cleaning of sowing machines and transport vehicles) and remains challenging in practice (28, 29). Moreover, this framework arguably reduced the significance of the issue of co-existence to questions concerning economic aspects for individuals (e.g. farmers), rather than recognizing that agricultural practices are interwoven in dynamic social, economic and political systems (30, 31). For the criteria in the NGTA, information on co-existence is required to enable a coherent analysis.

The ethical issue of glufosinate-ammonium

A significant ethical issue arises as soy DAS-68416-4 x MON89788 is meant to be resistant to gluphosinate-ammonium, a class of herbicide that is banned in Norway (except a limited use on apples) due to the risks to human health and the environment. It seems ethically ambiguous and inconsistent to import a plant that is resistant to this herbicide, thereby allowing the use and development of a harmful herbicide in other countries, while considering the herbicide as too harmful to be used in Norway. Additionally. This troubles the fulfilment of the criteria of *sustainable development*, as this criteria is meant to be considered in a global context. Information on how this can be ethically justified is therefore highly warranted.

Summary

In order to meet the requirements for the NGTA, the regulator is encouraged to ask the Applicant to submit information relevant for the assessment of the criteria of ethically justifiable, benefit to society and sustainability assessment, as well as a correction of the outdated information. An important part that is lacking is information about the consequences of the cultivation of soy DAS-68416-4 x MON89788 for the producing countries and how the sites of field trials relate to the sites of cultivation. Furthermore, the information provided by the Applicant must be relevant for the specific agricultural context of these countries and should also stress the need for information on integrated weed management strategies (32). Moreover, the information should contain issues such as changes in herbicide use, development of herbicide resistant weed, potential for gene flow and possible socio-economic impacts such as poor and/or small-scale farmers in producing countries, share of the benefits among sectors of the society and as explained, effects of co-existence of different agricultural systems. Furthermore, soy DAS-68416-4 x MON89788 is tolerant to gluphosinate-ammonium which is banned for use in Norway. Banning the use of gluphosinate-ammonium based herbicides domestically due to health and environmental concerns, while indirectly supporting its use in other countries would be ethically ambiguous and goes against the criteria of sustainable development. Additionally, the Applicant does not attempt to demonstrate a benefit to society, a reference of the consumers' attitude on GM soy, or the demand within Norway for soy DAS-

68416-4 x MON89788 and does therefore not provide sufficient information as required by the NGTA.

Table 1: Questions to the Applicant

Sustainability	*How does the cultivation of soy DAS-68416-4 x MON 89788 affect the use of glyphosate?*
	How is the current use of glyphosate in the sites of cultivation and what approaches are used to minimize the use of glyphosate?
Herbicide-resistant weed	*What kind of management strategies are taken to prevent the increase of herbicide-resistant weed?*
	Who will be affected if the amount of resistant weeds increases?
	How is the burden of increase of resistant weeds distributed and what strategies are in place to compensate this?
	How do the sites of the field trial relate to the proposed sites for cultivation? What are the differences and how may these affect the adequacy of the assessment of the field trials?
Benefit to society	*Is soy DAS-68416-4 x MON 89788 available for further breeding and research? If so, under which circumstances?*
	Is there a demand for soy DAS-68416-4 x MON 89788 in Norway?
	Does soy DAS-68416-4 x MON 89788 contribute to business development and value creation in Norway, including new job opportunities?
Assessing alternatives	*Will soy DAS-68416-4 x MON 89788 benefit Norwegian consumers more than the other alternatives available from conventional or organic agricultural practices? If so, how?*
Ethically justifiable	*What are the different public values and visions on the development, introduction or use of soy DAS-68416-4 x MON 89788 within Norway and how does the development of soy DAS-68416-4 x MON 89788 relates to these?*
	Does the development, introduction or use of soy DAS-68416-4 x MON 89788 contradict ideas about solidarity and equality between people, such as the particular consideration of vulnerable groups in the population?
Socio-economic impacts	*Which parties will be affected by the development, introduction or use of soy DAS-68416-4 x MON 89788 and how does this change their autonomy, practice and position compared to other stakeholders?*
	Does soy DAS-68416-4 x MON 89788 change the power dynamic among stakeholders? If so, how?
	Can the development, introduction or use of soy DAS-68416-4 x MON 89788 create significant ruptures or ecological relationships?
Co-existence	*Does the cultivation of soy DAS-68416-4 x MON 89788 affect other types of agricultural practices in the nearby areas? If so, how?*
	Is there a system in place for keeping GMO and non-GMO crops separate in the production and transport line? If so, who pays for this system?

Environmental risk issues in a Norwegian context

Soy is not cultivated in Norway and there is no wild relatives in the Norwegian environment. There are some varieties of soy that is cultivated in the south of Sweden and in Denmark.

Loss of gene modified soy seed through storage or transport would therefore not involve great risk for spread into the wild or spread of transgenes to wild relatives.

Molecular characterization, expressed proteins and herbicide use - special issues to consider in the present application

Stacked events

The stacked soy event DAS-68416-4 x MON89788 contains three distinct, inserted transgenes providing herbicide tolerance towards three different herbicides. This stack with the new combination of transgenes should be regarded as a new event, even if no "new" modifications have been introduced, as the combination itself in the stack is unique for that event. The gene-cassette combinations are new and unique and only minor conclusions could be drawn from the assessment of the parental lines, since unexpected effects (e.g. synergistic effects of the newly introduced proteins) cannot automatically be excluded. Stacked events are in general more complex than their single, parental lines, 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 within stacked traits cannot be excluded and whether or not the expressed proteins in the plant can give specific immunological effects or adjuvant effects in mammals has been discussed previously (33, 34).

Molecular characterization

For a full description of the molecular characterization of DAS-68416-4 and MON89788 the Applicant refers to the applications for authorization in the EU of DAS-68416-4 (EFSA-GMO-NL-2011-91) and MON-89788-1 (EFSA-GMO-NL-2006-36). GenØk has previously commented on DAS-68416-4 (EFSA-GMO-NL-2011-91) in 2011 and on MON89788 in applications regarding stacked events (see pages 6-8):

<u>The key findings from 2011 on molecular characterization of DAS-68416-4 (H_91):</u>

- Information on the inserted sequences – quality of **Southern analyses**: The sensitivity of the experiments to detect transgenic partial sequences other than the main insert was not assessed systematically. The Southern blots are not always ideal, no explanation of additional weak bands
- The Applicant did not perform a whole GM food study (e.g. 90-day toxicity study in rodents).
- The Applicant has not submitted the necessary information to be compliant with provisions under the Act, specifically those related to 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 acceptance **DAS-68416-4** as a foodstuff, which utilizes gluphosinate-ammoniumbanned in Norway) as one of the main agrochemical in its management, would question basic ethical and social utility criteria as laid out in the Norwegian Gene Technology Act. That is, we find that it would be ethically incongruous and a double standard of safety for Norway to ban the use of this herbicide domestically as a health concern, but support its use in countries

through the purchase and importation of its products that use it abroad. This line of reasoning is consistent with the provisions under the Act to assess ethical, social utility and sustainable development criteria not only for Norway, but for countries from which Norway imports food.

The key findings from 2016 (H_126), 2013 (H_108) and 2010 (H_73) regarding soy event MON89877 were:

- The vector cassette include the antibiotic resistance genes *aadA* and s*pec R*. The Applicant claims that no portion of this gene is incorporated into the plant but direct evidence of the conclusion is lacking.
- The regulator is encouraged to ask the Applicant to provide direct evidence of the lack of combinatorial effects arising from the expression of the stacked proteins in the plant, instead of relying on the assessment of non-harm of the target genes existing independently, before a conclusion of safety can be scientifically justified.
- Long term exposure-/feeding studies should be included in a risk assessment before a GM plant product is released on the marked for food/feed consumption.
- The regulator is encouraged to ask the Applicant to comment on the fate of potential herbicide residues.
- The Applicant should provide additional data using comprehensive set of smaller probes in order to evaluate the genetic stability of the event.
- The Applicant should provide the electropherograms for the sequence analysis in order to be able to check the quality of the sequencing.
- The Applicant should provide evidence that the antibodies used in the protein characterization would detect all novel in-planta produced isoforms.
- The Applicant should provide data to substantiate claims of specificity; either by using the in-planta produced proteins or by demonstrating equivalence between the test protein and the in-planta produced form.
- The Applicant should use plant version of the protein(s).
- The Applicant should include a chapter on identification of the transgenic proteins in the stack and not base conclusion of analysis made in single parental lines.
- The Applicant should perform analysis on the combined event (MON87708 x MON87798) and base conclusions on that rather than on the single events separately.
- The Applicant should perform repeated dose studies for analysis of transgenic proteins in combination for analysis of toxicological potential.
- The Applicant should provide data on the glycosylation status of the proteins to the allergenic risk assessment.

The Applicant claims that there is a low likelihood of molecular interactions between the different inserts and, therefore, low likelihood of any changes in the molecular characteristics of the inherited inserts in DAS-68416-4 x MON-89788-1 soybean (e.g. copy number, insert number, absence of backbone DNA and integrity of the individual inserts). The Applicant choose to not repeat the laboratory analysis of the full stack, which makes it difficult to say something about any unintended effects in this part. However, an analytical confirmation of the presence of the two inserts in the combined product is performed by Southern blot analysis illustrated in figure 3-6 and table 6. The size of the probes are big ranging from 552-1600 bp. Smaller probes are recommended.

Comments relevant for the assessment of the current application

There is no scientific literature available on the genetic construct and genetic stability of the stacked event DAS-68416-4 x MON 89788 in order to make an appropriate scientific evaluation. The Applicant should therefore provide information on the stability of the insert over multiple generations as well as compositional data and expression analyses over all growing seasons.

We expect that the analyzes performed by the Applicant should be of high scientific quality which also could meet the requirements for publication in peer reviewed and well-known international journals.

This application reflects the trend with stacked events with tolerance against several selective herbicides, which means that besides evaluating the potential risks arising from the genetic modification, it is also important to address possible concerns when it comes to changes in herbicide/pesticide management.

Protein expression and characterization of the newly expressed protein(s)

Expression levels of expressed, transgenic proteins AAD-12, PAT and CP4 EPSPS were analyzed using enzyme-linked immune-sorbent assay (ELISA) in various soy tissues from 10 field test sites in US.
Levels of detected proteins in the soy stack DAS-68416-4 x MON89788 were comparable to those of the single, parental events.

Toxicity and allergenicity

Toxicity

Based on the criteria of 1) history of safe use, 2) structural similarity to known toxins or other biologically active proteins causing adverse effects in humans or animals, and 3) if they exert acute toxicity to mammals, the proteins AAD-12, PAT and CP4 EPSPS are considered to be safe in relation to health.

No toxicity studies were performed with the whole GM food/feed due to the equivalence to conventional soy (according to the Applicant) and because of the safety evaluations previously made on the proteins expressed in this stack.

Allergenicity

Proteins CP4 EPSPS, PAT and AAD-12 have been tested for their allergenic potential through the recommendations by the Codex (35) and found not likely to have allergenic potentials and soy stack DAS-68416-4 x MON89788 to be as safe as conventional soy.

Potential interactions between newly expressed proteins

None, according to Applicant.

Hazard identification

According to the Applicant, there is no evidence for soy stack DAS68416-4 x MON89788 to be hazardous to humans or animals. The soy stack is considered equal to conventional soy.

Herbicides

Herbicide use on GM plants

Herbicide tolerant (HT) plants are sprayed with one or more of the relevant herbicide(s), which will kill weeds without harming the HT GM plant with the inserted transgenes. The use of HT GM plants may cause negative effects on ecosystem as well as animal/human health. Of particular concern are: 1) increased use of, and exposure to, toxic herbicides; 2) accelerated resistance evolution in weeds; 3) accumulation of herbicides in the plants since they are sprayed in the growing season; 4) combinatorial effects of co-exposure to several herbicides at the same time (relevant for plants with pyramided HT genes); and 5) points 1-4 indicate that the agricultural practice of growing HT GM plants, fails to fulfill the criteria for a sustainable agriculture.

Total use of herbicides

HT GM plants are documented to be a strong driver of increased use of glyphosate-based herbicides (the dominant herbicide tolerance trait until now). From 1995 to 2014 the global agricultural use of glyphosate rose 14.6 fold, from 51 million kg to 747 million kg and HT GM crops have been a major driver for this change. Moreover, by 2016, about 56 % of the global use of glyphosate was related to the use of HT GM crops (15).

Increased use and resistance evolution

Specific for the HT GM plants is that herbicides can be sprayed in higher doses than before, and repeatedly during the growth season of the plants. The increased use must be linked to resistance evolution in weeds. At present, 36 species of weeds are documented to be glyphosate resistant on a global scale (36). Such development may lead to a ‘treadmill’ where resistance triggers more applications/higher doses, which leads to stronger selection pressure for resistance, etc. and eventually the use of additional herbicides like atrazine, 2,4-D or others (37). Crop and herbicide monoculture makes the agroecosystem more vulnerable to further resistance development (38).

For 2,4-D, 32 species of weeds are shown to be resistant, and five of these (16%) were documented after 2015 (36).
For gluphosinate-ammonium, six species of weeds are shown to be resistant and 50 % of these were discovered after 2015 (36).

Sustainability

For the farmers, resistant weeds are a difficult obstacle to handle. However, evolution of resistance is the process by which it develops. Therefore, more research should be performed on the plurality of responses that can be done with integrated pest management, not only to delay resistance but to promote alternative and preferably non-toxic pest control systems (UN). Chemical treatment coupled with the unavoidable resistance development are major blocking factors to a sustainable agriculture. The accelerated use seen for glyphosate used on glyphosate tolerant GM plants can be expected to happen for *any* herbicide used as co-technology for HT GM plants, indicating that HT GM plants are not sustainable.

Environmental effects of herbicides

The use of herbicides like glyphosate also has the potential to affect ecosystem, animal and human health. The massive use of glyphosate, totaling 852 million kg globally by 2014 (15), which directly or indirectly will expose non-target biodiversity in terrestrial, soil and aquatic communities (39), represent a major source of environmental pollution.

Accumulating herbicide residues and health effects

Glyphosate accumulates in HT soybeans, more when the plant is sprayed later in the season (32). This may bring significant amounts of glyphosate into the food and feed chain. Bøhn and colleagues measured on average 9.0 mg of glyphosate in HT GM soybeans grown in Iowa (40).

Clearly, HT GM plants with tolerance to 2, 4-D, gluphosinate ammonium or other herbicides may serve as a vector for these chemicals into the global food and feed chains.

The increased awareness of glyphosate toxicity, coupled with the increased volume used, should potentially lead to stronger restrictions, for example lower acceptance level for glyphosate residues in food and feed (41). However, the maximum residue level (MRL) for glyphosate has been raised 200-fold from 0.1 to 20 mg/kg in Europe, and to 40 mg/kg in the US (42). This set of events has been termed “The Glyphosate Paradox” (41). The WHO/IARC categorization of glyphosate as *probably carcinogenic to humans (43)*, although disputed by EFSA (44), is underlining the significance of the controversy around the glyphosate-based herbicides.

2, 4-D was by WHO/IARC in 2015 classified as a *possible carcinogen to humans* (45).

Therefore, what we may see the starting point of is the replacement of glyphosate with other herbicides, of which 2, 4-D and dicamba are likely candidates. Given such development, the toxicity and non-target effects of herbicides that eventually replace glyphosate becomes more important.

Modeling studies have shown that long-term implications of large scale bioenergy crops can surpass toxicity thresholds for fish (bluegill) and humans in significant parts of relevant watersheds, particularly because of glyphosate, and thus negatively impact aquatic life and drinking water (46).

Given that 2, 4-D and dicamba (and other herbicides) may replace or add to the role of glyphosate, such modeling studies may have to be re-calibrated with a new attention to the concentration of these chemicals.

The chemical 2, 4-D is a systemic herbicide that leads to uncontrolled growth and death in broad leaf plants. Grasses and cereals like corn, oat, rice and wheat have relatively high tolerance to 2, 4-D, giving the option of using 2, 4-D as a post emergence herbicide on selected crops.

2, 4-D can be found in different chemical forms: as acid (basic form), inorganic salts, amines or esters (47). Plants absorb 2, 4-D through roots and leaves within 4-6 hours, the chemical follows the phloem of the plant and mimics the role of auxins (plant hormones) leading to disturbances, abnormal growth and eventually death.

Studies of toxicity in aquatic systems/organisms

The herbicide 2, 4-D has relative low toxicity in aquatic systems. For example, the EC_{50} for the cyanobacteria *Anabaena* CPB4337 was 25.23 mg/L. When this cyanobacteria was pre-exposed to the surfactant perfluorooctanic acid (PFOA), the toxicity of 2, 4-D increased, illustrating the important topic of interacting multiple stressors (48).

Studies in Daphnia

In *Daphnia magna*, the LC_{50}/EC_{50} acute toxicity is shown in the range 144 – 248 mg/L for 24 h, and 25 mg/L for 48 h, respectively (49, 50).
However, the issue on accumulation of herbicides in the HT plants, including metabolites, are not regularly tested as part of the risk assessment of HT plants. Bøhn et al. (40) documented high levels of glyphosate residues in HT GM soybeans grown in the USA, and the same research group have published papers showing that such residues have the potential for negatively to affect the feed quality of HT GM soybeans (42, 51). It is important to look at the potential metabolites of the herbicides in use and if these are documented to have a negative effect on health and environment.

Glyphosate tolerance

The *cp4 epsps* gene present in DAS-68416-4 x MON89788 soy confers tolerance to herbicides containing glyphosate.

Glyphosate kills plants by inhibiting the enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthase (EPSPS), necessary for production of important amino acids. There are also some microorganisms that have a version of EPSPS that is resistant to glyphosate inhibition.

Glyphosate has previously been announced as an herbicide with low toxicity for users and consumers as well as the environment surrounding agricultural fields (32, 52). However, glyphosate has recently received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (53), as well as from studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (54-56).

It has also been shown that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (57).

A number of publications indicate unwanted effects of glyphosate on health (56, 58), aquatic (59) and terrestric (53, 60) organisms and ecosystems. Also, a study of Roundup (containing glyphosate as the active ingredient) effects on the first cell divisions of sea urchins (61) is of particular interest to human health. The experiments demonstrated dysfunctions of cell division at the level of CDK1/Cyclin B activation (these proteins are involved in mitosis). Considering the universality among species of the CDK1/Cyclin B cell regulator, these results question the safety of glyphosate and Roundup on human health. In another study (54) it was demonstrated a negative effect of glyphosate, as well as a number of other organophosphate pesticides, on nerve-cell differentiation. Surprisingly, in human placental cells, Roundup was always more toxic than its active ingredient. The effects of glyphosate and Roundup were tested at lower non-toxic concentrations on aromatase, the enzyme responsible for estrogen synthesis (62). The glyphosate-based herbicide disrupts aromatase activity and mRNA levels and interacts with the active site of the purified enzyme, but the effects of glyphosate are facilitated by the Roundup formulation. The authors conclude that the endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. They suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.

Additionally, the International Agency for Reseach on cancer (IARC) released a report indicating that glyphosate is a "probably carcinogenic to humans"(63) an issue that is under debate.

Gluphosinate ammonioum tolerance

The stacked soy event DAS-68416-4 x MON89788 contains the *pat* gene from *Streptomyces viridochromogenes* that confers tolerance to herbicides containing gluphosinate-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. Gluphosinate ammonium is harmful by inhalation, swallowing and by skin contact. 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 gluphosinate ammonium is used (64-67). EFSA has concluded on the risk of gluphosinate ammonium, as especially harmful to mammals (68).

2, 4-D tolerance

The *aad-12* gene provides 2, 4-D (dichlorophenoxy) and arylphenoxypropionate tolerance in the soy stack DAS-68416-4 x MON89788. This herbicide has negative effects on the endocrine and immune system, and is thought to might have a role in cancer as well as affecting reproductively (http://www.pesticideinfo.org/Detail_Chemical.jsp) (see also the pages 21 and 22 toxicity related effects).

From the homepage of the Norwegian government,[2] the following is noted:

"Commission Implementing Regulation (EU) 2015/2033 of 13 November 2015 renewing the approval of the active substance 2,4-D in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011".

Thus, 2, 4-D is approved for use in Norway.

Summary:

- Soy event DAS-68416-4 x MON89788 is tolerant to glyphosate, gluphosinate ammonium, 2, 4-D. These herbicides are damaging to health and environment in different ways.
- Potential for accumulation of the herbicides should be considered in GM plants used in food and feed.

Main summary

Soy event DAS-68416-4 x MON89788 is tolerant to herbicides containing glyphosate, gluphosinate ammonium and 2, 4-D that has distinct degrees of health and environmental dangers upon use, thus the issue on accumulation should be considered for GM plants to be used in food and feed.
In addition, gluphosinate ammonium is banned for use in Norway.
The applicant should provide data relevant for assessment of social utility and sustainable development according to the NGTA(2).

2 https://www.regjeringen.no/no/sub/eos-notatbasen/notatene/2015/okt/plantevernmiddel---24-d/id2469257/

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