



## **ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT**

### *Advice on a notification for marketing of herbicide tolerant GM oilseed rape*

**Notifier:** Bayer CropScience

**Notification reference:** C/BE/96/01

**Product:** Oilseed rape genetically modified to introduce a pollination control hybrid system and tolerance to glufosinate ammonium, lines Ms8, Rf3 and Ms8xRf3.

**Scope:** For import and processing in the European community of Ms8, Rf3 and Ms8xRf3 oilseed rape and any progeny derived from these lines by conventionally breeding.

**Date:** 12 November 2005

**Advice of the Advisory Committee on Releases to the Environment (ACRE) under S.124 of the Environmental Protection Act 1990 (Part VI) to the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, Ministers of the Welsh Assembly Government and the Department of Environment (Northern Ireland).**

#### **ACRE advice after 45 day assessment period:**

ACRE previously advised that sufficient information had been provided by Bayer to demonstrate that the import and processing of Ms8, Rf3 and Ms8xRf3 GM oilseed rape in the EU does not pose any greater risk to human health and the environment as compared to non-GM oilseed rape (please see below: ACRE advice issued 22<sup>nd</sup> November 2004). We have now considered the Opinion from the EFSA GMO Panel on this notification and conclude that no new information has come to light that alters this advice. We consider that The Panel's Opinion is aligned with ACRE's view.

The scope of this notification also includes feed use. The GMO subgroup of the Advisory Committee on Animal Feedingstuffs (ACAF) has assessed the safety of Ms8, Rf3 and Ms8xRf3 GM oilseed rape and concluded that 'the Ms8xRf3 hybrid or the meal derived from the hybrid would be expected to behave as any other commercial rapeseed variety when fed to livestock' and 'in the absence of any safety concerns, ACAF does not see a need for any post-release monitoring'.

The cultivation of Ms8, Rf3 and Ms8xRf3 GM oilseed rape is not included in the scope of this notification and as such this advice does not address it.

We therefore conclude that the import, processing and use of Ms8, Rf3 and Ms8xRf3 oilseed rape as animal feed in the EU does not pose any greater risk to human health and the environment as compared to its non-GM counterparts.

**Comment:**

Since our last advice was issued in November 2004 (see below), EFSA has issued its Opinion on Ms8, Rf3 and Ms8xRf3 oilseed rape and the EU Commission has drafted a Decision on this notification. We anticipate that this Decision will be voted on at Regulatory Committee on December 5<sup>th</sup>, 2005. Member States will vote on Ms8, Rf3 and Ms8xRf3 oilseed rape for import and processing and for use as any other oilseed rape (this includes feed but not food use). Cultivation is not included within the scope of this notification.

We have considered the use of this product as animal feed under Directive 90/220/EEC before the dossier was transferred to Directive 2001/18/EC. On the basis of advice from experts on animal feed, we concluded that Ms8, Rf3 and Ms8xRf3 oilseed rapemeal was as safe as its non-GM counterparts if fed to animals. However, there was uncertainty as to whether the scope of this notification included feed use after the lead competent authority (Belgium) carried out its initial assessment under Directive 2001/18/EC. This was because the Belgian competent authority (CA) stated that feed approval should be dealt with under the EU Food and Feed Regulations (1829/2003). However, the Belgian CA did carry out an assessment of the feed safety of Ms8, Rf3 and Ms8xRf3 oilseed rape and concluded that 'there are no reasons to assume that the transgenic proteins of Ms8, Rf3 and Ms8xRf3 will have a toxic or allergenic effect upon the incidental consumption or upon use in feed'.

The EFSA GMO Panel also considered feed safety in its Opinion and concluded that 'Ms8, Rf3 and Ms8xRf3 oilseed rape is as safe as conventional oilseed rape for humans and animals and, in the context of the proposed uses, for the environment'.

As it is now clear that feed safety is within the scope of this notification under Directive 2001/18/EU, the GMO subgroup of the Advisory Committee on Animal feedingstuffs (ACAF) was asked for its advice on this aspect. Its conclusions are that 'the Ms8xRf3 hybrid or the meal derived from the hybrid would be expected to behave as any other commercial rapeseed variety when fed to livestock' and 'in the absence of any safety concerns, ACAF does not see a need for any post-release monitoring'.

In particular, ACAF noted that the 'results of field trials demonstrate the essential compositional similarity of the Ms8xRf3 hybrid and its most appropriate comparator. Consequently, both would be expected to deliver the same nutrition when fed to livestock. This was supported by the digestibility study in rabbits'. ACAF has therefore advised that it does not see a need for further animal studies.

ACAF also advised that although the glucosinolate content was consistently higher in the Ms8xRf3 hybrid than in the comparator, levels remained within accepted limits and fell within the range expected for rapeseed. Consequently there are no safety implications for livestock fed the Ms8xRf3 hybrid or for consumers of animal products'.

In terms of the proteins encoded by the introduced genes, Barnase (a ribonuclease produced in the male sterile line, Ms8) and Barstar (a specific inhibitor of the barnase protein, which is produced in the fertility restorer line, Rf3) are only detected in the

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flower buds of the hybrid but not in other tissues (notably the seed, which is fed to animals). However, PAT protein, which is encoded by the *bar* gene, could be detected in all tissues tested, including seeds. The safety of PAT was addressed in the notification through a number of *in vitro* digestibility tests made with pig gastric fluid and rumen fluid and with simulated gastric and intestinal fluids. These studies consistently showed that PAT is very rapidly degraded in the presence of gut proteases and at the optimum pH for their activity. Survival times were increased when pH values differed from the optimum (e.g. 10 minutes survival in pig gastric fluid adjusted to pH 4.0), but even at rumen pH, all activity was destroyed within 30 minutes. A GLP compliant acute toxicity study was also made with PAT protein expressed in a bacterial host. Female mice were given a single intravenous dose of 1 or 10 mg/kg body weight, monitored for 15 days and were then subjected to necropsy and macroscopic examination. No visible signs of systemic toxicity were evident.

Cultivation of Ms8, Rf3 and Ms8xRf3 GM oilseed rape in the EU is not within the scope of this notification (cultivation was included initially but was subsequently removed - as discussed in our previous advice, please see below) and as such is not dealt with in this advice.



## ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

### *Advice on a notification for marketing of herbicide tolerant GM oilseed rape*

<b>Notifier:</b>	Bayer CropScience
<b>Notification reference:</b>	C/BE/96/01
<b>Product:</b>	Oilseed rape genetically modified to introduce a pollination control hybrid system and tolerance to glufosinate ammonium, lines Ms8, Rf3 and Ms8xRf3.
<b>Scope:</b>	For import and processing in the European community of Ms8, Rf3 and Ms8xRf3 oilseed rape and any progeny derived from these lines by conventionally breeding.
<b>Date:</b>	22 November 2004

**Advice of the Advisory Committee on Releases to the Environment (ACRE) under S.124 of the Environmental Protection Act 1990 (Part VI) to the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, Ministers of the Welsh Assembly Government and the Department of Environment (Northern Ireland).**

**Secondary advice:** ACRE has considered the additional information provided concerning this notification for marketing of Ms8, Rf3 and Ms8xRf3 oilseed rape. The Committee notes that the scope of this notification has been reduced since it was last considered, and that now only import and processing of oilseed rape containing the transformation event Ms8 and Rf3 is included. Cultivation is excluded. The Committee also notes that use as animal feed is not included within the scope of this notification and that a separate application under Regulation 1829/2003 is planned.

On the basis of the reduced scope and the additional information provided, ACRE concludes that sufficient information has now been provided by the notifier to demonstrate that this GM oilseed rape does not pose any greater risk to human health and the environment than conventional oilseed rape.

The Committee is satisfied by the responses of the notifier to the questions raised in the primary advice on this notification.

### **Comment**

In its previous consideration, ACRE considered the notification on the basis of two possible usages – import and processing only, which had been given a positive assessment by the Belgian Competent Authority, and cultivation, which was included in the scope of the original notification, but had not received a favourable assessment from the Belgian Competent Authority. The Committee notes that the scope of the

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notification has now been reduced to include only import and processing, and to exclude cultivation. As a result issues concerning cultivation of oilseed rape Ms8xRf3 have not been considered further. In its primary advice on this notification (Appendix A), ACRE requested that the notifier provide:

- Details of the likely point(s) of import and processing of Ms8xRF3 oilseed rape in the UK, and information concerning standard operating procedures for handling Ms8xRf3 seed.
- A revised post-market monitoring plan

The notifier has provided the information requested, and the Committee is now content to agree with the assessment of the Belgian competent authority that consent for import and processing should be issued. In particular, the Committee accepts that the spillage of seed of Ms8xRf3 does not constitute a potential risk to the environment, and so case-specific monitoring for the establishment of feral populations should not be a requirement of the post-market monitoring plan. However, the Committee considers that the presence of Ms8xRf3 in such populations may have implications for coexistence, and therefore recommends that Bayer CropScience carries out some monitoring of feral oilseed rape populations for the purpose of establishing if, and where, Ms8xRf3 material may be present.



ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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<b>Notification Reference:</b>	C/BE/96/01
<b>Product:</b>	Oilseed rape genetically modified to introduce a pollination control hybrid system and tolerance to glufosinate ammonium, lines Ms8, Rf3 and Ms8xRf3.
<b>Scope:</b>	<u>Belgium Assessment report</u> <sup>1</sup> For import and processing in the European community of Ms8, Rf3 and Ms8xRf3 oilseed rape and any progeny derived from these lines by conventionally breeding. <u>Notification dossier</u> As above plus cultivation.
<b>Date:</b>	26 <sup>th</sup> March 2004

**Advice of the Advisory Committee on Releases to the Environment (ACRE) under S.124 of the Environmental Protection Act 1990 (Part VI) to the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, Ministers of the Welsh Assembly Government and the Department of Environment (Northern Ireland).**

**Primary advice:** ACRE has considered this notification for marketing of Ms8, Rf3 and Ms8xRf3 within the context of the Belgium assessment report and the full notification submitted by Bayer. In both cases the Committee does not consider that sufficient information has been provided by the notifier to enable the Committee to recommend that consent be granted.

Within the scope of the Belgium assessment report:

ACRE is satisfied at this stage on the basis of the evidence provided that the risk to human health and the environment arising from marketing this product for importation and processing in the UK will be no different from that of other oilseed rape. However before ACRE can complete its assessment the following information is required:

1. Details of the likely point(s) of import and processing of Ms8xRF3 oilseed rape in the UK, and information concerning standard operating procedures for handling Ms8xRf3 seed.

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<sup>1</sup> This notification does not request consent for use in animal feed or human food, which falls within the scope of Regulations 1829/2003 and 258/97. Oil derived from Ms8xRf3 already has approval for placing on the market granted in 1999.

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2. The post-market monitoring plan should be revised to cover import and processing only and in particular should include monitoring for spillage of Ms8xRf3 seed during import, transportation and processing and test for the establishment of feral populations of Ms8xRf3 oilseed rape. The plan should also include appropriate emergency plans should such populations be identified

### Within the scope of the Notification from Bayer

ACRE does not consider that sufficient information has been provided by the notifier to allow a full assessment of potential risks to human health and the environment of the cultivation of Ms8xRf3. Further information required is as follows:

1. An environmental risk assessment taking into consideration the impact of altered management practices associated with the cultivation of Ms8xRf3 oilseed rape.
2. Revised agricultural guidelines that explain how weeds can be managed in crops of Ms8xRf3 without resulting in adverse impacts on the environment relative to weed management in non-GM oilseed rape.
3. A revised post-market monitoring plan which takes account of any potential adverse effects identified in the environmental risk assessment and will monitor whether the management practices employed are successful in reducing those impacts to an acceptable level.
4. The Notifier is requested to consider the above points with respect to spring and winter sown oilseed rape.

### **Comment**

ACRE considered this notification in three stages 1) molecular characterisation of events Ms8 and Rf3, and with respect to 2) import and processing only and 3) cultivation, the environmental risk assessment and post-market monitoring plan.

#### 1) Genetic modification and molecular characterisation

ACRE noted that the data relating to molecular characterisation of Ms8 and Rf3 was very well presented. The Committee is very familiar with these transformation events and acknowledges that they were developed several years ago. Despite this the molecular and genetic data presented by the Notifier are of high quality and have been updated to take into account advances in molecular analytical technologies.

The genetically modified oilseed rape lines Ms8 and Rf3 were created by *Agrobacterium tumefaciens* mediated transformation. In each case the transforming plasmid contained two cassettes: for Ms8 the *barnase* and *bar* gene cassettes were inserted into the genome and for Rf3 the *barstar* and *bar* gene cassettes were inserted. The *barnase* gene confers male sterility on the recipient plant and the *barstar* gene confers fertility restoration – together the inserts introduce a hybrid pollination control system. The *bar* gene encodes the PAT enzyme which confers tolerance to glufosinate ammonium, the active ingredient of the herbicide Liberty®.

The full sequence of the inserted genetic material and flanking host sequences have been determined for both Ms8 and Rf3. Good genetic and molecular evidence is provided to demonstrate that the inserts are present at a single locus site and that there is no plasmid backbone sequence present at the site of insertion. Bioinformatic analysis of the flanking regions identified some similarity with sequences from *Arabidopsis thaliana* which is expected due to the close relationship between *Arabidopsis* and *Brassica* sp. Further, evidence was obtained that novel transcripts would not be generated as a consequence of the insertion event.

## ACRE advice during 60 day assessment period

On the basis of the data supplied by the applicant ACRE is content with the molecular characterisation of events Ms8 and Rf3, and concludes that the insertion of genetic material as described in events Ms8 and Rf3 does not introduce additional risks not found in conventional oilseed rape. ACRE is also satisfied that the detection protocols are of good quality and truly event specific.

### Environmental risk assessment and post-market monitoring plan:

#### 2) Within the scope of the Belgium Assessment report (import and processing):

ACRE considered the elements of the environmental risk assessment related to import and processing of Ms8xRF3 and agree with the conclusions of the Notifier and the Belgium authorities that import and processing of Ms8xRf3 does not pose a risk to human health or the environment. The Committee notes that consent for use of oil derived from Ms8xRF3 in human food has already been authorised on the basis of substantial equivalence.

ACRE considered the post-market monitoring plan provided (excluding elements related to cultivation). Bayer do not identify any requirements for case-specific monitoring in relation to import and processing of Ms8xRf3. The Committee agrees with the opinion of the Belgium authorities that a case specific monitoring plan should be provided to monitor for the presence of feral Ms8xRf3 populations. The Committee acknowledges the absence of such a plan in the submitted dossier is due, in part, to the fact that the current plan is submitted within the broader remit of cultivation.

ACRE requests that before authorisation for import and processing is granted the post-market monitoring plan must be revised within this remit. In particular the plan must take into account monitoring of the occurrence and effects of seed spill during transportation and processing of the oilseed rape seed. Based on current experience regarding movement of non-GM oilseed rape in the UK seed spill is likely to occur and will result in the survival and establishment of feral oilseed rape populations and their hybridisation with crop and other feral populations. It is accepted that the risk of harm to human health and the environment from seed spill is low, however there is an issue, in the UK, regarding the segregation of transgenic and non-transgenic material. Hence, ACRE request that Bayer review their monitoring plan taking into account methods of monitoring and reporting seed spill, incorporating a proposal as to how seed spill may be controlled. It should also include plans for monitoring and controlling establishment of feral populations as a result of seed spill.

Directive 2001/18/EC places a requirement to provide a monitoring plan for the occurrence of adverse effects not anticipated in the environmental risk assessment (general surveillance). ACRE agrees with the Belgium proposal that as a condition of consent the consent holder should be required to provide a more detailed general surveillance plan. Further details should include (1) precisely who will be requested to provide information; (2) what type of information will be requested and the frequency of requests; (3) how the company will ensure participation to ensure a robust assessment. The Committee recommends that monitoring reports should be provided by the applicant on an annual basis.

### Environmental risk assessment and post-market monitoring plan:

#### 3) Within the scope of the Notification from Bayer (import, processing and cultivation):

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ACRE considered the wider scope of the notification from Bayer seeking authorisation for cultivation of Ms8xRf3, taking into account the Belgium authorities reasoning for not recommending that consent be granted for cultivation.

The environmental risk assessment submitted by Bayer identified two specific issues which they propose to carry out case specific monitoring for; (1) establishment of genetically modified oilseed rape volunteers and (2) gene flow to wild relatives and establishment of herbicide tolerant weeds. A case specific post-market monitoring plan was provided to monitor the extent that these two issues would be realised. Two of the arguments put forward by the Belgium authorities not to grant consent for cultivation were based on gene flow and co-existence issues.

ACRE disagrees with the Belgium authorities' perspective on gene flow which focuses on limiting the potential for vertical gene flow. The Committee considers the focus of attention should be on the consequences of gene flow rather than its occurrence. It is acknowledged that there is potential for gene flow from oilseed rape via volunteers and cross-pollination to wild relatives, however the potential for gene flow will be no different for Ms8xRf3 to that of non-GM oilseed rape. The environmental risk assessment does not identify any reason to believe that the consequences of gene flow would present a safety issue to humans or the environment. Further the Committee recognises that there are ways of limiting gene flow by methods of good agricultural practise and in particular it would be in the farmers' interest to limit the occurrence of volunteers in future crops. In addition gene flow to wild relatives is a rare event the rate of which will decrease with distance from the source.

The issue of co-existence, although not formally part of the risk assessment under Directive 2001/18, was considered by the Committee, in particular the extent to which the agricultural guidelines and separation distances will be able to achieve the 0.9% labelling threshold. One important point which ACRE would like to emphasise is that the issues surrounding co-existence are not safety related.

Co-existence is an issue both between fields and within the field. With respect to issues of co-existence between fields the Committee felt that separation distances will be sufficient to ensure that the 0.9% threshold can be met. Within fields it is possible to ensure segregation of GM and non-GM material by good agricultural practice. The main issue is persistence of volunteers if farmers choose to grow non-GM oilseed rape after cultivation of a GM crop or when several different herbicide tolerant GM oilseed rape events are authorised. The Committee does not expect that volunteers will be a problem for co-existence provided that agricultural best practice is employed. Members considered whether strict volunteer management required for co-existence may itself bring an adverse environmental impact, and thought that although this could not be ruled out that volunteer control through the crop rotation is already very good due to a combination of good agricultural practice and herbicide use. However Members did not feel they had enough information to predict unequivocally whether volunteers will have an impact on co-existence. The Committee awaits publication of the follow-up results from the Farm Scale Evaluations with respect to this issue. Finally ACRE noted that the level of adventitious contamination is equally dependent on manufacturers ensuring seed purity.

ACRE considered the effects brought about by changes in management of the GM oilseed rape when compared with conventional management of oilseed rape. The Committee disagreed with the conclusion of Bayer in the environmental risk assessment that changes in herbicide use will not result in any adverse environmental impact. Directive 2001/18 states that notifiers must take account of indirect effects as a result of differences in management practices. The UK Farm

## ACRE advice during 60 day assessment period

Scale Evaluations<sup>2</sup> clearly show that management practices associated with cultivation of spring sown GM herbicide tolerant oilseed rape result in adverse effects on arable weed populations and higher trophic levels when compared with conventionally managed oilseed rape.

While the notifier indicates that Ms8xRf3 oilseed rape can be managed to minimise the impacts on biodiversity, details of such management regimes and evidence of their effectiveness are not provided. Such information is required before consent for cultivation can be fully assessed. Finally ACRE did not consider that there was sufficient information available to consider the impact on biodiversity of management practices associated with winter sown oilseed rape.

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<sup>2</sup> *Phil. Trans. R. Soc. Lond. B* (2003) **358**, 1777-1913