Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to genetically modified crops (Bt176 maize, MON810 maize, T25 maize, Topas 19/2 oilseed rape and Ms1xRf1 oilseed rape) subject to safeguard clauses invoked according to Article 16 of Directive 90/220/EEC [1]

(Question No EFSA-Q-2005-294)

Opinion adopted on 29 March 2006

SUMMARY

During the late 1990s and in 2000, a number of Member States invoked Article 16 of Directive 90/220/EEC, the so-called 'safeguard clause'. This safeguard clause provides that, where a Member State has justifiable reasons to consider that a genetically modified organism (GMO) which has received consent for placing on the market, constitutes a risk to human health or the environment, it may provisionally restrict or prohibit the use and/or sale of that GMO on its territory. Genetically modified (GM) Bt176 maize (*Zea mays* L.), T25 maize and MON810 maize were authorised under Directive 90/220/EEC for all uses including cultivation and covering any progeny derived from crosses with any traditionally bred maize. Ms1 and Rf1 oilseed rape (*Brassica napus* L. ssp. *oleifera*) lines were authorised under Directive 90/220/EEC for production of seeds of all hybrids derived from crosses of these two lines (Ms1xRf1) and from crosses with any traditionally bred oilseed rape, but not extended to the use for human food or animal feed, without prejudice to any future assessment. Topas 19/2 oilseed rape was authorised under Directive 90/220/EEC for handling in the environment during import and before and during storage and processing. Subsequently these GM plants were subjected to the safeguard clause by certain Member States. Following the advice of the former Scientific Committees, the European Commission submitted draft decisions in 2004, requesting that the Member States concerned should lift their national safeguard measures. However, the draft decisions were not supported by a majority of Member States and the European Council suggested that the European Commission should assess further whether the national measures were justified.

Hence, the European Commission consulted the European Food Safety Authority (EFSA) and requested a scientific opinion under Article 29(1) and in accordance with Article 22(5)c of Regulation (EC) No 178/2002. The GMO Panel addressed the specific questions raised by the Commission with regard to Bt176, T25, MON810 maize and Ms1xRf1 and Topas 19/2 oilseed rape on the basis of generally available scientific

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data and earlier assessments by the GMO Panel, but stated that it was not in a position to comment on the quality of the earlier applications or their compliance with the current legislation.

The GMO Panel concludes that the likelihood of adverse effects due to the presence of the antibiotic resistance marker genes (ARMGs) in Bt176 and T25 maize is extremely low. This is further supported by the fact that no gene transfer from Bt176 maize to culturable bacteria has been detected under field conditions, and that T25 maize contains only a partial *bla*$_{TEM-1}$ gene, which is, therefore, non-functional. Supported by the assessment of several applications on hybrids containing MON810 maize, the GMO Panel affirms its conclusions with respect to the potential impact of Cry1Ab toxin on biodiversity, that MON810 maize is unlikely to have adverse effects on human and animal health or the environment.

Concerning Ms1xRf1 and Topas 19/2 oilseed rape, the GMO Panel affirms that, in the unlikely scenario of establishment and spread of herbicide tolerant oilseed rape, a selective advantage would only occur in the case of treatments with the complementary herbicides. Therefore, having recommended the setting-up of appropriate management systems to minimize accidental loss and spillage of GM oilseed rape during transportation, storage, handling in the environment and processing into derived products, the GMO Panel considers that it is unlikely that there will be adverse effects for human and animal health or the environment as a consequence of accidental spillage of Topas 19/2 and Ms1xRf1 and subsequent establishment of GM oilseed rape plants.

In conclusion, the GMO Panel is of the opinion, that with respect to the specific questions raised by the European Commission and on the basis of current scientific knowledge, there is no reason to believe that the continued placing on the market of Bt176, T25 and MON810 maize, and Ms1xRf1 and Topas 19/2 oilseed rape is likely to cause any adverse effects for human and animal health or the environment under the conditions of their respective consents.

Key words: GMO, Bt176, T25, MON810, Ms1xRf1, Topas 19/2, oilseed rape, maize, safeguard clause, human/animal health, environment, Directive 90/220/EEC.

TABLE OF CONTENTS

BACKGROUND

On 10 November 2005, EFSA received a request from the European Commission concerning the GMOs subject to safeguard clauses invoked under Article 16 of Directive 90/220/EEC (EC, 1990) which was repealed by Directive 2001/18/EC (EC, 2001). The mandate for the request was discussed at the plenary meeting of the GMO Panel on 6 - 7 December 2005.

During the late 1990s and in 2000, a number of Member States invoked the so-called safeguard clause on a particular GM crop under Article 16 of Directive 90/220/EEC to provisionally restrict or ban the use or the sale of that particular GM crop in their territories. The Member States were Luxemburg for Bt176 maize; Germany for Bt176 maize; Austria for Bt176, MON810 and T25 maize; France for Ms1xRf1 and Topas 19/2 oilseed rape; and Greece for Topas 19/2 oilseed rape.

Genetically modified (GM) Bt176 maize (*Zea mays* L.), T25 maize and MON810 maize were authorised under Directive 90/220/EEC for all uses including cultivation and covering any progeny derived from crosses with any traditionally bred maize. Ms1 and Rf1 oilseed rape (*Brassica napus* L. ssp. *oleifera*) lines were authorised under Directive 90/220/EEC for production of seeds of all hybrids derived from crosses of these two lines (Ms1xRf1) and from crosses with any traditionally bred oilseed rape, but not extended to the use for human food or animal feed, without prejudice to any future assessment. Topas 19/2 oilseed rape was authorised under Directive 90/220/EEC for handling in the environment during import and before and during storage and processing. Subsequently these GM plants were subjected to safeguard clauses by certain Member States. Following each invocation, the Scientific Committees of the European Commission were consulted as to whether the information provided by the Member States as justification for the bans impacted on the original risk assessment performed by the Scientific Committees. The Scientific Committees, in all opinions, deemed that this was not the case for any of the safeguard clauses (SCP, 1999; 1999a,c,d; 2000; 2001a). However, the bans remained in place subject to revision of the regulatory framework.

In December 2003, the European Commission requested the Member States named above to re-consider their safeguard clauses in view of the new regulatory framework for GMOs and, if necessary, to re-submit them under Article 23 of Directive 2001/18/EC (which replaced Article 16 of Directive 90/220/EEC). France, Luxemburg, Austria and Greece responded stating that they intended to maintain their safeguard clauses under Directive 2001/18/EC. Austria and Greece also submitted further information in support of their bans. In April 2004 this additional information was submitted to EFSA for assessment. The GMO Panel concluded that the additional information did not invalidate the original risk assessments for the GMOs in question (EFSA, 2004c,d). Consequently, the Commission submitted draft decisions under Directive 2001/18/EC, initially to the Regulatory Committee, requesting the Member States concerned to lift their national safeguard measures. On 29 November 2004, the Regulatory Committee failed to reach a qualified majority either in favour of or against any of these draft decisions. Draft proposals were subsequently transmitted to the Council for agreement on 26/27 April 2005. A qualified majority against the draft decisions was returned for all eight proposals at the Environment Council on 24 June 2005. The Council also made a declaration as follows:

'*The Council considers that there is still a degree of uncertainty in relation to the safeguard measures associated with the placing on the market of these GMOs. It calls on the Commission to gather further scientific evidence and to further assess whether the national measures are justified and whether the authorisation of these GMOs under Directive 90/220/EEC still meets the safety requirements of Directive 2001/18/EC*'.

Under Council Decision 1999/468/EC (EC, 1999), the Commission is required either to submit amended proposals to the Council, or to re-submit its original proposals or to present legislative proposals on the basis of the Treaty. Taking account of the Council

statement and the pending WTO ruling[2], prior to any further action, the Commission requested EFSA to provide a scientific opinion. The nature of the request was with respect to any scientific information which indicates that the GMOs in question pose a potential risk to human health or the environment under the conditions of their consents and which has not been accounted for to date. The Commission indicated specific questions to be taken into account for the individual GMOs (detailed below) in carrying out this assessment. The Commission also seeks to ensure that the scientific assessment of the safety of the GMOs in question is completely up-to-date noting that the initial opinions of the Scientific Committee on Plants (SCP) (with regard to the original information as submitted justification for these cases) are several years old.

The GMO Panel agreed to address the specific questions raised by the Commission with regard to Bt176, T25 and MON810 maize, and Ms1xRf1 and Topas 19/2 oilseed rape on the basis of generally available scientific data and earlier assessments by the GMO Panel. However, EFSA indicated to the Commission that, as EFSA was not involved in earlier assessments of these GMO applications under Directive 90/220/EEC and as no documentation regarding the former assessments was submitted to EFSA, the GMO Panel was not in a position to comment on the quality of the earlier applications or their compliance with the current legislation. The GMO Panel notes that pending the renewal of consents, updates to notifications for these products will have to be submitted before 17 October 2006 according to Article 17 of Directive 2001/18/EC or within nine years from the date on which the products were first placed on the market, but in no case earlier than three years after the date (18 April 2004) of application of Regulation 1829/2003/EC according to Articles 8(4) and 20(4) of the Regulation. Renewal applications are to be in line with the EFSA Guidance Document on the risk assessment of GM plants and derived food and feed (EFSA, 2004a).

TERMS OF REFERENCE

EFSA is requested, under Article 29(1), and in accordance with Article 22(5)(c) of Regulation (EC) No 178/2002, to provide a scientific opinion as soon as possible, as to whether:

- There is any scientific reason to believe that the continued placing on the market of the GMOs subject to the safeguard clauses are likely to cause any adverse effects for human health or the environment under the conditions of consent.

- In particular, EFSA was requested to take account of the specific information highlighted below (text in italics) and any further scientific information that has arisen subsequent to the previous scientific opinions assessing the safety of these GMOs.

[2] In May 2003, the United States (US), Canada and Argentina launched a WTO (World Trade Organisation) dispute settlement process against the European Union (EU), because of the *de facto* moratorium on any new placing on the market of GMOs and because of the national bans on certain GMOs.
See http://www.wto.org/english/tratop_e/dispu_e/find_dispu_cases_e.htm#results

ASSESSMENT

1. Introduction

Several authorisations for the placing on the market of GMOs were granted under the previous Directive 90/220/EEC, which was repealed by Directive 2001/18/EC on 17 October 2002. The different GMOs subject to the safeguard clauses (i.e. Bt176, T25 and MON810 maize (*Zea mays* L.), and Ms1xRf1 and Topas 19/2 oilseed rape (*Brassica napus* L. ssp. *oleifera*)) were evaluated at the national and EU level prior to their market approval and following the invocation of the safeguard clause under Directive 90/220/EEC.

Bt176 maize

Bt176 maize (C/F/94/11-03), which is genetically modified for resistance to lepidopteran pests and for tolerance to glufosinate-ammonium herbicides, was authorised for all uses in the European Union by Commission Decision 97/98/EC of 23 January 1997 (EC, 1997) and final consent was granted by the French competent authority on 4 February 1997.

Bt176 maize has been the subject of opinions of the Scientific Committees for Pesticides (SCP, 1996; 1997), Animal Nutrition (SCAN, 1996; 1997), Food (SCF, 1996; 1997) and Plants (SCP, 1999b; 2000). Although the EFSA Scientific Panel on GMOs was neither involved in earlier assessments of the initial Bt176 notification, nor in the related Article 16 measures, Bt176 maize was evaluated by the GMO Panel in the context of a safeguard clause invoked under Article 23 of Directive 2001/18/EC (EFSA, 2004c).

MON810 maize

MON810 maize (C/F/95/12-02), which is genetically modified for resistance to lepidopteran pests, was authorised in the European Union for all uses with the exception of food by Commission Decision 98/294/EC on 22 April 1998 (EC, 1998a) and final consent was granted by the French competent authority on 3 August 1998. Maize derivatives for food use were placed on the market in accordance with Article 5 of Regulation (EC) 258/97 on 6 February 1998 (EC, 1998b).

MON810 maize has been the subject of opinions of the Scientific Committee on Plants (SCP, 1998; 1999a,b). Although the EFSA was neither involved in earlier assessments of the initial MON810 notification, nor in the related Article 16 measure, MON810 maize was evaluated by the GMO Panel in the context of applications on hybrids containing MON810 (EFSA, 2004f; 2005a,b,c,d,e) as well as of safeguard clauses invoked under Article 23 of Directive 2001/18/EC (EFSA, 2004c; 2005f).

T25 maize

T25 maize (C/F/95/12-07), which is genetically modified for tolerance to glufosinate-ammonium herbicides was authorised in the European Union for all uses with the exception of food by Commission Decision 98/293/EC on 22 April 1998 (EC, 1998c) and final consent was granted by the French competent authority on 3 August 1998. Maize derivatives for food use were placed on the market in accordance with Article 5 of Regulation (EC) 258/97 on 6 February 1998.

T25 maize was considered in evaluations by the Scientific Committee for Plants (SCP, 1998a, 2001a, 2001b, 2001c). Although the EFSA was neither involved in earlier assessments of the initial T25 notification, nor in the related Article 16 measure, T25 maize was evaluated by the GMO Panel in the context of a safeguard clause invoked under Article 23 of Directive 2001/18/EC (EFSA, 2004c).

Topas 19/2 oilseed rape

Topas 19/2 spring oilseed rape, which is genetically modified for tolerance to glufosinate-ammonium herbicides, was authorized for import, storage and processing in the European Union by Commission Decision (98/291/EC) of 22 April 1998 (EC, 1998d) and final consent was granted by the competent authority of the United Kingdom on 9 June 1998.

Topas 19/2 oilseed rape has been the subject of opinions by the Scientific Committee for Plants (SCP, 1998b; 1999). Although the EFSA was neither involved in earlier assessments of the initial Topas 19/2 notification, nor in the related Article 16 measures, Topas 19/2 oilseed rape was evaluated by the GMO Panel in the context of a safeguard clause invoked under Article 23 of Directive 2001/18/EC (EFSA, 2004d).

Ms1xRf1 oilseed rape

Ms1 and Rf1 oilseed rape lines, which are genetically modified for tolerance to glufosinate-ammonium herbicides and contain a male sterility gene and a male fertility restorer gene respectively, were authorized in the European Union respectively for production of hybrid Ms1xRf1 seeds by Commission Decision 96/158/EC (EC, 1996) and for import, processing and growing of Ms1xRf1 by Commission Decision 97/392/EC (EC, 1997a). The final consent for seed production (notification C/UK/94/M1/1) was granted by the competent authority of the United Kingdom on 28 February 1996. France did not grant the final consent for import, processing and growing purposes of Ms1xRf1 (notification C/F/95/05/01/A). Oil produced from Ms1xRf1 oilseed rape for food use was placed on the market in accordance with Article 5 of Regulation (EC) 258/97 on 12 May 1997 (EC, 1998b).

2. Assessment of the specific questions raised by the European Commission

Bt176 and T25 maize

The European Commission raised the following issues with maize events Bt176 and T25: *These maize lines both contain an ampicillin ARMG in some form. EFSA, in its opinion adopted on 2 April 2004, with respect to their clinical importance, categorised ARMGs into three groups with different potentials for compromising human health and the environment. EFSA concluded that, with regard to safety, there was no rationale for inhibiting the use of ARMGs in group one but that the second group, which included ampicillin, should not be present in GM plants to be placed on the market. Whilst it is clear that new approvals would not be granted for GMOs containing the ampicillin ARMG, the Commission wishes to consult EFSA as to its opinion on the current safety implications to human health and the environment of the Bt176 and T25 maize varieties, considering that both varieties contain a form of the ampicillin ARMG and have been approved for all uses.*

The GMO Panel has evaluated the potential risks associated with the use of specific antibiotic resistance genes as marker genes (ARMGs) taking into account their current usage in clinical and veterinary medicine, the likely occurrence of horizontal gene transfer from GM plants to microbes and the potential impact of horizontal gene transfer where a naturally occurring resistance to the relevant antibiotics exists in the microbial gene pool. These factors will impact on the likelihood of any adverse effects on humans or the environment of ARMGs used in GM plants (EFSA, 2004d). The GMO Panel considers the frequency of horizontal gene transfer from GM plants to other organisms as very low for all ARMGs assessed by the GMO Panel. This, in itself, is an important consideration with regard to any risk posed by the use of ARMGs. With respect to the clinical importance of certain antibiotics, the Panel has categorised ARMGs into three groups with different potentials for compromising human health and the environment. The *bla*$_{TEM-1}$ gene used in Bt176 and T25 maize, conferring resistance to ampicillin, falls in the second group of ARMGs. The GMO Panel has published an opinion (EFSA, 2004e) indicating that the use of these genes should be avoided in future GM plants to be placed on the market, on the basis of the revised legal framework. Ampicillin and its derivatives are antibiotics of clinical importance but the resistance conferred by the *bla*$_{TEM-1}$ gene is common on mobile genetic elements in a range of bacteria present in the environment. This is discussed in more detail in the opinion of the GMO Panel (EFSA, 2004d). Therefore, the GMO Panel agrees with the previous safety assessments carried out by the Scientific Committee on Plants on Bt176 (SCP, 1999b; 2000) and on T25 (SCP, 1998a; 2001a,b,c), stating that the likelihood of adverse effects due to the presence of the ARMGs in Bt176 and in T25 maize is extremely low. This is further supported by the fact that no gene transfer from Bt176 transgenic maize to culturable bacteria has been detected under field conditions (Badosa *et al*., 2004). T25 maize contains only a partial *bla*$_{TEM-1}$ gene, which is, therefore, non-functional (SCP, 1998a).

Topas 19/2 and Ms1xRf1 oilseed rape

The European Commission raised the following issues with these oilseed rape events: *Recent studies in Japan have revealed the presence of GM oilseed rape plants around a number of ports. Oilseed rape is imported into Japan but is not cultivated and it has been concluded that these plants arose from GM seed that has been accidentally spilled during unloading at the ports and subsequent transport. There are no wild relatives of oilseed rape in Japan and the Japanese have concluded that there is no environmental impact from the GM plants.*

Oilseed rape is both imported and cultivated in Europe. Wild relatives of oilseed rape are also present in Europe. If plants do establish from GM seed that has been accidentally spilled during unloading and transport of imported oilseed rape commodities then there may be a possibility of transfer of the modified sequences through cross-pollination. Such transfer could be to conventional oilseed rape crops in the neighbourhood and recent reports also claim transfer to wild relatives in the environment.

The original notifications for the above two varieties detailed the risk of accidental spillage as negligible. However, in view of the above recent reports, the Commission in adopting a decision to place GT73 oilseed rape on the market for import and processing adopted an accompanying recommendation containing provisions to address accidental spillage (EC, 2005a,b). The recommendation included provisions for monitoring, by the consent holder, of potential accidental spillage and establishment of the GM oilseed rape plants with the necessary measures for reporting and control.

The Commission wishes to consult EFSA as to its opinion concerning the consequences of accidental spillage of Topas 19/2, Ms1xRf1 and GT73 oilseed rape and subsequent establishment of GM oilseed rape plants taking account of recent studies and reports.

In February 2005, the Japanese Environmental Studies Institute reported the presence of oilseed rape genetically modified for tolerance to an herbicide around Japanese port facilities. However, the GMO Panel confirms its previous opinion that the presence of transgenic spring oilseed rape volunteers or feral plants is not a hazard in itself and is not likely to cause ecological damage compared with conventional oilseed rape (EFSA, 2004b; 2005g). Studies with herbicide-tolerant oilseed rape have not shown any enhanced weediness or fitness, except when the complementary herbicide is applied (Crawley *et al*., 2001). The GMO Panel concludes that the likelihood for unintended environmental effects due to the establishment and spread of herbicide-tolerant oilseed rape will not be different from that of traditionally bred oilseed rape. Even if feral populations of spring oilseed rape did become established and if transgene flow should occurr to cultivated oilseed rape and/or wild *Cruciferae* in natural habitats [for reviews see Eastham and Sweet, 2001; Chevre *et al*., 2003], a selective advantage would only result if the complementary herbicide was to be applied. Glufosinate is rarely used to control weeds in oilseed rape or in crops grown in rotation with it. It is primarily used as a desiccant in these crops. It is not used to control plants in semi-natural or natural habitats. Without the complementary herbicide application, the traits will have a neutral effect on the fitness of the potential hybrids, as confirmed by long-term experience from Canada (Warwick *et al*., 2004). However, volunteers or feral plants may become established in certain managed areas like farming systems or port facilities and thus the evolution of transgenic populations is feasible. These plants can be managed by other herbicides (Warwick *et al*., 2004; Devos *et al*., 2004). The GMO Panel advises that appropriate management systems should be in place to minimize accidental loss and spillage of transgenic oilseed rape during transportation, storage, handling in the environment and processing into derived products (EFSA, 2004b; 2005g).

In conclusion, the GMO Panel considers that, on the basis of current scientific knowledge, it is unlikely that there will be adverse effects for human and animal health or the environment as a consequence of accidental spillage of Topas 19/2, Ms1xRf1 or GT73 oilseed rape and subsequent establishment of GM oilseed rape plants.

MON 810 maize

The European Commission raised the following issues with maize event MON810: *The Commission is aware that EFSA has recently delivered opinions on a number of 'stacked-gene' GMO products containing the MON810 transformation event (as to their safety for human health and the environment when placed on the market). It is, therefore, considered that the safety of the MON810 transformation itself has been repeatedly evaluated as part of these assessments. The Commission seeks confirmation as to this and the continued safety of this event.*

The GMO Panel assessed several applications on hybrids containing MON810 (EFSA, 2005 a,b,c,d,e). In this context, the GMO Panel has assessed the molecular characterisation of the MON810 event together with data on the levels of Cry1Ab protein, compositional analysis and assessment of toxicology and allergenicity of the respective hybrids. Further, the GMO Panel has assessed available data from the literature concerning the environmental impacts of Cry1Ab. No reports of adverse environmental impacts from comparable Cry1Ab expressing maize have been observed. Reports and reviews of studies of the effects of Cry1Ab on biodiversity, including the

abundance of non-target and biocontrol species, indicate that significant adverse environmental effects due to *Bt* maize cultivation are unlikely (Amman, 2005; Clark *et al*., 2005; Dolezel *et al*., 2005; Eizaguirre *et al*., 2006; Rodrigo-Simon *et al*., 2006; Romeis *et al*., 2006). The GMO Panel therefore affirms its conclusions that, on the basis of current scientific knowledge, MON810 maize is unlikely to have adverse effects on human and animal health or to the environment in the context of its proposed uses.

CONCLUSIONS

The GMO Panel is of the opinion that, with respect to the specific questions raised by the European Commission and on the basis of current scientific knowledge, there is no reason to believe that the continued placing on the market of Bt176, T25 and MON810 maize, and Ms1xRf1 and Topas 19/2 oilseed rape (which are subject to safeguard clauses) is likely to cause adverse effects for human and animal health or to the environment, under the conditions of their respective consents.

DOCUMENTATION PROVIDED TO EFSA

Letter to Mr. Herman Koëter, dated 10 November 2005 with ref. DG SANCO D4/KN/cc (2005) 440925, from Mrs. Paola Testori Coggi from Health & Consumer Directorate-General regarding a note to the EFSA on safeguard clauses.

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SCIENTIFIC PANEL MEMBERS

Hans Christer Andersson, Detlef Bartsch, Hans-Joerg Buhk, Howard Davies, Marc De Loose, Michael Gasson, Niels Hendriksen, John Heritage, Sirpa Kärenlampi, Ilona Kryspin-Sørensen, Harry Kuiper, Marco Nuti, Fergal O'Gara, Pere Puigdomenech, George Sakellaris, Joachim Schiemann, Willem Seinen, Angela Sessitsch, Jeremy Sweet, Jan Dirk van Elsas and Jean-Michel Wal.