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**REPRÉSENTATION PERMANENTE DE LA FRANCE**
**AUPRÈS DE L'UNION EUROPÉENNE**

**Le Représentant Permanent Adjoint**

Bruxelles, le 6 mai 2009

Réf. : n°1236/PLC/ip
ITEC/560/2009

Madame la Directrice,

Je vous prie de bien vouloir trouver ci-joint une lettre des Ministres de l'Environnement, de l'Agriculture et/ou de la Santé de 12 Etats membres demandant un examen approfondi du dossier de renouvellement du maïs Monsanto 810 qui puisse apporter des réponses aux interrogations soulevées par l'évaluation de l'Espagne et par les différentes clauses de sauvegarde.

Je vous prie d'agréer, Madame la Directrice, mes respectueux hommages.

Philippe L'EGLISE-COSTA

Madame Catherine GESLAIN-LANEELLE
Directrice de l'Agence européenne de sécurité des aliments
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**Ministry of Health – Austria**

**Ministry of Agriculture, Forestry, Environment and Water Management –Austria**

**Ministry of Environment and Water - Bulgaria**

**Ministry of Agriculture, Natural Resources and Environment – Cyprus**

**Ministry of the Environment – Czech Republic**

**Ministry of Ecology, Energy, Sustainable Development and Town and Country Planning – France**

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LE GOUVERNEMENT
DU GRAND-DUCHÉ DE LUXEMBOURG
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**Ministry of the Environment - Poland**

Dear Madam,

The application for the renewal of MON810 authorisation is currently being examined.

In keeping with the Council's work on GMOs under the French Presidency of the European Union in the second half of 2008, we would like this re-assessment underway to provide all the Member States, especially those that have invoked safeguard clauses, with responses to all the arguments and concerns they have raised so as to be in a position to answer the general public's concerns. It should be noted that these questions are behind some of the concerns that prompted the invoking of safeguard clauses. In this regard, we would like EFSA to finalise its assessment work based on the additional information that EFSA itself, the assessor Member State and the other Member States requested for the appraisal of this case.

The various meetings between scientists of the Member States invoking safeguard clauses and EFSA experts have pointed up elements, detailed in the appendix, that have not been answered and to which the assessment underway by EFSA and the management measures subsequently proposed by the Commission should respond.

For example, one of the outstanding questions concerns the risk of the development of resistance in target species to the Cry1Ab protein produced by MON810 maize. This risk is now largely acknowledged: France and Hungary raised it in connection with the safeguard clause; Spain indicated in its environmental risk assessment (ERA) of MON810 renewal that there is a risk of insects developing resistance to the Cry1Ab protein in the medium or long run; and EFSA also acknowledged the existence of this risk at the SCFCAH meeting on 16 February 2009. Spain and EFSA consequently advocate specific monitoring and the introduction of resistance "management" plans. The risk assessment should therefore consider the possibility of the development of resistance and assess the available risk management measures so that the appropriate ones be set in the authorisation decision (e.g. refuge zones, distances, monitoring...to be adapted to concerned territories).

Another important question awaiting an answer is that of the impact of MON810 crops on non-target species. Spain's assessment states that the elements provided by Monsanto do not include any studies on non-target European lepidoptera and that the petitioner omitted to include these lepidoptera in the potentially affected populations. EFSA has asked Monsanto for more information on this question and it is important that the information provided should adequately represent the European species and territories and be precise enough for a decision to be made.

It is vital for the assessment underway to provide substantiated answers to all the questions raised by the Member States and their scientific experts in order to, a) ensure the completeness of the risk assessment including the description of uncertainties for each identified risks and b) enable the Member States to scrutinize a decision on the renewal of the authorisation to cultivate MON810 and, where necessary, define in the authorisation decision the management measures required to minimise any potential impact of these crops on the environment. Given that the current authorisation does not call for any specific measures to be put in place to tie in with the cultivation of MON810, the questions now raised by the safeguard clauses and the MON810 renewal assessment can only be answered once a new decision proposal addressing these concerns has been examined. Last but not least, this assessment should be consistent with the conclusions of the Council of European Ministers meeting of 4 December 2008 and should demonstrate the requested improvements to the environmental assessment, especially regarding medium- and long-term environmental impacts and consideration of the particularities of ecosystems and geographic areas, in particular sensitive and/or protected areas.

We therefore ask EFSA to consider the appended outstanding questions in greater depth with the scientific teams that raised them before any opinion can be expressed on the renewal of authorisation to cultivate MON810.

This letter is also sent to Mr. Stavros DIMAS European Commissioner for the Environment.

Yours sincerely,

**The Austrian Minister for Health and**
**The Austrian Minister for Agriculture, Forestry, Environment and Water Management:**

**Alois Stöger** **Nikolaus Berlakovich**

**The Bulgarian Minister of Environment and Water**

**Dzhevdet Chakarov**

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**Michalis Polynikis Charalambides**

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**Jean-Louis Borloo** **Chantal Jouanno**

**The French Minister of Agricultures and Fisheries**

Michel Barnier

**The Greek Minister of Rural Development and Food and**
**The Greek Deputy Minister of Environment**

**Sotiris Hatzigakis** **Stavros Kalogiannis**

**The Hungarian Minister of Environment and Water and**
**The Hungarian Minister for Agriculture and Rural Development:**

**Gráf József**

SZABÓ Imre

**The Irish Minister for the Environment, Heritage and Local Government**

**John Gormley**

**The Latvian Minister of the environment and**
**The Latvian Minister of Agriculture**

**Mr.Raimons Vejonis** **Mr. Janis Düklavs**

**The Minister of Health from Luxembourg**

**Mars Di Bartolomeo**

**The Prime Minister of Malta**

**Lawrence Gonzi**

**The Polish Minister of the Environment**

**Maciej Nowicki**

# APPENDIX

# MAIN UNRESOLVED POINTS ARISING FROM THE SPANISH ASSESSMENT OF MON810 AND THE SAFEGUARD CLAUSES REGARDING MON810

## A)IMPACTS ON NON-TARGET FAUNA

The first important question awaiting an answer is that of the impact of MON810 crops on non-target species. Spain's assessment states that the elements provided by Monsanto do not include any studies on non-target European lepidoptera and that the petitioner omitted to include these lepidoptera in the potentially exposed populations. EFSA has asked Monsanto for more information on this question and it is important that the information provided should adequately represent the European species and territories and be precise enough for a decision to be made.

### 1) Non-target fauna: Spanish assessment

The Spanish assessment asks Monsanto to include in its dossier the references to the publications concerned and a summary of the findings of these publications (§ 3 and 4 of point 5.5, p. 7).

Monsanto's dossier furthermore presents a table of potential adverse effects on populations exposed to MON810. Spain states that these elements do not reflect any studies on non-target European lepidoptera. Spain also notes that Monsanto has not included these lepidoptera in the potentially affected populations (§ 4 and 5 of point 5.5, p. 7). It considers that these aspects have therefore not been resolved and must be addressed in detail by the monitoring plan.

Spain moreover states that the general monitoring proposed by Monsanto consists merely of questionnaires, which are incapable of revealing any adverse effects. It clearly deems that putting these questionnaires to farmers is not a suitable way to assess the unexpected effects of MON810 and that post-authorisation studies need to be conducted (§ 3 and 5 of point 6.1, pp. 10 and 11).

The Spanish assessment hence expresses the need for authorisation to impose a precise monitoring plan, which is not the case with the current authorisation.

### 2) Non-target fauna: French safeguard clause

In EFSA's comments on the French safeguard clause, it states that the length of the studies on the environmental impacts of the proteins examined does not generally cover the field lifetimes observed for these proteins. The question as to whether they have no effect over this length of time therefore remains unanswered.

Furthermore, EFSA's opinion (p. 25) does not dispute the findings regarding the effects of the Cry1Ab protein on certain parasitoids and pollinating insects, nor the possibility of consequently turning a

parasitoid into a pest. The question as to the effect of this protein on the functioning of the ecosystems and the vulnerability of the crops to new pests therefore remains unanswered.

Moreover, field observations in different geographic and meteorological conditions can give rise to different findings, positive or negative. Since these findings relate to different contexts, they do not offset each other. Yet, in this chapter, the opinion often draws a sort of "middling" conclusion from this wide range of situations without any real biological significance; the use of a theoretical model with reassuring findings could therefore be challenged compared with the findings of much more contrasting field observations (p. 11). Lastly, on a number of occasions, the opinion appears to consider that although measured environmental effects are similar in scale to other variations observed elsewhere due to the natural variability of the soils (p. 18) and places (p. 21), or are "relatively minor in comparison with known toxic chemicals" (p. 19), they are nonetheless negligible. This is far from evident given the large variability of the contexts. This question therefore also remains unanswered.

More generally, the opinion's wording tends to systematically play down the studies that find an effect (pp. 15, 16, 20, 21 and 22), but not those that come up with negative findings when the test conditions are similar. Yet the opinion acknowledges on page 15 and again on page 22 (conclusion to paragraph 2.1.3.8[1] that the studies' multiple factors are more likely to conceal than reveal existing effects; caution in interpretation should consequently apply inversely or at least in a balanced manner. This question therefore remains unanswered.

**3) Non-target fauna: additional comments from Austria:**

The data provided by the applicant are insufficient to perform a comprehensive risk assessment, e.g. to exclude effects on non-target organisms. Most tests for Cry1Ab were done with the isolated protein derived from bacteria and not with whole plants. The relevance of such studies is questionable. Studies providing evidence of unspecific toxicity due to Bt-toxin on non-target organisms have been published and several studies addressing these problems were made available to the European Commission and EFSA.
Austria relies on sustainable agriculture and emphasises a high level of protection for biodiversity. Concerning MON810 major environmental impact issues were not adequately addressed by the applicants. The major points of criticism are:
1. Remaining uncertainties concerning unintended effects on non-target organisms.
2. Uncertainties of the specificity of Cry1Ab on target and non-target organisms (e.g. only a very limited number of non-target organisms were tested). Cry1Ab specificity is a hypothesis.
3. It is highly questionable whether ERA data from a specific European region may be extrapolated to other regions in Europe. Generalizations are not justified.

There are several biodiversity hotspots in Austria with even high rates in farmland regions. A total of 215 different butterfly species were found in Austria. 152 of them were located in agricultural areas and most of these butterflies are characterized as endangered and some of them are on the red list of endangered species. Interim results of an ongoing large scaled study on biodiversity in Austria confirm this sensitivity.
These endangered butterfly species have to be protected from additional harm possibly resulting from MON810 cultivation.

In result the Austrian environment shows a high degree of biodiversity and is characterized by a small scale agricultural system. The data presented by the applicant are not sufficient to prove the safety of the transgenic maize lines due to the lack of relevant data; uncertainties are not addressed at all.

[1] "This confirms that studying all lepidopteran species that could be potentially exposed to Bt-maize pollen may be difficult in practice, especially if potential effects are to be detected (Lang, 2004; Gathmann et al., 2006b) against a wide range of existing environmental and agronomic stressors currently influencing lepidopteran populations (Aviron et al., 2006; Gathmann et al., 2006b.)."

**4) Non-target fauna: additional comments from Hungary:**

Taking into account that there is a great regional variation in species composition and abundance, and that agricultural practices in Europe significantly diverge, potential effects of MON810 on non-target organisms strongly depend on geographical factors. Therefore, different biogeographical regions within the EU – including the Pannonian – should be taken into account in the environmental risk assessment of MON810 which can not be found in the Monsanto documentation. In our opinion, there is a need on an in-depth analysis in this regard. Furthermore, concrete scientific studies assessing the potential effects on non target species including *Lepidoptera* are needed. These experiments should be carried out in different biogeographical regions of the EU, not in other regions of the World and own experiments of Hungary should also be taken into account (see supporting documents of the Hungarian safeguard clause).

Regarding the potential adverse effects of MON810 on non-target soil organisms, a Hungarian peer-reviewed article (Bakonyi et al. 2006) call the attention that (a) potential negative effects must be evaluated on species-level because different species react differently, (b) during the feeding of a certain *Collembolan* species, it gave a preference to the isogenic line instead of the Bt-maize. Also in an other article (Meissle et al. 2005), significant statistical differences have been found in this regard. There is a need on a thorough assessment of these issues.
Furthermore, in the framework of the risk assessment, a very limited number of other non-target organisms were tested. Many scientific studies have given evidence that non target species such as *Hymenopteras* populations, *Trichoptera* species can be adversely affected by MON 810. We believe that there is a need on further and detailed information in this respect.
Experimental data provided by Hungary should also be taken into account when assessing the environmental effects of MON810, especially on our protected *Lepidopteran* species including the protected *Inachis io* or *Vanessa atalanta*, where larval stages overlap with the pollen shed by maize. Postponed development and mortality of a part of larval population has been demonstrated by Hungary in the supporting documents of its safeguard clause.

**5) Non-target fauna: additional comments from Luxembourg**

EFSA has not yet issued an opinion on the Luxembourg safeguard clause of 23 March 2009. However, in its argument in support of the safeguard clause, Luxembourg stresses the effects on non-target organisms based on studies, some of which are very recent.

The argument shows that many field and laboratory studies have been conducted to evaluate the impact of Bt maize crops on non-target organisms. Some of these studies find minor effects (Pilcher *et al.* 1997; Romeis *et al.* 2004) while other studies demonstrate significant negative effects on non-target species (Hilbeck *et al.* 1998; Dutton *et al.* 2002; Meissle *et al.* 2005). A meta-analysis based on published data (Marvier *et al.* 2007) also shows that MON810 maize crops, compared with non-genetically modified lines, have an effect on the abundance of non-target insects.

In a review article (Hilbeck and Schmidt 2006), the authors estimate that approximately 50% of the studies examined dealing with non-target effects report adverse effects on one or more of the parameters studied and that the observed effects are often unpredictable in terms of extent and type of impact.

A recent study (Schmidt *et al.* 2009) shows that two-spot ladybirds (*Adalia bipunctata*) exposed to active proteins Cry1Ab and Cry3Bb (similar to those produced by the MON810 and MON863 maize lines) post greater mortality at the preimaginal stage as of doses of 5 microgrammes/ml. However, no difference is observed in the length of development and general weight of the insects that have reached adulthood. The researchers conclude that the higher mortality rate points to a direct toxic effect associated with the active proteins and therefore raise the question as to their specificity of action

given that the Cry1Ab toxin is supposed to act selectively on lepidopteran insects when the ladybird is a member of the Coleoptera.

The studies on exposure of non-target organisms to Bt maize concentrate mainly on land organisms with only scant coverage of aquatic organisms. A recent study of an aquatic organism (Bohne *et al.* 2008) finds long-term adverse effects on the growth of water fleas (*Daphnia magna*) fed on MON810 maize residues. The authors of this study note that the question of the causality of the observed effects remains open, but that their findings go hand in hand with the results of other studies (Lovie *et al.* 2005; Rosi-Marshall *et al.* 2007), also suggesting the need to conduct other studies involving non-target aquatic organisms.

The Luxembourg authorities consider that the cause of the unexpected toxicity of Cry1Ab in the two-spot ladybird needs to be found. The same goes for the adverse effects on non-target aquatic invertebrates, organisms for which there is not enough study of their exposure to the Cry1Ab toxin. As regards this toxin, whose mode of action is not entirely understood (Crickmore 2005) and for which new aspects have been found (Broderick *et al.* 2006), its unexpected effects on non-target organisms could be associated with different mechanisms.

**6) Non-target fauna: additional comments from Ireland**

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(It is important to note that the following commentary is based on information provided in the Appendix only as the Spanish Assessment Report referred to within that text was not available for review). It would appear reasonable that a precise monitoring plan is put in place re the development of resistance in insects however specific monitoring for non-target could be problematic given the complex array of interactions (agronomic and environmental) which can potentially influence lepidopteran populations. It is agreed that European species and territories should be adequately represented and where there is reason to believe that potential effects (relevant interactions) may exist then specific monitoring would be warranted. However it is important that monitoring is "relevant" as monitoring for the sake of monitoring would be wasteful in terms of resources (financial and personnel). Specific monitoring might also miss out on potential effects elsewhere while a more broad form of monitoring might reveal important areas for more targeted research.

In relation to the commentary provided in the Appendix for non-target fauna and the French Safeguard Clause there are many specific issues raised. As indicated by EFSA's scientific opinion, the environmental impacts of the proteins examined does not generally cover the field lifetimes observed for these proteins, however it is also noted that while Bt-toxins can be degraded or inactivated in soil within weeks, a small fraction can persist far longer under certain conditions. The opinion references laboratory studies which have shown that the Cry1Ab protein can bind on clay minerals and humic substances in soil, thereby reducing its availability to microorganisms and that this reduced availability decreases degradation of the Cry1Ab protein. Under these conditions it is therefore apparent that the duration of a lot of the "studies" were well within the ranges indicated for persistence of Cry1Ab protein in the soil. It is unclear however as whether or not longer studies to coincide with field lifetimes would illustrate any effect unless some form of cumulative effect is anticipated. While the scientific opinion refers to little or no evidence on cumulative effects it may be prudent for future studies on persistence of protein in the soil and potential environmental impacts to have corresponding timelines for comparison purposes.

The complex trophic chain effects on parasitoids appears somewhat inconclusive with respect to normal functioning of ecosystems and while EFSA's opinion does not dispute the findings regarding the effects of the Cry1Ab protein on certain parasitoids and pollinating insects, the GMO panel is of the view that the information provided does not provide any new or additional scientific evidence that would invalidate the previous risk assessments of maize MON810 for the non-target organisms. Given the complexity of ecosystem functioning and the inconclusive character of much of the studies

referenced some further research in this area would be recommended to further inform authorisation procedures.

It is possible that different geographic and meteorological conditions can potentially give rise to positive or negative conditions and this could be due in part to several factors including rainfall, temperature, topography and soil type. While it would very difficult to have representative data for all localised conditions it would appear reasonable that the main "regions" within Europe are considered to represent the different contexts that exist.

The measurement of environmental effects is a complex area and there is a strong element of the unknown or unconfirmed effects with respect to potential impact, which makes it difficult to determine whether the findings actually do "constitute a risk to human health or the environment". Comparison with natural variability factors and existing scenarios (known toxic chemicals etc.) is a valid method of risk assessment however it is difficult to pinpoint the exact cause and effect of a particular protein when a range of acceptable effects is evident. It is also difficult to compare when test conditions are not that similar or where different approaches/methodologies have been adopted. There is no doubt that some of the findings appear more robust than others and that additional research is warranted in some areas (Soil microbial activity etc.) so as to inform better the overall risk assessment process such as that currently being carried out for MON810.

## B)DEVELOPMENT OF RESISTANCE IN TARGET SPECIES

One of the outstanding questions concerns the risk of the development of resistance in target species to the Cry1Ab protein produced by MON810 maize. This risk is now largely acknowledged: France raised it in connection with the safeguard clause; Spain indicated in its environmental risk assessment (ERA) of MON810 renewal that there is a risk of insects developing resistance to the Cry1Ab protein in the medium or long run; and EFSA also acknowledged the existence of this risk at the SCFCAH meeting on 16 February 2009. Spain and EFSA consequently advocate specific monitoring and the introduction of resistance "management" plans.

The French scientists who met with the GMO Panel point out that the elements provided to date in the bibliography presented by EFSA do not lend sufficient support to the fact that the appearance of resistance can be sustainably managed by a refuge zone strategy. They report that the studies cited by EFSA contain no elements to assess resistance selection speed or conclude that the risks of European corn borer and Mediterranean corn borer resistance associated with large-scale maize cultivation in Europe could be managed by the proposed strategy. Spain explains in its assessment that the monitoring in place in recent years has found no evidence of the development of resistance due to MON810. However, it is obvious from the elements put forward by EFSA that there is no way of knowing from this observation whether we are looking at a long-term situation or whether resistance selection imperceptible today could pose problems in coming years. For this reason, the French scientists stress that it is vital to have precise selection speed data. The assessment underway will therefore need to clearly answer the question of managing the risk of resistance.

### 1) Development of resistance in insects: Spanish assessment

The Spanish assessment considers that there is a risk of development of resistance to the Cry1Ab protein in insects in the medium to long run (point 5.7, p. 8 and § 4 of point 6 at the bottom of p. 9). Spain believes the solution lies in drawing up insect resistance management plans with case-specific monitoring. On this point, Monsanto proposes monitoring. Spain emphasises that such monitoring does not rule out the need to build up the refuge zones (point 6.1, p. 10). The Spanish assessment document points up two potential environmental risks, which need to be addressed by monitoring and studies after "the placing on the market" and therefore specific management measures. Yet the current

authorisation does not call for any specific measures to be put in place to tie in with the cultivation of MON810.

**2) Development of resistance in insects: French safeguard clause**

In its comments on the French safeguard clause, the study put forward by EFSA's opinion (p. 10, Alves et al., 2006) to refute the appearance of resistance in the European corn borer is based on a particularly small number of individuals. It does not enable an across-the-board conclusion to be drawn on the frequency of major genes for resistance in populations of European corn borers and Mediterranean corn borers, as is posited by the opinion.

The estimates of the frequency of major genes for resistance in Mediterranean corn borer populations are higher than the frequencies for which the refuge zone strategy has been shown to be effective. Moreover, such effectiveness is tied in with other conditions that are not demonstrated as being satisfied by the studies put forward: recessive nature of the resistance and sufficient crossbreeding of resistant and non-resistant populations. For the European corn borer, although the frequency of the appearance of these resistance alleles is at a good level, there is a total lack of knowledge of the genetic structure, and hence cross-breeding, of European corn borer populations at regional level; likewise, the extent of resistance dominance is unknown.

Therefore, in both cases, the opinion's conclusion that the appearance of resistance can be sustainably managed by this refuge zone strategy is not substantiated. The data put forward in the studies cited do not allow for resistance selection speed to be judged. The elements put forward in the opinion therefore do not enable the conclusion to be drawn that the risks of resistance in the European corn borer and the Mediterranean corn borer due to large-scale cultivation of maize in Europe can be managed by the proposed strategy. Furthermore, it seems risky to bring into play an undefined "appropriate management" of the risk to come to a categorical assessment of this risk, as EFSA does on page 11 of the opinion.[2]

Last but not least, EFSA's assessment of the risk is made without reference to the goal sought: is it to prevent the appearance of resistance or to slow the appearance of resistance, and for how long? This omission raises a major question as to the interpretation and relevance of the conclusions drawn by the opinion.

[2] "The GMO Panel considers that the likelihood of occurrence is low in corn borer populations if appropriate resistance management is implemented."

**3) Development of resistance in insects: additional comments from Hungary**

The Plant Protection Research Institute of the Hungarian Academy of Sciences has carried out studies on MON810 in order to measure the development of Bt-resistance. The effects have been traced in 20 generations of one grain storage pest and increased tolerance was observed as early as in the 3rd and 4th generations. This is indicative of likely rapid expiry of the useful life of the variety and of rapid decline of its effectiveness. These Hungarian findings (for details see supporting documents of the Hungarian safeguard clause) should also been addressed in the environmental risk assessment.

**4) Development of resistance in insects: additional comments from Ireland**

(It is important to note that the following commentary is based on information provided in the Appendix only as the Spanish Assessment Report referred to within that text was not available for review). The GMO Panel concludes that the large-scale cultivation of maize MON810 over several years will increase the selection pressure on corn borers, which could result in the potential development of resistance. In relation therefore to this risk it would be expected that any new authorisation would request the monitoring of resistance development in target pests under case-specific monitoring as part of the overall requirements for a well-defined appropriate insect resistance management plan.

The GMO opinion states that as yet under field conditions and after several years of cultivation, no resistance has been reported for maize MON810. However it is also noted that the cultivation of Bt-maize in the EU is currently on a limited scale in a few geographic regions. It is also noted that in some cases (pests of cotton and maize) an increased frequency
of resistance alleles has been observed in some field populations while in other cases (i.e. other lepidopteran pests) no field-evolved resistance has been reported for Bt-proteins. While the opinion of the GMO panel considers that the likelihood of occurrence is low in corn borer populations if appropriate resistance management is implemented there are still some inconclusive aspects concerning the frequency and speed of the appearance of resistant alleles and crossbreeding (resistant and non-resistant populations) which future authorisations of Bt maize would need to address.

The questions raised today by those put by the Spanish assessment and the safeguard clauses can therefore only be answered once a new decision addressing these concerns has been examined.

**Ministry of Health – Austria**

**Ministry of Agriculture, Forestry, Environment and Water Management –Austria**

**Ministry of Environment and Water - Bulgaria**

**Ministry of Agriculture, Natural Resources and Environment – Cyprus**

**Ministry of the Environment – Czech Republic**

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**Ministry of Agriculture and Rural Development –Hungary**

**Ministry of Environment and Water – Hungary**

**Department of the Environment, Heritage and Local Government - Ireland**

**Ministry of Agriculture – Latvia**

MINISTRY OF THE ENVIRONMENT

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It is vital for the assessment underway to provide substantiated answers to all the questions raised by the Member States and their scientific experts in order to, a) ensure the completeness of the risk assessment including the description of uncertainties for each identified risks and b) enable the Member States to scrutinize a decision on the renewal of the authorisation to cultivate MON810 and, where necessary, define in the authorisation decision the management measures required to minimise any potential impact of these crops on the environment. Given that the current authorisation does not call for any specific measures to be put in place to tie in with the cultivation of MON810, the questions now raised by the safeguard clauses and the MON810 renewal assessment can only be answered once a new decision proposal addressing these concerns has been examined. Last but not least, this assessment should be consistent with the conclusions of the Council of European Ministers meeting of 4 December 2008 and should demonstrate the requested improvements to the environmental assessment, especially regarding medium- and long-term environmental impacts and consideration of the particularities of ecosystems and geographic areas, in particular sensitive and/or protected areas.

We therefore ask EFSA to consider the appended outstanding questions in greater depth with the scientific teams that raised them before any opinion can be expressed on the renewal of authorisation to cultivate MON810.

This letter is also sent to Mr. Stavros DIMAS European Commissioner for the Environment.

Yours sincerely,

**The Austrian Minister for Health and**
**The Austrian Minister for Agriculture, Forestry, Environment and Water Management:**

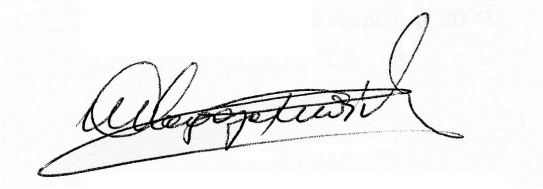
**Alois Stöger**

**Nikolaus Berlakovich**

**The Bulgarian Minister of Environment and Water**

**Dzhevdet Chakarov**

**The Cypriot Ministry of Agriculture, Natural Resources and Environment**



**Michalis Polynikis Charalambides**

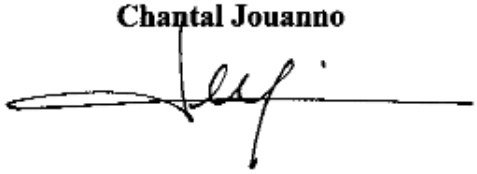
**The Czech Deputy Prime Minister and Minister of the Environment**

**Martin Bursík**

**The French Ministre d'Etat, Minister for Ecology, Energy, Sustainable Development and Town and Country Planing and The French Secretary of State for Ecology**

**Jean-Louis Borloo**

**Chantal Jouanno**



**The French Minister of Agricultures and Fisheries**

**Michel Barnier**

**The Greek Minister of Rural Development and Food and**
**The Greek Deputy Minister of Environment**

**Sotiris Hatzigakis** **Stavros Kalogiannis**

**The Hungarian Minister of Environment and Water and**
**The Hungarian Minister for Agriculture and Rural Development:**

SZABÓ Imre

**Gráf József**

**The Irish Minister for the Environment, Heritage and Local Government**

**John Gormley**

**The Latvian Minister of the environment and**
**The Latvian Minister of Agriculture**

**Mr.Raimons Vejonis** **Mr. Janis Düklavs**

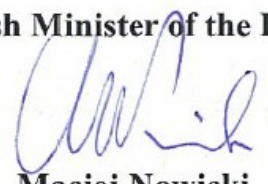
**The Minister of Health from Luxembourg**

**Mars Di Bartolomeo**

**The Prime Minister of Malta**

**Lawrence Gonzi**

**The Polish Minister of the Environment**



**Maciej Nowicki**

# APPENDIX

# MAIN UNRESOLVED POINTS ARISING FROM THE SPANISH ASSESSMENT OF MON810 AND THE SAFEGUARD CLAUSES REGARDING MON810

## A)IMPACTS ON NON-TARGET FAUNA

The first important question awaiting an answer is that of the impact of MON810 crops on non-target species. Spain's assessment states that the elements provided by Monsanto do not include any studies on non-target European lepidoptera and that the petitioner omitted to include these lepidoptera in the potentially exposed populations. EFSA has asked Monsanto for more information on this question and it is important that the information provided should adequately represent the European species and territories and be precise enough for a decision to be made.

### 1) Non-target fauna: Spanish assessment

The Spanish assessment asks Monsanto to include in its dossier the references to the publications concerned and a summary of the findings of these publications (§ 3 and 4 of point 5.5, p. 7).

Monsanto's dossier furthermore presents a table of potential adverse effects on populations exposed to MON810. Spain states that these elements do not reflect any studies on non-target European lepidoptera. Spain also notes that Monsanto has not included these lepidoptera in the potentially affected populations (§ 4 and 5 of point 5.5, p. 7). It considers that these aspects have therefore not been resolved and must be addressed in detail by the monitoring plan.

Spain moreover states that the general monitoring proposed by Monsanto consists merely of questionnaires, which are incapable of revealing any adverse effects. It clearly deems that putting these questionnaires to farmers is not a suitable way to assess the unexpected effects of MON810 and that post-authorisation studies need to be conducted (§ 3 and 5 of point 6.1, pp. 10 and 11).

The Spanish assessment hence expresses the need for authorisation to impose a precise monitoring plan, which is not the case with the current authorisation.

### 2) Non-target fauna: French safeguard clause

In EFSA's comments on the French safeguard clause, it states that the length of the studies on the environmental impacts of the proteins examined does not generally cover the field lifetimes observed for these proteins. The question as to whether they have no effect over this length of time therefore remains unanswered.

Furthermore, EFSA's opinion (p. 25) does not dispute the findings regarding the effects of the Cry1Ab protein on certain parasitoids and pollinating insects, nor the possibility of consequently turning a

parasitoid into a pest. The question as to the effect of this protein on the functioning of the ecosystems and the vulnerability of the crops to new pests therefore remains unanswered.

Moreover, field observations in different geographic and meteorological conditions can give rise to different findings, positive or negative. Since these findings relate to different contexts, they do not offset each other. Yet, in this chapter, the opinion often draws a sort of "middling" conclusion from this wide range of situations without any real biological significance; the use of a theoretical model with reassuring findings could therefore be challenged compared with the findings of much more contrasting field observations (p. 11). Lastly, on a number of occasions, the opinion appears to consider that although measured environmental effects are similar in scale to other variations observed elsewhere due to the natural variability of the soils (p. 18) and places (p. 21), or are "relatively minor in comparison with known toxic chemicals" (p. 19), they are nonetheless negligible. This is far from evident given the large variability of the contexts. This question therefore also remains unanswered.

More generally, the opinion's wording tends to systematically play down the studies that find an effect (pp. 15, 16, 20, 21 and 22), but not those that come up with negative findings when the test conditions are similar. Yet the opinion acknowledges on page 15 and again on page 22 (conclusion to paragraph 2.1.3.8[1] that the studies' multiple factors are more likely to conceal than reveal existing effects; caution in interpretation should consequently apply inversely or at least in a balanced manner. This question therefore remains unanswered.

**3) Non-target fauna: additional comments from Austria:**

The data provided by the applicant are insufficient to perform a comprehensive risk assessment, e.g. to exclude effects on non-target organisms. Most tests for Cry1Ab were done with the isolated protein derived from bacteria and not with whole plants. The relevance of such studies is questionable. Studies providing evidence of unspecific toxicity due to Bt-toxin on non-target organisms have been published and several studies addressing these problems were made available to the European Commission and EFSA.
Austria relies on sustainable agriculture and emphasises a high level of protection for biodiversity. Concerning MON810 major environmental impact issues were not adequately addressed by the applicants. The major points of criticism are:
1. Remaining uncertainties concerning unintended effects on non-target organisms.
2. Uncertainties of the specificity of Cry1Ab on target and non-target organisms (e.g. only a very limited number of non-target organisms were tested). Cry1Ab specificity is a hypothesis.
3. It is highly questionable whether ERA data from a specific European region may be extrapolated to other regions in Europe. Generalizations are not justified.

There are several biodiversity hotspots in Austria with even high rates in farmland regions. A total of 215 different butterfly species were found in Austria. 152 of them were located in agricultural areas and most of these butterflies are characterized as endangered and some of them are on the red list of endangered species. Interim results of an ongoing large scaled study on biodiversity in Austria confirm this sensitivity.
These endangered butterfly species have to be protected from additional harm possibly resulting from MON810 cultivation.

In result the Austrian environment shows a high degree of biodiversity and is characterized by a small scale agricultural system. The data presented by the applicant are not sufficient to prove the safety of the transgenic maize lines due to the lack of relevant data; uncertainties are not addressed at all.

[1] "This confirms that studying all lepidopteran species that could be potentially exposed to Bt-maize pollen may be difficult in practice, especially if potential effects are to be detected (Lang, 2004; Gathmann et al., 2006b) against a wide range of existing environmental and agronomic stressors currently influencing lepidopteran populations (Aviron et al., 2006; Gathmann et al., 2006b.)."

**4) Non-target fauna: additional comments from Hungary:**

Taking into account that there is a great regional variation in species composition and abundance, and that agricultural practices in Europe significantly diverge, potential effects of MON810 on non-target organisms strongly depend on geographical factors. Therefore, different biogeographical regions within the EU – including the Pannonian – should be taken into account in the environmental risk assessment of MON810 which can not be found in the Monsanto documentation. In our opinion, there is a need on an in-depth analysis in this regard. Furthermore, concrete scientific studies assessing the potential effects on non target species including *Lepidoptera* are needed. These experiments should be carried out in different biogeographical regions of the EU, not in other regions of the World and own experiments of Hungary should also be taken into account (see supporting documents of the Hungarian safeguard clause).

Regarding the potential adverse effects of MON810 on non-target soil organisms, a Hungarian peer-reviewed article (Bakonyi et al. 2006) call the attention that (a) potential negative effects must be evaluated on species-level because different species react differently, (b) during the feeding of a certain *Collembolan* species, it gave a preference to the isogenic line instead of the Bt-maize. Also in an other article (Meissle et al. 2005), significant statistical differences have been found in this regard. There is a need on a thorough assessment of these issues.
Furthermore, in the framework of the risk assessment, a very limited number of other non-target organisms were tested. Many scientific studies have given evidence that non target species such as *Hymenopteras* populations, *Trichoptera* species can be adversely affected by MON 810. We believe that there is a need on further and detailed information in this respect.
Experimental data provided by Hungary should also be taken into account when assessing the environmental effects of MON810, especially on our protected *Lepidopteran* species including the protected *Inachis io* or *Vanessa atalanta*, where larval stages overlap with the pollen shed by maize. Postponed development and mortality of a part of larval population has been demonstrated by Hungary in the supporting documents of its safeguard clause.

**5) Non-target fauna: additional comments from Luxembourg**

EFSA has not yet issued an opinion on the Luxembourg safeguard clause of 23 March 2009. However, in its argument in support of the safeguard clause, Luxembourg stresses the effects on non-target organisms based on studies, some of which are very recent.

The argument shows that many field and laboratory studies have been conducted to evaluate the impact of Bt maize crops on non-target organisms. Some of these studies find minor effects (Pilcher *et al.* 1997; Romeis *et al.* 2004) while other studies demonstrate significant negative effects on non-target species (Hilbeck *et al.* 1998; Dutton *et al.* 2002; Meissle *et al.* 2005). A meta-analysis based on published data (Marvier *et al.* 2007) also shows that MON810 maize crops, compared with non-genetically modified lines, have an effect on the abundance of non-target insects.

In a review article (Hilbeck and Schmidt 2006), the authors estimate that approximately 50% of the studies examined dealing with non-target effects report adverse effects on one or more of the parameters studied and that the observed effects are often unpredictable in terms of extent and type of impact.

A recent study (Schmidt *et al.* 2009) shows that two-spot ladybirds (*Adalia bipunctata*) exposed to active proteins Cry1Ab and Cry3Bb (similar to those produced by the MON810 and MON863 maize lines) post greater mortality at the preimaginal stage as of doses of 5 microgrammes/ml. However, no difference is observed in the length of development and general weight of the insects that have reached adulthood. The researchers conclude that the higher mortality rate points to a direct toxic effect associated with the active proteins and therefore raise the question as to their specificity of action

given that the Cry1Ab toxin is supposed to act selectively on lepidopteran insects when the ladybird is a member of the Coleoptera.

The studies on exposure of non-target organisms to Bt maize concentrate mainly on land organisms with only scant coverage of aquatic organisms. A recent study of an aquatic organism (Bohne *et al.* 2008) finds long-term adverse effects on the growth of water fleas (*Daphnia magna*) fed on MON810 maize residues. The authors of this study note that the question of the causality of the observed effects remains open, but that their findings go hand in hand with the results of other studies (Lovie *et al.* 2005; Rosi-Marshall *et al.* 2007), also suggesting the need to conduct other studies involving non-target aquatic organisms.

The Luxembourg authorities consider that the cause of the unexpected toxicity of Cry1Ab in the two-spot ladybird needs to be found. The same goes for the adverse effects on non-target aquatic invertebrates, organisms for which there is not enough study of their exposure to the Cry1Ab toxin. As regards this toxin, whose mode of action is not entirely understood (Crickmore 2005) and for which new aspects have been found (Broderick *et al.* 2006), its unexpected effects on non-target organisms could be associated with different mechanisms.

**6) Non-target fauna: additional comments from Ireland**

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(It is important to note that the following commentary is based on information provided in the Appendix only as the Spanish Assessment Report referred to within that text was not available for review). It would appear reasonable that a precise monitoring plan is put in place re the development of resistance in insects however specific monitoring for non-target could be problematic given the complex array of interactions (agronomic and environmental) which can potentially influence lepidopteran populations. It is agreed that European species and territories should be adequately represented and where there is reason to believe that potential effects (relevant interactions) may exist then specific monitoring would be warranted. However it is important that monitoring is "relevant" as monitoring for the sake of monitoring would be wasteful in terms of resources (financial and personnel). Specific monitoring might also miss out on potential effects elsewhere while a more broad form of monitoring might reveal important areas for more targeted research.

In relation to the commentary provided in the Appendix for non-target fauna and the French Safeguard Clause there are many specific issues raised. As indicated by EFSA's scientific opinion, the environmental impacts of the proteins examined does not generally cover the field lifetimes observed for these proteins, however it is also noted that while Bt-toxins can be degraded or inactivated in soil within weeks, a small fraction can persist far longer under certain conditions. The opinion references laboratory studies which have shown that the Cry1Ab protein can bind on clay minerals and humic substances in soil, thereby reducing its availability to microorganisms and that this reduced availability decreases degradation of the Cry1Ab protein. Under these conditions it is therefore apparent that the duration of a lot of the "studies" were well within the ranges indicated for persistence of Cry1Ab protein in the soil. It is unclear however as whether or not longer studies to coincide with field lifetimes would illustrate any effect unless some form of cumulative effect is anticipated. While the scientific opinion refers to little or no evidence on cumulative effects it may be prudent for future studies on persistence of protein in the soil and potential environmental impacts to have corresponding timelines for comparison purposes.

The complex trophic chain effects on parasitoids appears somewhat inconclusive with respect to normal functioning of ecosystems and while EFSA's opinion does not dispute the findings regarding the effects of the Cry1Ab protein on certain parasitoids and pollinating insects, the GMO panel is of the view that the information provided does not provide any new or additional scientific evidence that would invalidate the previous risk assessments of maize MON810 for the non-target organisms. Given the complexity of ecosystem functioning and the inconclusive character of much of the studies

referenced some further research in this area would be recommended to further inform authorisation procedures.

It is possible that different geographic and meteorological conditions can potentially give rise to positive or negative conditions and this could be due in part to several factors including rainfall, temperature, topography and soil type. While it would very difficult to have representative data for all localised conditions it would appear reasonable that the main "regions" within Europe are considered to represent the different contexts that exist.

The measurement of environmental effects is a complex area and there is a strong element of the unknown or unconfirmed effects with respect to potential impact, which makes it difficult to determine whether the findings actually do "constitute a risk to human health or the environment". Comparison with natural variability factors and existing scenarios (known toxic chemicals etc.) is a valid method of risk assessment however it is difficult to pinpoint the exact cause and effect of a particular protein when a range of acceptable effects is evident. It is also difficult to compare when test conditions are not that similar or where different approaches/methodologies have been adopted. There is no doubt that some of the findings appear more robust than others and that additional research is warranted in some areas (Soil microbial activity etc.) so as to inform better the overall risk assessment process such as that currently being carried out for MON810.

## B)DEVELOPMENT OF RESISTANCE IN TARGET SPECIES

One of the outstanding questions concerns the risk of the development of resistance in target species to the Cry1Ab protein produced by MON810 maize. This risk is now largely acknowledged: France raised it in connection with the safeguard clause; Spain indicated in its environmental risk assessment (ERA) of MON810 renewal that there is a risk of insects developing resistance to the Cry1Ab protein in the medium or long run; and EFSA also acknowledged the existence of this risk at the SCFCAH meeting on 16 February 2009. Spain and EFSA consequently advocate specific monitoring and the introduction of resistance "management" plans.

The French scientists who met with the GMO Panel point out that the elements provided to date in the bibliography presented by EFSA do not lend sufficient support to the fact that the appearance of resistance can be sustainably managed by a refuge zone strategy. They report that the studies cited by EFSA contain no elements to assess resistance selection speed or conclude that the risks of European corn borer and Mediterranean corn borer resistance associated with large-scale maize cultivation in Europe could be managed by the proposed strategy. Spain explains in its assessment that the monitoring in place in recent years has found no evidence of the development of resistance due to MON810. However, it is obvious from the elements put forward by EFSA that there is no way of knowing from this observation whether we are looking at a long-term situation or whether resistance selection imperceptible today could pose problems in coming years. For this reason, the French scientists stress that it is vital to have precise selection speed data. The assessment underway will therefore need to clearly answer the question of managing the risk of resistance.

### 1) Development of resistance in insects: Spanish assessment

The Spanish assessment considers that there is a risk of development of resistance to the Cry1Ab protein in insects in the medium to long run (point 5.7, p. 8 and § 4 of point 6 at the bottom of p. 9). Spain believes the solution lies in drawing up insect resistance management plans with case-specific monitoring. On this point, Monsanto proposes monitoring. Spain emphasises that such monitoring does not rule out the need to build up the refuge zones (point 6.1, p. 10). The Spanish assessment document points up two potential environmental risks, which need to be addressed by monitoring and studies after "the placing on the market" and therefore specific management measures. Yet the current

authorisation does not call for any specific measures to be put in place to tie in with the cultivation of MON810.

**2) Development of resistance in insects: French safeguard clause**

In its comments on the French safeguard clause, the study put forward by EFSA's opinion (p. 10, Alves et al., 2006) to refute the appearance of resistance in the European corn borer is based on a particularly small number of individuals. It does not enable an across-the-board conclusion to be drawn on the frequency of major genes for resistance in populations of European corn borers and Mediterranean corn borers, as is posited by the opinion.

The estimates of the frequency of major genes for resistance in Mediterranean corn borer populations are higher than the frequencies for which the refuge zone strategy has been shown to be effective. Moreover, such effectiveness is tied in with other conditions that are not demonstrated as being satisfied by the studies put forward: recessive nature of the resistance and sufficient crossbreeding of resistant and non-resistant populations. For the European corn borer, although the frequency of the appearance of these resistance alleles is at a good level, there is a total lack of knowledge of the genetic structure, and hence cross-breeding, of European corn borer populations at regional level; likewise, the extent of resistance dominance is unknown.

Therefore, in both cases, the opinion's conclusion that the appearance of resistance can be sustainably managed by this refuge zone strategy is not substantiated. The data put forward in the studies cited do not allow for resistance selection speed to be judged. The elements put forward in the opinion therefore do not enable the conclusion to be drawn that the risks of resistance in the European corn borer and the Mediterranean corn borer due to large-scale cultivation of maize in Europe can be managed by the proposed strategy. Furthermore, it seems risky to bring into play an undefined "appropriate management" of the risk to come to a categorical assessment of this risk, as EFSA does on page 11 of the opinion.[2]

Last but not least, EFSA's assessment of the risk is made without reference to the goal sought: is it to prevent the appearance of resistance or to slow the appearance of resistance, and for how long? This omission raises a major question as to the interpretation and relevance of the conclusions drawn by the opinion.

[2] "The GMO Panel considers that the likelihood of occurrence is low in corn borer populations if appropriate resistance management is implemented."

**3) Development of resistance in insects: additional comments from Hungary**

The Plant Protection Research Institute of the Hungarian Academy of Sciences has carried out studies on MON810 in order to measure the development of Bt-resistance. The effects have been traced in 20 generations of one grain storage pest and increased tolerance was observed as early as in the 3rd and 4th generations. This is indicative of likely rapid expiry of the useful life of the variety and of rapid decline of its effectiveness. These Hungarian findings (for details see supporting documents of the Hungarian safeguard clause) should also been addressed in the environmental risk assessment.

**4) Development of resistance in insects: additional comments from Ireland**

(It is important to note that the following commentary is based on information provided in the Appendix only as the Spanish Assessment Report referred to within that text was not available for review). The GMO Panel concludes that the large-scale cultivation of maize MON810 over several years will increase the selection pressure on corn borers, which could result in the potential development of resistance. In relation therefore to this risk it would be expected that any new authorisation would request the monitoring of resistance development in target pests under case-specific monitoring as part of the overall requirements for a well-defined appropriate insect resistance management plan.

The GMO opinion states that as yet under field conditions and after several years of cultivation, no resistance has been reported for maize MON810. However it is also noted that the cultivation of Bt-maize in the EU is currently on a limited scale in a few geographic regions. It is also noted that in some cases (pests of cotton and maize) an increased frequency
of resistance alleles has been observed in some field populations while in other cases (i.e. other lepidopteran pests) no field-evolved resistance has been reported for Bt-proteins. While the opinion of the GMO panel considers that the likelihood of occurrence is low in corn borer populations if appropriate resistance management is implemented there are still some inconclusive aspects concerning the frequency and speed of the appearance of resistant alleles and crossbreeding (resistant and non-resistant populations) which future authorisations of Bt maize would need to address.

The questions raised today by those put by the Spanish assessment and the safeguard clauses can therefore only be answered once a new decision addressing these concerns has been examined.