Vår ref:2017/H_RX_006
Deres ref: 2017/4374

Høringsuttalelse av fornyelsessøknad om markedsføring av genmodifisert sukker bete/sukkerroe H7-1

EFSA/GMO/RX/006

Under EU forordning 1829/2003

Sendt til

Miljødirektoratet

av

GenØk-Senter for biosikkerhet
Juni 2017

Vår ref:2017/H_RX_006
Deres ref: 2017/4374

Miljødirektoratet
Postboks 5672 Sluppen
7485 Trondheim
Dato: 12.06.2017

Vedlagt er innspill fra GenØk – Senter for Biosikkerhet på offentlig høring av fornyelsessøknad **EFSA/GMO/RX/006**, genmodifisert sukker bete/sukkerroe H7-1 fra Monsanto Europe S.A./N.V. under EU forordning 1829/2003. Fornyelsessøknaden gjelder bruksområdene mat, fòr, import og prosessering.

Vennligst ta kontakt hvis det er noen spørsmål.

Med vennlig hilsen,

Idun Merete Grønsberg
Forsker II
GenØk – Senter for biosikkerhet
idun.gronsberg@genok.no

Bidragsyter(e):
Odd-Gunnar Wikmark
Forsker II
GenØk-Senter for biosikkerhet

Lilian van Hove
Forsker III
GenØk-Senter for biosikkerhet

Innhold/Content

Høringsuttalelse – genmodifisert sukker bete H7-1, EFSA/GMO/RX/006, under EU forordning 1829/2003.

Fornyelsessøknad EFSA/GMO/RX/006 omhandler genmodifisert sukkerbete H7-1 til bruksområdene mat, for, import og prosessering.

Den genmodifiserte sukkerbeten har toleranse mot herbicider som inneholder glyfosat via det innsatte genet *cp4epsps*.

Denne sukkerbeten er ikke godkjent for noen av de omsøkte bruksområdene i Norge.

Oppsummering

GenØk–Senter for biosikkerhet, viser til høring av fornyelsessøknad EFSA/GMO/RX/006 om H7-1 sukker bete som omfatter bruksområdet import og prosessering og til bruk i fòr og mat eller inneholdende ingredienser produsert fra denne sukker beten.

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

- Genmodifisert sukkerbeteH7-1 er ikke godkjent i Norge for noen av de omsøkte bruksområdene.
- H7-1 er tolerant mot sprøytemidler som inneholder glyfosat som har økt interesse vedrørende potensielle helse-og-miljø farer ved bruk.
- Fornyelsessøknaden om sukker bete H7-1 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 reapplication EFSA/GMO/RX/006 on H7-1 sugar beet 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 reapplication:

- The gene modified sugar beet, event H7-1 is not approved for any application in Norway.
- The sugar beet event H7-1 is tolerant to herbicides containing glyphosate that has an increasing interest concerning the potential health and environmental dangers upon use.
- The reapplication on sugar beet event H7-1 lacks data and information relevant for assessment of criteria on ethically justifiability, social utility and sustainability.

Repplication on EFSA/GMO/RX/006

The event H7-1 sugar beet contains a gene providing herbicide tolerance *(cp4 epsps)*.

Previous evaluations

The Norwegian Scientific Committee for Food Safety (VKM) has commented on the application for H7-1 sugar beet (EFSA/GMO/UK/2004/08) use in food/feed stuff (1) with the following issues:

- Sugar beet event H7-1 is considered as substantially equivalent to its natural counterpart when it comes to nutritional content
- There are no health related concerns when it comes to exposure of the CP4 EPSPS proteins to animals.
- The sugar from sugar beet is not considered to be substantially different compared to sugar from unmodified sugar beet and does not exert any adverse effect on health as food additive.
- Byproducts of H7-1 used in feed does not exert any change in the health related risks as compared to unmodified sugar beet.

The Norwegian Biotechnology Advisory Board (Bioteknologirådet) commented on the application on sugar beet (EFSA/GMO/DE2008/63) (2) for food, feed purposes, with the following comments/questions:

- There is no sequence data showing that the flanking sequence surrounding the H7-1 insert being genomic sugar beet –DNA.
- There seem to be no homology searches to known allergens of toxins for the flanking sequences.
- Sequences attached at that time was already old, and from 2003.
- Norway has its own bete called "strandbete", which is potentially available to hybridize with this transgenic sugar beet. It can happen through pollen is present. However, this can also happen through the process of development of "stokkløpere" (outgrowings from plant, able to survive /grow on its own) and then lead to spread of plants.
- There should be an increased focus of the potential effects glyphosate on health.
- Issues related to sustainability, ethically justifiability and social utility should be considered by the applicant for assessment in Norway.

The European Food Safety Authority has published an opinion on the application EFSA/GMO/UK/2008/08 (3) with the following comments:

- "The GMO Panel concluded that products from sugar beet H7-1 are safe as food and feed, and, that the nutritional value of the sugar beet H7-1 and the derived sugar beet products is comparable to that of analogous products from conventional sugar beet".
- The EFSA GMO Panel considers that no environmental risk assessment is needed due to the scope of the application (food and feed).

- No restrictions on handling or use is needed for products produced from sugar beet H7-1based on the performed risk assessment. Neither is production of ecosystems, environments etc.
- There is no indications of adverse effects from sugar beet H7-1 with the intended uses.

GenØk has not commented on sugar beet H7-1 previously.

Social utility and sustainability issues on the sugar beet H7-1, EFSA/GMO/RX/006

In Norway, an impact assessment follows the Norwegian Gene Technology Act (NGTA) (4) 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) (5). 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 (6-11).

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 12). The information provided in this re-application is limited and is mainly based on the application a decade ago. That means that the 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 sugar beet H7-1 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.

Sustainability

Sugar beet H7-1 contains a modified *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 pages 18-20, as well as in villages in areas where glyphosate is systematically used as part of the GM crops tolerance to glyphosate (13). 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 (14-16). As sugar beet H7-1 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 the cultivation of sugar beet H7-1. 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 sugar beet H7-1 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.

Currently, sugar beet H7-1 is cultivated in Canada, Japan and the USA. The data on which the applicant relies in its re-application is derived from field trials at five different locations in the USA between 1998-2003. Additionally, as the aim of the Applicant is to also cultivate sugar beet H7-1 in Europe, field trials have also taken place in France, the UK, Germany, Italy and Belgium from 1998. Although we recognize that value of having field trials in so many different sites, no field trials have been performed in Japan or Canada – the two countries were sugar beet H7-1 is currently cultivated. Furthermore, in the re-application, the Applicant states that *"The results of a review of the peer-reviewed scientific data on the GMO […] that have become available since the original authorization, updated bioinformatics analyses and studies performed by the applicants do not change in any way the conclusions of the original risk assessment"* (page 3, summary). However, weed resistance has increased significantly in the USA, Canada and Japan since 1998[1]. Additionally, the Applicant provides no information 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. 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.

Impacts in producer countries

To perform an accurate assessment of the sustainability criteria as laid down in the NGTA, more information is needed to evaluate the impact this GMO has on the producing countries. The sustainability criteria is referring to a global context, including the contribution to

[1] http://weedscience.org/Summary/Country.aspx Status of Herbicide Resistance in USA, Canada and Japan, accessed on 26th May 2017.

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 sugar beet H7-1 is cultivated.

Even if information is provided, that does not mean that the same conclusions will be drawn. Within science, there can also be ambiguity about how 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 in relation to the field trials. The difference between the field trials and the sites of cultivation can affect the adequacy of the evaluation of sugar beet H7-1. It is therefore important that the Applicant provides information on how the difference between the site of field trials and of cultivation sites may affect the evaluation of sugar beet H7-1.

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 sugar beet H7-1needs to demonstrate how it will benefit Norway. However, no information on this part is provided by the Applicant. It is important to evaluate how GM crops in general, GM sugar beet in particular, and the use of GM sugar beet in food and feed are valued by Norwegian consumers. 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 sugar beet. Although the empirical data available on the attitude of Norwegian citizens towards GM is limited (e.g. 19, 20) and more empirical research on this is warranted to investigate consumers' attitude, demand and acceptance, a report 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, and only 15 percent were positive (21).

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 sugar beet) 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 (9, 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 sugar beet H7-1 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 sugar beet 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. 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 (2008) has investigated consequences on co-existence of Bt maize in Spain among small-scale farmer and has found that co-existence is very difficult. Farmers in some areas even have given up growing non-GM maize. Even though the this re-application does not contain cultivation, it is important to obtain information about the strategies adopted to ensure co-existence with conventional and organic farmers. Information about consequences for co-existence in the countries intended for cultivation of sugar beet H7-1 should be provided. This information should demonstrate how the Applicant aims to 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 (25). Indeed, although a framework for maintaining co-existence in Europe was established in 2003 (26) this effectively meant technical measurements and recommendations (e.g. cleaning of sowing machines and transport vehicles) and remains challenging in practice (27, 28). 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 (29, 30). For the criteria in the NGTA, information on co-existence is required to enable a coherent analysis.

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. An important part that is lacking is information about the consequences of the cultivation of sugar beet H7-1 for the producing countries. The information provided by the Applicant must be relevant for the specific agricultural context of this country and should also stress the need for information on integrated weed management strategies in those countries (31). 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. Additionally, the Applicant does not attempt to demonstrate a benefit to society, a reference of the consumers' attitude on GM sugar beet, or the demand within Norway for sugar beet H7-1 and does therefore not provide sufficient information as required by the NGTA.

Table 1: Questions to the Applicant

Sustainability	*How does the cultivation of sugar beet H7-1 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?
Benefit to society	*Is sugar beet H7-1 available for further breeding and research? If so, under which circumstances?*
	Is there a demand for sugar beet H7-1 in Norway?
	Does sugar beet H7-1 contribute to business development and value creation in Norway, including new job opportunities?
Assessing alternatives	*Will sugar beet H7-1 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 sugar beet H7-1 within Norway and how does the development of sugar beet H7-1 relates to these?*
	Does the development, introduction or use of sugar beet H7-1 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 SUGAR BEET H7-1 and how does this change their autonomy, practice and position compared to other stakeholders?*
	Does sugar beet H7-1 change the power dynamic among stakeholders? If so, how?
	Can the development, introduction or use of sugar beet H7-1 create significant ruptures or ecological relationships?
Co-existence	*Does the cultivation of sugar beet H7-1 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

Sugar beet is not cultivated in Norway at present. Some varieties was grown during world war 2, the production has however not been economically profitable[2] and is climate dependent.

There is a wild relative of sugar beet growing in Norway, called "strandbete" or *Beta vulgaris* ssp. *Maritima*, growing mainly on the coastline around the Oslofjord and up to Stavanger[3]. It is also known that sugar beet can hybridize with wild relatives. Thus, there is a potential for spread of transgenes from gene modified to unmodified, wild population of sugar beet. In addition, seed from sugar beet can survive and be dormant for long periods before they start sprouting, in addition to the development of "stokkløpere"[4] from the plants that can give rise to new plants.

We highlight this issue, even though the application is not for cultivation.

2 https://snl.no/sukkerbete
3 http://www.artsdatabanken.no/ScientificName/155217
4 https://snl.no/stokkl%C3%B8ping_-_botanikk

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

Sugar beet H7-1 was developed by KWS SAAT SE and Monsanto Company and provides tolerance to glyphosate based herbicides, conferred by the expression of CP4 EPSPS protein. It is therefore associated with the trademark Roundup Ready®.

Molecular characterization

The applicant states "that this renewal application is accompanied by [..] any other new information which has become available with regard to the evaluation of the safety in use of the food/feed and the risks of the food/feed to animals, humans or the environment (*see* Annex 3 of this renewal application)" and draws the conclusion that "the new information, including independent peer-reviewed literature, updated bioinformatic analyses and studies performed by the applicant, that has become available since H7-1 was authorized, do not change in any way the conclusions of the original risk assessment."

Annex III contains information regarding detection method, validation, choice of primers/probes and information regarding reference material. Accompanying the application, we have also looked at an EFSA opinion (3) and a German report (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) on the environmental risk assessment and monitoring plan (32). The other two remaining documents are a short summary of the applicant and the application for renewal (3 pages). No information of additional bioinformatics analysis, literature reviews or additional studies are supplied. Literature searches in scientific databases (www.pubmed.com) does not reveal a vast body of research on GM sugar beet.

Gene flow

As noted by Bioteknologinemda (now Bioteknologirådet) in 2009 (http://www.bioteknologiradet.no/filarkiv/2010/07/genialt4-2009_s10_genmodifisert_sukkerbete.pdf) sugar beet has a high potential for spreading seeds through waterways and sea currents. Studies shows that up to 30% of the seeds are viable even after 20 weeks in salt water. In addition, sugar beet have a high cross-over potential to other cultivated beet varieties and wild populations, such as the rare and endangered species strandbete (*Beta vulgaris ssp. Maritima*). The high outcrossing rate of sugar beet is supported by a paper by Sanchez et al., (33) that found Chilean sugar beet to have an outcrossing potential from medium to high, depending on the region analysed.

Comments relevant for the assessment of the current application

The presence of wild relatives of sugar beet in Norway is relevant for the assessment of potential for spread of transgenes in Norway (see section on p.14).

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

Toxicity and allergenicity

Bioinformatic analyses on allergenicity and toxicity

Since 2004, when the original application was submitted, and 2007 when it was approved, significant progress and development of databases and algorithm of database-searches has been achieved. There is no information on updated searches of potential allergenic (or toxicological) motifs of the expressed traits.

Potential interactions between newly expressed proteins

Only CP4 EPSPS is expressed from transgenes. Interaction assessment is not relevant.

Hazard identification

No data available in the documents available.

Summary:

- No new bioinformatics studies have been performed for the assessment of allergenicity of toxicity.

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 (16).

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 is also linked to resistance evolution in weeds. At present, 36 species of weeds are documented to be glyphosate resistant on a global scale (34). 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 (35). Crop and herbicide monoculture makes the agroecosystem more vulnerable to further resistance development (36).

Sustainability

For the farmers, resistant weeds are a difficult obstacle to handle. 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 development of resistance are factors not contributing to sustainable agriculture.

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 (16), which directly or indirectly will expose non-target biodiversity in terrestrial, soil and aquatic communities (37), 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 (31). 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 (38).

The increased awareness of glyphosate toxicity, coupled with the increased volume used should increase the awareness to the maximum residue level (MRL) for glyphosate that has been raised 200-fold from 0.1 to 20 mg/kg in Europe,, and to 40 mg/kg in the US (39). This set of events has been termed "The Glyphosate Paradox" (40). The WHO/IARC categorization of glyphosate as *probably carcinogenic to humans (41)*, although disputed by EFSA (42), is underlining the significance of the controversy around the glyphosate-based herbicides.

Glyphosate tolerance

The *cp4 epsps* gene present in H7-1 sugar beet 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 (31, 43). However, glyphosate has recently received more risk-related attention due to its potential for negative effects on both aquatic and terrestrial ecosystems (44), as well as from studies in animals and cell cultures that have indicated possible negative health effects in rodents, fish and humans (45-47).

It has also been shown that agriculture of GM plants is associated with greater overall usage of pesticides than the conventional agriculture (48).

A number of publications indicate unwanted effects of glyphosate on health (47, 49), aquatic (50) and terrestric (44, 51) organisms and ecosystems. Also, a study of Roundup (containing glyphosate as the active ingredient) effects on the first cell divisions of sea urchins (52) 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 (45) 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 (53). 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.
Glyphosate has recently been under significant debate in Europe for its potential health risk. There is no updated information on herbicide residues in sugar beet based on 10 years of approval in EU.
Additionally, the International Agency for Research on caner (IARC) released a report where glyphosate was considered as "probably carcinogenic to humans"(54), an issue which is under debate.

Summary:

- A herbicide tolerance gene is inserted into sugar beet H7-1.
- Glyphosate has and increased focus due to potential health related effects.
- Attention should be given to the potential for accumulation of glyphosate in sugar beet.

Main summary

Sugar beet event H7-1 is tolerant to herbicides containing glyphosate that has increased focus due to potential for 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, sugar beet has wild relatives in Norway, thus, there is a potential for cross hybridization between transgenic sugar beet and wild relatives in Norway, when present.
The applicant should provide data relevant for assessment of social utility and sustainable development according to the NGTA (4).

References.

1. Safety NSCfF. UTTALELSE VEDRØRENDE KWS SAAT AG OG MONSANTOS GENMODIFISERTE SUKKERROE H7-1 RR (EFSA/GMO/UK/2004/08). Uttalelse. VKM, organismer Ffg; 2005 2005/08/24. Report No.: 05/314 Contract No.: 05/314.
2. Bioteknologinemnda. Søknad EFSA/GMO/DE/2008/63: Genmodifisert sprøytemiddeltolerant sukkerbetelinje H7-1 fra KWS SAAT AG og Monsanto til import, prosessering, mat og fôr og dyrking under EUforordning 1829/2003 (første innspillsrunde). 2009:4.pp.
3. European Food Safety A. Opinion of the Scientific Panel on genetically modified organisms [GMO] related on an application (Reference EFSA GMO UK 2004 08) for the placing on the market of products produced from glyphosate tolerant genetically modified sugar beet H7-1, for food and feed uses, under Regulation (EC) No 1829/2003 from KWS SAAT AG and Monsanto. EFSA Journal. 2006;4(12):431-n/a.
4. Gene Technology Act, NGTA(1993).
5. Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory Text with EEA relevance, (2015).
6. European Commission. Responsible Research and Innovation. Europe’s Ability to Respond to Societal Challenges. KI-31-12-921-EN-C: Available from: ec.europe.eu; 2012.
7. Hoven Jvd. Options for strengthening Responsible Research and Innovation. Report of the Expert Group in the State of the Art in Europe on Responsible Research and Innovation. KI-NA-25-766-EN-C: Available from: ec.europe.eu; 2013.
8. Strand R, Spaapen J, Bauer M, Hogan E, Revuelta G, Stagl S, et al. Indicators for promoting and monitoring Responsible Research and Innovation. Report from the Expert Group on Policy Indicators for Responsible Research and Innovation. KI-NA-26-866-EN-N: Available from: ec.europe.eu; 2015.
9. Hartley S, Gillund F, van Hove L, Wickson F. Essential Features of Responsible Governance of Agricultural Biotechnology. PLoS Biol. 2016;14(5):e1002453.
10. Pavone V, Goven J, Guarino R. From risk assessment to in-context trajectory evaluation-GMOs and their social implications. Environmental Sciences Europe. 2011;23(1):1.
11. Binimelis R, Myhr AI. Inclusion and Implementation of Socio-Economic Considerations in GMO Regulations: Needs and Recommendations. Sustainability. 2016;8(1):62.
12. Bioteknologirådet. Herbicide-resistant genetically modified plants and sustainability. Oslo, Norway: Bioteknologirådet; 2014.
13. Vazquez MA, Maturano E, Etchegoyen A, Difilippo FS, Maclean B. Association between Cancer and Environmental Exposure to Glyphosate. International Journal of Clinical Medicine. 2017;8(02):73.
14. Dill GM, Sammons RD, Feng PCC, Kohn F, Kretzmer K, Mehrsheikh A, et al. Glyphosate: Discovery, Development, Applications, and Properties. Glyphosate Resistance in Crops and Weeds: John Wiley & Sons, Inc.; 2010. p. 1-33.

15. Benbrook CM. Impacts of genetically engineered crops on pesticide use in the US - the first sixteen years. Environmental Sciences Europe. 2012;24(1):24.
16. Benbrook CM. Trends in glyphosate herbicide use in the United States and globally. Environmental Sciences Europe. 2016;28(1):1-15.
17. Bøhn T, Cuhra M, Traavik T, Sanden M, Fagan J, Primicerio R. Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM soybeans. Food chemistry. 2014;153:207-15.
18. Dolezel M MM, Eckerstorfer M, Hilbeck A, Heissenberger A, Gaugitsch H. Standardising the Environmental Risk Assessment of Genetically Modified Plants in the EU. Final report. Bonn, Germany: Umweltsbundesamt GmbH, regulation B-G; 2009 April 2009.
19. Chern WS, Rickertsen K, Tsuboi N, Fu T-T. Consumer acceptance and willingness to pay for genetically modified vegetable oil and salmon: A multiple-country assessment. 2003.
20. Grimsrud KM, McCluskey JJ, Loureiro ML, Wahl TI. Consumer attitudes to genetically modified food in Norway. Journal of Agricultural Economics. 2004;55(1):75-90.
21. Bugge AB, Rosenberg TG. Fremtidens matproduksjon. Forbrukernes syn på genmodifisert mat: GMO-mat eller ikke? Oslo: Forbruksforskningsinstituttet SIFO; 2017.
22. Stilgoe J, Owen R, Macnaghten P. Developing a framework for responsible innovation. Research Policy. 2013;42(9):1568-80.
23. Hilbeck A, Binimelis R, Defarge N, Steinbrecher R, Székács A, Wickson F, et al. No scientific consensus on GMO safety. Environmental Sciences Europe. 2015;27(1):4.
24. Fischer K, Ekener-Petersen E, Rydhmer L, Björnberg K. Social Impacts of GM Crops in Agriculture: A Systematic Literature Review. Sustainability. 2015;7(7):8598.
25. Devos Y, Demont M, Dillen K, Reheul D, Kaiser M, Sanvido O. Coexistence of genetically modified (GM) and non-GM crops in the European Union. A review. Agronomy for Sustainable Development. 2009;29(1):11-30.
26. European Commission. Commission addresses GM crop co-existence. Brussels: Press Release, IP/03/314; 2003.
27. Purnhagen K, Wesseler J. The Principle (s) of Co-existence in the Market for GMOs in Europe: Social, Economic and Legal Avenues. The Coexistence of Genetically Modified, Organic and Conventional Foods: Springer; 2016. p. 71-85.
28. Herrero A, Binimelis R, Wickson F. Just existing is resisting: The everyday struggle against the expansion of GM crops in Spain. Sociologia Ruralis. 2017.
29. Binimelis R, Wickson F, Herrero A. Agricultural Coexistence. 2016.
30. Herrero A, Wickson F, Binimelis R. Seeing gmos from a systems perspective: The need for comparative cartographies of agri/cultures for sustainability assessment. Sustainability. 2015;7(8):11321-44.
31. Duke SO, Powles SB. Glyphosate: a once-in-a-century herbicide. Pest Management Science. 2008;64(4):319-25.
32. Lebensmittersicherheit BfVu. APPLICATION EFSA-GMO-DE-2008-63 UNDER REGULATION (EC) Nº 1829/2003 FROM KWS SAAT AG AND MONSANTO EUROPE, S.A. CONCERNING THE PLACING ON THE MARKET OF GLYPHOSATE-TOLERANT SUGAR BEET H7-1 FOR CULTIVATION. Environmental risk assessment and monitoring plan. 2010 2010/12/03.

33. Sánchez MA, Cid P, Navarrete H, Aguirre C, Chacón G, Salazar E, et al. Outcrossing potential between 11 important genetically modified crops and the Chilean vascular flora. Plant biotechnology journal. 2016;14(2):625-37.
34. Heap I. The International Survey of Herbicide Resistant Weeds Weedscience.org: Weedscience.org; 2017 [cited 2017 14.March]. Available from: http://www.weedscience.org/.
35. Binimelis R, Pengue W, Monterroso I. "Transgenic treadmill": Responses to the emergence and spread of glyphosate-resistant johnsongrass in Argentina. Geoforum. 2009;40(4):623-33.
36. Beckie HJ, Tardif FJ. Herbicide cross resistance in weeds. Crop Protection. 2012;35:15-28.
37. Venter HJ, Bøhn T. Interactions between Bt crops and aquatic ecosystems: A review. Environmental Toxicology and Chemistry. 2016:n/a-n/a.
38. Bohn T, Cuhra M, Traavik T, Sanden M, Fagan J, Primicerio R. Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM soybeans. Food chemistry. 2014;153:207-15.
39. Cuhra M, Traavik T, Dando Ml, Primicerio R, Holderbaum DF, B?hn T. Glyphosate-Residues in Roundup-Ready Soybean Impair Daphnia magna Life-Cycle. Journal of Agricultural Chemistry and Environment. 2015;Vol.04No.01:13.
40. Cuhra M, Bøhn T, Cuhra P. Glyphosate: Too Much of a Good Thing? Frontiers in Environmental Science. 2016;4(28).
41. Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology. 2015;16(5):490-1.
42. European Food Safety A. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal. 2015;13(11):4302-n/a.
43. Giesy JP, Dobson S, Solomon KR. Ecotoxicological Risk Assessment for Roundup® Herbicide. In: Ware GW, editor. Reviews of Environmental Contamination and Toxicology: Continuation of Residue Reviews. New York, NY: Springer New York; 2000. p. 35-120.
44. Blackburn LG, Boutin C. Subtle effects of herbicide use in the context of genetically modified crops: a case study with glyphosate (Roundup). Ecotoxicology (London, England). 2003;12(1-4):271-85.
45. Axelrad JC, Howard CV, McLean WG. The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon. Toxicology. 2003;185(1-2):67-78.
46. Benachour N, Sipahutar H, Moslemi S, Gasnier C, Travert C, Seralini GE. Time- and dose-dependent effects of roundup on human embryonic and placental cells. Archives of environmental contamination and toxicology. 2007;53(1):126-33.
47. Dallegrave E, Mantese FD, Coelho RS, Pereira JD, Dalsenter PR, Langeloh A. The teratogenic potential of the herbicide glyphosate-Roundup in Wistar rats. Toxicology letters. 2003;142(1-2):45-52.
48. Benbrook C. Impacts of Genetically Engineered Crops on Pesticide Use in the United States: The First Thirteen Years. The Organic Center: The Organic Center; 2009.
49. Malatesta M, Caporaloni C, Gavaudan S, Rocchi MB, Serafini S, Tiberi C, et al. Ultrastructural morphometrical and immunocytochemical analyses of hepatocyte nuclei from mice fed on genetically modified soybean. Cell structure and function. 2002;27(4):173-80.

50. Solomon KR, Thompson DG. Ecological risk assessment for aquatic organisms from over-water uses of glyphosate. Journal of toxicology and environmental health Part B, Critical reviews. 2003;6(3):289-324.
51. Ono MA, Itano EN, Mizuno LT, Mizuno EH, Camargo ZP. Inhibition of Paracoccidioides brasiliensis by pesticides: is this a partial explanation for the difficulty in isolating this fungus from the soil? Medical mycology. 2002;40(5):493-9.
52. Marc J, Mulner-Lorillon O, Boulben S, Hureau D, Durand G, Belle R. Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. Chemical research in toxicology. 2002;15(3):326-31.
53. Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini G-E. Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase. Environmental Health Perspectives. 2005;113(6):716-20.
54. Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology.16(5):490-1.