GenØk - Centre for Biosafety

# Impact assessment of maize MON 87460 from Monsanto (EFSA/GMO/NL/2009/70)

**With conclusion in Norwegian**

**Anne I. Myhr and David Quist**

**GenØk – Centre for Biosafety**

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# Konklusjon

GenØk –Senter for Biosikkerhet viser til brev fra Direktoratet for Naturforvaltning (DN) angående høring relatert til MON 87460 for bruksområdene import, prosessering, mat og fôr. Søknaden gjelder ikke dyrkning.

Maisplanten MON 87640 er modifisert med hensikt på å oppnå økt tørketoleranse. Transformasjons prosessen har blitt mediert ved hjelp av Agrobacterium og sentrale innsatte gener er *cspB* og *nptII*. *CspB* (Cold shock protein B) er isolert fra bakterien *Bacillus Subtilis* og har en funksjon som skal føre til redusert avlingstap under forhold med redusert vanntilgang. *NptII* er et antibiotikaresistensmarkør gen med opprinnelse i bakterien *E.coli* og gir planten resistens mot antibiotika som kanamycin og neomycin. *nptII* er introdusert i planten som seleksjonsmarkør for identifikasjon av transformater under regenerasjon.

Informasjonen som er tilgjengelig fra søker er ikke tilstrekkelig for uavhengig evaluering av vitenskapelig kvalitet i søknaden. Det foreligger ingen resultater fra analyser eller detaljerte forsøksoppsett til oppklaring av DNA sekvens, lokalisering av transgenet i maisgenomet, protein uttrykk, toksikologiske/immunologiske effekter eller foringsforsøk i relevante dyremodeller. Det er heller ikke opplyst hvorvidt søker har frigitt frø fra den genetisk modifiserte planten og relevante ikke-GMO kontroll planter. Dette er nødvendig for at fri og uavhengig forskning med denne planten skal være mulig.

Genøk ønsker å påpeke at det er kunnskapshull med hensyn på mulige helseeffekter ved MON 87640. Maislinjen 87640 uttrykker et nytt protein (cspB) og GenØk etterlyser derfor studier med hensyn på mulige helseeffekter. Søker har utført analyser av ernæringsmessige viktige komponenter, men denne studien har ikke vært tilgjengelig. Søker har heller ikke utført subkronisk föringsforsøk på rotter.

Ut fra medisinske- og veterinærmedisinske hensyn mener GenØk at en overføring til mage/tarm bakterieflora via mat eller fôr av antibiotikaresistensgenet *nptII* (som gir resistens mot blant annet kanamycin og neomycin) bør forhindres. Vi ønsker også å påpeke at GM planter med antibiotika resistensgener er ikke tillatt omsatt i Norge.

Søker gir ikke opplysninger som adresserer vurderingskriteriene bærekraft, samfunnssnytte og etiske aspekter som forutsettes anvendt i den norske Genteknologiloven. I denne sammenheng er det viktig å få dokumentert om MON 87640 fører til redusert avlingstap under forhold med redusert vanntilgang, samt erfaringer med hensyn på effekter på miljø, helse og samfunnsaspekter hos bønder som dyrker denne planten. Denne type dokumentasjon er ikke vedlagt søknad om omsetting av MON 87640.

GenØk vil derfor foreslå med hensvisning til de overnevnte kunnskapshull og viser til føre-var prinsippet og avslår søknaden om omsetting av MON 87640 i Norge.

**About the plant**

MON 87460 was developed through *Agrobacterium*-mediated transformation of conventional maize variety embryos and expresses cold shock protein B (*CspB*) from *Bacillus subtilis* and *nptII* from Tn5 of Escherichia coli. The *nptII* gene give the plant resistance to antibiotics (as kanamycin and neomycin) and the CspB confers the potential production of reduced yield loss under water-limited conditions compared to conventional maize.

***Information relating to the genetic modification***

In general, the parts of the application made available for comments lack details about experiments and/or methods produced by the applicant necessary to assess the validity of the stated conclusions.

The applicant should provide extensive sequence data on both the constructs and flanking sequences in the final hybrid and in subsequent generations of offspring in order to investigate the stability of the insert and described within.

The MON 87460 event includes the *nptII* expression cassette flanked by two functional loxP sites. The loxP recombination site is recognized by the P1 bacteriophage Cre recombinase. Given that: 1) the *nptII* gene is regulated by the 35S promoter that is known to be active also in bacteria, and 2) the functional antibiotic resistance marker is flanked on both sites by loxP recombination sites, an enhanced recombination potential in bacterial environments with functional CRE proteins is present. Thus, it is reasonable to assume that the *nptII* gene in this event has an increased likelihood of successful recombination and expression in exposed bacterial recipients. The Cre producing PI bacteriophage is known to have a broad host range and can be found in a range of bacteria naturally present in the gastrointestinal tract of mammals and humans.

The applicant reports unintended sequence deletions at both ends of the inserted cassette following host transformation. Such complex rearrangements are known to give rise to unintended expression, regulatory and pleiotropic effects. The applicant does not give any information of the functional consequences on the expression or regulation of the recombinant protein or for endogenous gene expression, or even further bioequivalence studies to substantiate the claim of equivalence of bacterial versions of the transgenic protein used in safety testing and the actual (admittedly modified from the native) protein produced by the host maize plant. Such information is essential to scientifically evaluate statements of safety.

***Information in relation to animal and human health***

According to the applicant, MON 87460 does not pose any adverse effects for humans and animals. Although the applicant has performed an analysis which demonstrated compositional and nutritional equivalence of grain and forage from MON 87460 and conventional maize, they have not performed any analysis that establishes the types of changes that might be unwanted (e.g. toxicological or immuno-stimulatory) or undesirable in exposed organisms.

Lastly, the applicant's claims of safety stated in part 7.8 are based largely on assumptions and lack of existing evidence, rather than empirical data established through actual scientific testing. The oral toxicity studies utilized target proteins outside of the expression environment of the host maize plant, ignoring the known effects of host expression and changes possible through transgenesis. Therefore, the presented studies are insufficient to demonstrate the safety of the heterologous proteins expressed in MON87460.

Perhaps most importantly, we are reminded of the general prohibition of ARM genes in GM-plants in Norway. MON 87460 contains *nptII* that give the plant resistance to antibiotics (as kanamycin and neomycin). The Norwegian parliament in 1997 established provisions that prohibit the production and import of GM products that contain genes that give antibiotic resistance.

***Information in relation to environmental effects***

The application is made for consent to import and use MON 87460, but not including the cultivation of varieties of MON 87460 in the EU. Due to the very little amount of maize grown in Norway there is a low probability for hybridisation with maize in agriculture. The climatic condition is also reducing the probability for germination and establishment resulting in the development of mature plants of MON 87460 in the Norway.

**Precautionary approach to risk assessment**

The Precautionary principle requires commitment to the idea that full scientific proof of a causal link between a potentially damaging operation and a long term environmental impact is not required to take action in order to avoid negative effects on health and the environment. Due to the lack of information available in the scientific literature genetic stability, expression of inserted proteins or immune effects as well as the lack of experience with the new event (cspB) of the MON 87460, we find that these uncertainties warrant further research and advise observance of the precautionary principle until the assumptions and claims made by the applicant can be verified. The current level of evidence, and given data does not justify confidence in the stated conclusions by the applicant.

**Available information for risk assessment evaluation**

This evaluation is for the most part based on the applicants' own submitted information. The directly relevant peer-reviewed literature is very limited but we have tried to extract relevant indirect information from the peer-reviewed literature.

All product-related safety testing should have an independent, unbiased and transparent character. This goes both for the production of data for risk assessment, and for the evaluation of those data. The level of detail provided, and the subtle effects of funding bias well documented to occur in product safety research, leaves open significant doubt concerning the scientific validity of the purported claims of safety made by the applicant. Transparent reporting of data and methods would significantly increase the possible reproducibility and verifiability of the research within.

**On confidentiality of information**

The documentation accompanying GMO applications may be problematic for four reasons. The first problem regards transparency and confidentiality. Some of this information is available on the internet, through the European Food Safety Authority (EFSA), but varying parts essential for independent essential are confidential. The problem of confidentiality that is linked to the documentation provided by the GMO applications has several implications. Access to peer-reviewed quality data is essential for a "sound science" risk assessment where independent verification of methods, data and results can be performed. However, the reliability and scientific quality of applicant data, where it has been independently examined, has shown not to warrant strong claims to safety. In this case, we did not find any experimental data on the safety of MON 87460 available in the peer-reviewed literature. The available documentation is supplied with references, but a substantial part of these references point back to the research departments of the applicant itself, are considered confidential business information and therefore not accessible. Another problem is partly particular to the Norwegian situation, namely that important aspects are lacking. Most apparent is of course the lack of information about sustainable development and societal utility.

**Sustainability**

In addition to the EU regulatory framework for GMO assessment, impact assessment in Norway follows the Norwegian Gene Technology Act, which states that "in deciding whether or not to grant the application, significant emphasis shall also be placed on whether the deliberate release represent a benefit to the community and a contribution to sustainable development" hence, in the Norwegian context the contribution to sustainable development should be assessed together with an evaluation of the societal utility in applications of use and release of GMOs.

The purpose of MON 87460 is to achieve drought tolerance that is an interesting trait with regard to potential for growth under climatic difficult conditions. Hence, the plant may contribute to increased food security under in dry or water limited conditions, however, Monsanto do not provide any documentation that supports that MON 87460 is effective in producing a viable yield under such conditions, or the *portion of contribution to abiotic stress attributable to the genetic modification and the portion attributable to the base genetic of the host plant*. Documentation with regard to yield loss under dry and water-limited conditions, particularly during flowering and grain fill periods when maize yield potential is most sensitive to stress, should therefore be provided in order to assess the added value of the recombinant trait.

The Norwegian Gene Technology Act, also established consideration health and environmental effects in other countries, such as where GMOs are grown, often in developing countries. MON 87460 has been tested in six field sites in the U.S and four field sites in Chile. The protein expression, the composition, the safety, the agronomic and the phenotypic characteristics of MON 87460 have been studied at multiple locations that cover a range of environmental conditions. No documentation on irrigation practices is however provided from these field sites. Such data should be provided since environmental conditions (e.g. water availability via irrigation), as well as agronomic and phenotypic characteristics, may affect protein expression. There are also no data on whether MON

87460 has any implications on agriculture practises or the surrounding environment. With maize in general there are great differences between; regional growing environments, scales of farm fields, crop management practices, local/ regional target and non-target species considered most important in the agro-ecosystem, interactions between cultivated crops, and surrounding biodiversity. Toxicity and environmental impact data on other species (e.g. regionally appropriate non target insects, including other non-domesticated herbivores) and regional environments (local growing regions) would be needed to accurately determine environmental impacts to local fauna of by MON 87460 and its degradation products, i.e. resulting from ingestion by herbivores and decomposition in the soil of plant material and root exudates. Such information merits consideration under the Norwegian Gene Technology Act.

**Societal utility**

The concept of societal utility is found in the Gene Technology Act §10. The NBAB have chosen to separate the assessment of societal utility with regard to a) the products properties, and b) the development and use of the product, and has elaborated the following questions to be addressed;

*The products properties;*

*Is there a need for this product?*

*May the product solve or contribute to solve a societal problem?*

*Is the product better than equivalent products on the market?*

*Are there any alternative products that may solve or contribute to solve the societal problem in questions?*

*The development and use of the product;*

*Does it help to create new opportunities?*

*Does it help to create new opportunities in urban areas?*

*Does it help to create new opportunities in other countries?*

*Does it entail problems for existing production that need to be conserved?*

*Does it entail problems for existing production in other countries?*

Maize is not a critical resource in Norway as food, but is of high relevance to the feed FM-free, this may change in the future. The applicant of MON 87460 argues that consumption is safe based on the presumed safety provided by other GM maize varieties. The majority of feeding studies, while currently unverifiable, support the claims that the GM maize is as safe as the non-GM counterpart, although there are uncertainties as described in the beginning of this document. Whether the GM maize is a better product than non-GM maize in terms of consumer health is still an unresolved issue.

Further, potential drought tolerance trait provided by MON 87460 is not a relevant factor for Norway, given that drought is not a problem; hence MON 87460 has little to no benefit to Norwegian agriculture. In other parts of the worlds where drought are a major problem or where there are not well developed water irrigation systems, the use of MON 87460 holds promises for societal benefits as food security by reducing yield loss.

**Conclusion**

In summary, the information provided by the applicant on MON87460 is insufficient to establish the either the efficacy of the intended trait, or scientific methodology or data interpretations used to support claims of safety are actually valid. Given that most of the assertions of safety are based on untested assumptions, rather than actual hard evidence established through experimental observation, leaves us to conclude that the evidence presented insufficient for a science-based evaluation of risk.

Where there is supposedly evidence available, it is not subject to verification as it is not reported or not made available. The burden of proof of stated rests with those making the claim of safety, and the proof is lacking in this case. Further, the significant gaps of knowledge in the bioequivalence of the intended insertion cassette vs. the actual (truncated) expression cassette derived from the transformation of MON87460 leaves a broad uncertainty as to the real efficacy or safety of the intended product. Without such information, it is impossible to see how either the applicant, or anyone assessing the available information, could reason a definitive conclusion of safe use. This, along with the prohibited use of antibiotic resistance genes in transgenic organisms in Norway, compels our recommendation to not approve MON 87460 for the requested use.