Vår ref:2015/H_120
Deres ref: 2015/9902

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 02.11.15

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring under EU forordning 1829/2003 av oppsummert søknad for **EFSA/GMO/NL/2013/120**, soya «event» **FG72xA5547-127**, fra Bayer CropScience AG og M.S. Technologies, LLC, som gjelder mat, fòr, import og prosessering av genmodifisert soya **FG72xA5547-127.**

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

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Vår ref:2015/H_120
Deres ref: 2015/9902

Assessment of the summary of the dossier under 1829/2003/EU of EFSA/GMO/NL/2013/120 soy.

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 **FG72xA5547-127 soya**. Søker har ikke inkludert noe av den informasjonen omkring samfunnsnytte og bærekraft av **FG72xA5547-127 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 offentlig høring for **FG72xA5547-127 soya** i bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra **FG72xA5547-127 soya.**

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 **FG72xA5547-127 soya** til import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra **FG72xA5547-127 soya.**

Basert på den informasjonen vi har tilgjengelig er vår konklusjon at norske myndigheter ikke godkjenner bruk av **FG72xA5547-127 soya** 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/2013/120 SOY.

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 **FG72xA5547-127 soy**, 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 **FG72xA5547-127 soy** we can not give a full assessment of this stacked event.*
Our assessment is therefore based on the information from the summary of the technical dossier and the data presented there.

We have previously commented on the following:

- EFSA/GMO/BE/2011/98, Soy event FG72 (January 2012).

Specific recommendations

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

- The regulator is encouraged to ask the Applicant to address to what level, and if, the *bla* gene product is expressed in FG72xA5547-127 soy, as this is unclear from the summary.
- We recommend a mapping of the ARM genes present in the environment for more knowledge about the background level
- We find it ethically unacceptable to use glufosinate-ammonium and isoxaflutole based herbicides domestically due to animal and ecosystem health concerns, while supporting its use in other countries. Importing this plant would represent an unacceptable double standard for Norway, and we ask the regulators to reconsider the practice of separating health and environmental risk by national borders or regions.
- The applicant should include a full evaluation of the co-technology intended to be used with FG72xA5547-127 soy, namely glyphosate, isoxaflutole- and glufosinate-ammonium-based herbicides. Particular focus should be given to the 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.
- 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 FG72 x A5547-127 soy 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: Changes in pesticide use, emergence of herbicide resistant weeds, potential for gene flow and possible impacts among farmers practicing different production forms for soy cultivation in the producing country(ies) and share of the benefits among sectors of the society
- We do not recommend an approval of the FG72 x A5547-127 soy as it contains the antibiotic resistance genes *bla.*The use of antibiotic resistance genes as selectable markers in GM plants is not considered to contribute to sustainable development.
- We do not recommend an approval of the FG72 x A5547-127 soy as it is tolerant to gulfosinate-ammonium and isoxaflutole which are banned in Norway.

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 FG72xA5547-127 soy**. 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 **FG72xA5547-127 soy**, 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/2013/120 SOY.

About the event

The stacked event **FG72xA5547-127** soy was made by crossing of the single parental lines FG72 and A5547-127 using traditional breeding methods.

The application of the soy event FG72xA5547-127 is for food, feed, import and processing.

None of the parental lines are approved in Norway for any of the applications.

Soy event FG72xA5547-127 is not approved for food, feed, import or processing in EU. Parental line FG72 is approved for this.

The soy event FG72xA5547-127 is not approved for any applications in a third country.

Assessment findings

We do not have access to the full technical dossier for soy event FG72xA5547-127, thus we base our assessment on the summary provided by the Environmental Agency.

The event FG72xA5547-127 soy is a stacked event that has tolerance to the herbicides glyphosate through the *2mEPSPS* gene (gene from *Zea Mays*), gluphosinate-ammonium through the *pat* gene (from *Streptomyces viridochromogenes*) and isoxaflutole through the gene *hppdPfW336* (from *Pseudomonas fluorescens*). In addition, it contains an antibiotic resistance marker (ARM) gene called *bla* (from *Escherichia coli*).

Molecular characterization

Evaluation of the molecular characteristics of the FG72xA5547-127 soy

A proper evaluation of the molecular characteristics can not be done due to lack of acess to full technical dossier.

Concerns of the genomic location of the inserts

A proper and full evaluation of the location of the inserts can not be performed due to lack of access to full technical dossier.

Antiobiotic resistance marker (ARM) genes

The stacked event FG72xA5547-127contains one ARM gene called *bla* encoding the enzyme beta lactamase giving resistance towards antibiotics like ampicillin, an antibiotic used in human medicine.

The prevalence of this gene in natural environments still need more exploration, even though some studies in the Arctic regions have been performed where data indicate that the prevalence of ampicillin (and tetracyclin) resistant isolates are low (Glad et al., 2010).

As we do not have access to the full dossier, we do not know if the *bla* gene is expressed in the GM plants. Also, in the summary of the technical application, an analysis of expression of this gene is not mentioned, and thus probably not analysed, but this remains unclear.

The Norwegian Scientific Committee for Food Safety (VKM) has commented on health and environmental issues related to the use of ARM genes in GM plants (VKM, 2005) where they acknowledges that there is little information on the prevalence of such ARM genes in the environment and in Norway.

We strongly encourage the onset of ARM gene mapping in the environment for more knowledge on background level.

The Norwegian Genetechnology Act (NGTA) accounts for GMOs that are able to germinate, while the Food Act regulate import and production of processed, non-germinating products

from GMOs for food and feed. Through NGTA, the principles of social utility, ethical considerations and sustainable development are evaluated for each GMO before approval, thus many GMOs with ARM genes are prohibited because they are not considered as not contributing to these principles. The regulations in the Food Act prohibits food and feed that contains GMOs that are detectable in the end product (see section on "*The use of antibiotic resistance genes as selectable markers*" p.11 for details).

By this, the stacked event **FG72xA5547-127 soy** is not allowed for food, feed, import or processing in Norway if it contains detectable levels of the ARMs involved.

Based on this and the potential of horizontal gene transfer (HGT) to other bacteria, the use of ARM genes in GM plants must be reconsidered and further restricted.

Recommendation:

- The regulator is encouraged to ask the Applicant to address to what level and if the *bla* gene product is expressed in FG72xA5547-127 soy, as this is unclear from the summary.
- We recommend a mapping of the ARM genes present in the environment for more knowledge about the background level.

Herbicide tolerance traits

This FG72xA5547-127 soy event contains three herbicidal tolerance genes, namely *2mepsps*, *hppdPfW336* and *pat* providing tolerance to the herbicides glyphosate, isoxaflutole and glufosinate-ammonium.

Glyphosate and RoundUp tolerance

The gene *2mEPSPS* confers tolerance to glyphosate containing herbicides in the FG72xA5547-127 transgenic soy.

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). An overview of these, including published literature on their toxicity, is given in Mesnage et al. (Mesnage et al., 2015a). Although a general belief is that Roundup contains glyphosate and additional *inert* substances, the adjuvants may in some cases be more toxic than the glyphosate active ingredient itself (Howe et al., 2004, Peixoto, 2005). 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, Cavalli et al., 2013), 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).

Isoxaflutole tolerance

Isoxaflutole is a herbicide in the isoxazole class of herbicides. This herbicide is a pigment synthesis inhibitor (also called a "bleacher") with trade name "Balance[r]".

According to MSDS provided by Bayer CropScience (2009) for "Balance® 750WG Herbicide", this herbicide is classified as hazardous with "possible risk of harm to the unborn child". Also, if accidental release takes place, people and animals should stay away, spillage should be contained and prevented from entering drains or watercourses. The MSDS for Bayer also states that Isoxaflutole represents a "negligible, if any, increased cancer risk for humans" and that it is very toxic to aquatic organisms. It is also "potentially mobile during heavy rainfall".

In the evaluation of the parental line FG72 by EFSA (EFSA, 2015) the use of the herbicide isoxaflutole was not evaluated as the scope of that application excluded cultivation.
The stack FG72xA5547-127 application here also excludes cultivation. However, it has to be mentioned due to the level of toxicity posed by the herbicide in use and the fact that we do not know in what dosages this herbicide is to be used. Also, the combination of all the herbicides on the same plant makes it necessary to evaluate whether these chemicals will accumulate and at what concentrations in food and feed products.
The actual MRL (maximum residue limit) was recently lowered by EFSA These changes also accounts for Norway. However, Isofluxatole is banned in Norway.

Glufosinate ammonioum tolerance

The *PAT* gene confer tolerance to herbicides containing gluphosinate ammonium.

Glufosinate-ammonium belongs to a class of herbicides that is banned in Norway and in EU (except for a limited use on apples) due to both acute and chronic effects on mammals including

humans. Studies have shown that glufosinate-ammonium is harmful by inhalation, ingestion and skin contact and that serious health risks may result from exposure over time. Observations of patients poisoned by glufosinate-ammonium have found that acute exposure causes convulsions, circulatory and respiratory problems, amnesia and damages to the central nervous system (CNS) (Watanabe 1998). Chronic exposure in mice has been shown to cause spatial memory loss, changes to certain brain regions, and autism-like traits in offspring (Calas et al., 2008, Laugeray et al., 2014). According to EFSA, the use of glufosinate-ammonium will lead to farm workers being exposed to herbicide levels that exceed acceptable exposure levels during application.

Recommendations:

- We find it ethically unacceptable to use glufosinate-ammonium and isoxaflutole based herbicides domestically due to animal and ecosystem health concerns, while supporting its use in other countries. Importing this plant would represent an unacceptable double standard for Norway, and we ask the regulators to reconsider the practice of separating health and environmental risk by national borders or regions.

- The applicant should include a full evaluation of the co-technology intended to be used with FG72xA5547-127 soy, namely glyphosate, isoxaflutole- and glufosinate-ammonium-based herbicides. Particular focus should be given to the 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.

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 to properly assess these issues.

The use of antibiotic resistance genes as selectable markers

The FG72 x A5547-127 soy is genetically modified to contain an antibiotic resistance gene (*bla*). The use of antibiotic resistance genes as selectable markers for transformation of GM plants is controversial, and measures are taken to limit this practice due to the dramatic increase in antibiotic resistant bacterial strains globally. Norwegian authorities are encouraging a very restrictive approach to the use of GM plants with antibiotic resistance genes and work for

international prohibitions in this area. The Norwegian Food Act (2003) prohibits the use of GM plants with such genes, and GM plants that possess such genes have also previously been prohibited under the NGTA, partly because they are not considered to contribute to sustainable development globally. The EFSA panel concludes that the antibiotic resistance gene *bla* should be restricted to field trial purposes and not be present in GM plants placed on the market, as these genes confer resistance to antibiotics which are used for therapy in defined areas of human and veterinary medicine (EFSA 2004). Consequently, we do not recommend an approval of the FG72 x A5547-127 soy as this GM soy contain the antibiotic resistance genes *bla*.

Environmental and health impacts of the co-technology: glyphosate, glufosinat-ammonium and isoxaflutole
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 FG72 x A5547-127 soy confers tolerance to herbicides containing glyphosate, glufosinate-ammonium and isoxaflutole.

Both Glufosinate-ammonium and isoxaflutole are herbicides that are banned in Norway. Glufosinate-ammonium have both acute and chronic effects on mammals, including humans. Isoxaflutole is probably carcinogenic in humans and may be harmful to human fetuses. Recent studies have also 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 glyphosate and RoundUp)

Glyphosate resistant weeds in soy 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 soy (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 FG72 x A5547-127 soy 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, glufosinate ammonium and isoxaflutole after the introduction of FG72 x A5547-127 soy, more information about the use of these herbicides in the producing country(ies) are needed.

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

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

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 FG72 x A5547-127 soy 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).

Social and economic impacts from gene flow and co-existence management
The cultivation of GM plants in general is causing problems with regard to co-existence. An evaluation of the occurrence of volunteer plants in the producing countries and suggested control strategies is important for a sustainability assessment. Information about the strategies adopted to ensure co-existence with conventional and organic soy 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.

Assessment of alternatives
It is also important to evaluate whether alternative options (e.g. the parental non-GM version of the FG72 x A5547-127 soy) may achieve the same outcomes in a safer and ethically justified way. Furthermore, in order to evaluate whether the FG72 x A5547-127 soy contributes to social utility, it is important to consider current and future demand for this GM soy product for food, feed and processing purposes in Norway and to what extent this demand is/can be satisfied by existing sources.

Ethical considerations

While it is understood that the Applicant has not applied for deliberate release of the FG72 x A5547-127 soy in Norway, the acceptance of a product in which the intended use involves the use of a product banned in Norway, as the glyphosinate-ammonium and isoxaflutole, would violate basic ethical and social utility criteria, as laid out in the NGTA. Therefore, we find that it would be ethically incongruous to support a double standard of safety for Norway on one hand, and safety for countries from which Norway may import its food and feed on the other. This line of reasoning is consistent with the provisions under the NGTA to assess ethical, social utility and sustainable development criteria not only for Norway, but for countries from which Norway imports food and feed. Specifically, this issue is relevant particularly in the revised guidelines for impact assessment pursuant to the Act of 2005 Section 17, *"Other consequences of the production and use of genetically modified organisms"* points 2 and 3, "*ethical considerations that may arise in connection with the use of the genetically modified organism(s)*», and "*any favorable or unfavorable social consequences that may arise from the use of the genetically modified organism(s)*", respectively.

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 FG72 x A5547-127 soy 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: Changes in pesticide use, emergence of herbicide resistant weeds, potential for gene flow and possible impacts among farmers practicing different production forms for soy cultivation in the producing country(ies) and share of the benefits among sectors of the society
- We do not recommend an approval of the FG72 x A5547-127 soy as it contains the antibiotic resistance genes *bla.*The use of antibiotic resistance genes as selectable markers in GM plants is not considered to contribute to sustainable development.
- We do not recommend an approval of the FG72 x A5547-127 soy as it is tolerant to gulfosinate-ammonium and isoxaflutole, which are banned in Norway. Banning the use of glufosinate-ammonium and isoxaflutole based herbicides domestically due to health and environmental concerns, while supporting its use in other countries would be ethically unacceptable.

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 FG72 x A5547-127 soy and does therefore not provide sufficient information as required by the NGTA. We do not recommend an approval of the FG72 x A5547-127 soy as it contains the antibiotic resistance genes *bla.* The use of antibiotic resistance genes as selectable markers in GM plants is not considered to contribute to sustainable development. We do not recommend an approval of the FG72 x A5547-127 soy as it is tolerant to glufosinate-ammonium and isoxaflutole which are banned in Norway. Banning the use of glufosinate-ammonium and isoxaflutole based herbicides domestically due to health and environmental concerns, while supporting its use in other countries would be ethically unacceptable.

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