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SCIENTIFIC OPINION

Scientific Opinion on Guidance for the risk assessment of genetically modified plants used for non-food or non-feed purposes[1]

EFSA Panel on Genetically Modified Organisms (GMO)[2, 3, 4]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

This Opinion discusses the risk assessment issues associated with Genetically Modified (GM) plants used for non-food or non-feed purposes (*e.g.* for the production of industrial or medicinal products, biofuel or for phytoremediation), and outlines the applicable legal framework and the recommended scientific methods for their risk assessment. A comparative approach is advocated but will need to be applied carefully. Consumption is not expected with these GM plants used for non-food or non-feed purposes, but accidental oral, dermal, ocular and inhalatory exposure is possible and assessments of toxicity and allergenicity are discussed. This Opinion recommends that exposure assessments take account of any strategies to reduce exposure or gene flow proposed by the applicant. It is considered that existing guidance on the environmental risk assessment of GM plants is adequate but that additional emphasis should be given to issues such as gene transfer and the exposure of non-target organisms, particularly wildlife feeding on these GM plants. The Opinion further describes the importance of risk management systems, such as post-market environmental monitoring, standard production protocols/stewardship, or confinement strategies to reduce exposure to the GM plant.

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[1] On a request from EFSA, Question No EFSA-Q-2007-176, adopted on 22 April 2009.

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[4] The GMO Panel acknowledges Reinhilde Schoonjans for her contribution to this Opinion.

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KEY WORDS:

Molecular farming, plant production platforms, GMO, GM plants, risk assessment, non-food, non-feed, phytoremediation, ornamental use, plant-made industrial compound (PMI), plant-made medicinal product (PMP), Directive 2001/18/EC, Regulation (EC) No 1829/2003, Regulation (EC) No 726/2004, Regulation (EEC) No 2309/93.

SUMMARY

In view of new types of GM plants under development, the European Food Safety Authority (EFSA) asked its Panel on Genetically Modified Organisms (GMO Panel) to establish guidance for the risk assessment of GM plants used for non-food or non-feed purposes. A working group of selected GMO Panel Members and external *ad hoc* experts was formed to prepare the Opinion. A draft opinion was prepared and submitted to the European Commission for legal consultation and the European Medicines Agency for comments prior to online consultation with the public and stakeholders. The submitted comments were considered and the draft amended where appropriate. The amended Opinion was submitted to the EFSA GMO Panel for final adoption on 22 April 2009.

The scope of this Opinion covers GM plants and plant parts deliberately released into the environment via cultivation, import or processing for a wide range of potential non-food or non-feed uses, such as the production of industrial or medicinal products, energy production, phytoremediation, landscape improvement and ornamental use.

In view of the many possible combinations of type of genetic modification, type of plant and location of the genetic modification in the plant, the guidance given is generic and does not pre-empt the case-specific risk assessment of future applications.

The EFSA Guidance Document for the risk assessment of GM plants and derived food and feed contains information on the requirements for the preparation and presentation of the GM plant application. The present Opinion supplements this Guidance Document by discussing issues for the assessment of GM plants used for non-food or non-feed purposes that would need special attention or may have more/less stringent requirements compared with the risk assessment requirements for GM plants for food and feed purposes.

The Guidance Document with the templates for submission of dossiers, together with this Opinion on the additional elements for the risk assessment of plants for non-food or non-feed purposes, is to be taken into account by future applicants. EFSA herewith advises applicants/regulators to read this Opinion in parallel with the Guidance Document. A regulatory flowchart is provided showing the interplay between the intended uses of a GM plant and the respective EU legislation applicable. The flowchart also gives an overview of the regulatory bodies that are involved in scientific risk assessment and the ones that are responsible for risk management and decisions on authorisations.

When a notification under Directive 2001/18/EC is to be evaluated by EFSA, it is expected that the necessary data for the environmental risk assessment (including aspects of human and animal health) are all provided in a comprehensive technical dossier submitted to EFSA. In case the GM plant is used to produce a medicinal product, it is expected that this technical dossier includes relevant data as expected in a marketing authorisation application as submitted to EMEA. Possible deviations from this requirement have to be scientifically substantiated by the applicant. EFSA and EMEA support the idea that an innovator wishing to bring a plant-derived medicinal product to the market should consult closely with regulatory authorities to ensure that all appropriate regulatory steps are undertaken.

The EFSA GMO Panel considers that for GM plants used for non-food or non-feed purposes the comparative approach is valid, but will need to be applied carefully. For these plants, the

assessment of the potential impact of the differences identified in the comparative analysis is particularly important with regard to accidental intake by humans, livestock and wildlife animals, the exposure of farmers and workers handling the GM plants, and the exposure of passers and of people living in the vicinity.

The focus of the evaluation for human and animal safety is on the risks resulting from oral exposure through accidental intake (through inadvertent entry in the food and feed chain via admixture or gene flow or through accidental consumption in the field) of the GM plants/plant parts used for non-food or non-feed purposes by humans and animals.

The risk assessment for plants used for non-food or non-feed purposes has to take into account the confinement measures when applied. To allow for a quantitative risk assessment, this is to be integrated in a two-step risk assessment. In a first step, risks for human and animal health and the environment of the GMO need to be assessed based on an exposure assessment without the consideration of the confinement measures and in a second step, confinement measures as proposed and applied by the applicant should be taken into account.

The use of GM plants for non-food or non-feed purposes, for example the production of novel compounds, expands the role of crop plants. The target products could have adverse effects when in contact with humans, animals or the environment, or when consumed by humans or animals. Where new potential GM plant risks are identified, the plants are likely to require more specific risk management conditions, such as methods of production stewardship, defined confinement measures, safety thresholds and inspections.

To assess the reliability of confinement (and how the effectiveness of confinement will be monitored) the following should be taken into account. The effectiveness of confinement measures may be influenced by external factors such as abiotic and biotic conditions. The applicant therefore should provide data that allow the assessment of confinement measures under all environmental conditions envisaged taking worst-case scenarios into account. In this regard it may be necessary and useful for the applicant to narrow the geographical area in which he seeks permission for the product.

Applicants should describe for each GM product the details and rationale for the proposed physical and biological confinement strategy, where applicable. The proposal should specify the methodology used and its effectiveness in reducing accidental intake or preventing gene flow into the environment. Methods of enforcing monitoring and emergency measures for restricting gene flow should also be described. Regarding non-food or non-feed GM plants that produce bio-active substances that are stable, or that persist for a long term in the environment, it should be considered whether the confinement should also prevent or reduce herbivory and leakage through drainage or sewage.

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BACKGROUND AS PROVIDED BY EFSA

An increasing number of GM plants are being developed for a wide range of non-food or non-feed purposes. Some are developed to manufacture non-food or non-feed products (molecular farming[5]). Examples are plants that produce medicinal products such as vaccines and antibodies (reviewed by Spök et al. (2008)), diagnostic products, industrial enzymes, or raw materials for the production of biopolymers, biofuels, paper and starch. In addition, other non-food or non-feed purposes of GM plants may include energy production, phytoremediation, landscape improvement and ornamentals.

The EFSA GMO Panel is mandated to carry out the scientific risk assessment of GMO[6] applications submitted for EU market authorisation to European Member States or the European Commission. On its own initiative the EFSA GMO Panel also engages in self-tasking activities that aim to further elaborate GMO risk assessment criteria in challenging or new areas of scientific development.

In September 2004, EFSA published guidance for the preparation and presentation of GM plant applications submitted within the framework of Regulation (EC) No 1829/2003 on GM food and feed and of Directive 2001/18/EC on the deliberate release into the environment of GMOs. This "Guidance Document for the Risk Assessment of GM Plants and Derived Food and Feed", was first elaborated in 2006 (EFSA, 2006), and is regularly updated. The reference "the Guidance Document" as used herein, refers to the applicable guidance in support of Regulation (EC) No 1829/2003 and Directive 2001/18/EC. References to particular sections of the Guidance Document refer to the last update of the above mentioned Guidance Document for the Risk Assessment of GM Plants and Derived Food and Feed (EFSA, 2008b). The Guidance Document is a generic document and describes the case-by-case risk assessment of GM plants and derived food and feed according to the principles as set out in Annex II of Directive 2001/18/EC of the European Parliament and of the Council and Regulation (EC) No 1829/2003 of the European Parliament and of the Council. Furthermore, the Guidance Document provides templates for the preparation and presentation of the applications for EU market authorisation.

Based on risk assessment experience and new advancements in science, EFSA regularly updates its Guidance Document and the GMO Panel decided that additional guidance needed to be developed for the environmental risk assessment of GM plants used to produce medicinal products ("plant-made medicinal products") for human and veterinary use (Regulation (EEC) 2309/93 (EC, 1993)) as well as for other non-food or non-feed purposes (*e.g.* "plant-made industrial compounds" and GM plants for phytoremediation).

On 26 September 2005 EFSA agreed to initiate a self-tasking activity on this issue and mandated the EFSA GMO Panel to give its Opinion on comprehensive guidance for the assessment of genetically modified plants used for non-food or non-feed purposes to supplement the Guidance Document.

[5] Plant molecular farming is the use of GM plants in agriculture (only open field is in the remit of this document) for the production of novel compounds rather than for the production of food or livestock feed.

[6] As defined in Article 2 (2) of Directive 2001/18/EC.

The main objective of this Opinion is to identify issues for the assessment of GM plants used for non-food or non-feed purposes that would need special attention or may have more/less stringent requirements compared with the risk assessment requirements for GM plants for food and feed purposes as now described in the Guidance Document. The Opinion therefore indicates where there are differences in the risk assessment for GM plants developed for non-food or non-feed purposes. Existing risk assessment requirements that need specific consideration for GM plants used for non-food or non-feed purposes are also being addressed. The Opinion furthermore refers to EU legislation and guidelines applicable for these GM plants and comprises recommendations useful for the applicant, risk assessor and risk manager. As the Guidance Document, also this Opinion is a generic Opinion to cover the wide range of possible GM plants for non-food or non-feed purposes and without pre-empting the case-by-case risk assessment of particular applications. The European Commission together with the Member States may wish to elaborate on the basis of this Opinion further legally binding guidelines for GM plants for non-food or non-feed purposes, as now takes place for the updated Guidance Document for GM food and feed.

As for all generic guidance for risk assessment, EFSA invited also for this Opinion experts from the EU Member States, from the stakeholders in the food, agricultural and environment sectors or consumer's organisations, as well as the broader public to comment and contribute to this work. For this purpose, the draft document was published during 3 months on the EFSA website and comments were invited online.

Following this consultation, the Opinion was amended and adopted by the EFSA GMO Panel.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The GMO Panel was mandated:

- To identify possible gaps in the present Guidance Document concerning the risk assessment of GM plants used as production platforms for non-food or non-feed products[7];
- To critically review the present Guidance Document for its suitability to the applications for "molecular farming" to be expected in the near future;
- To identify potential routes for the admixture of GM plants used as production platforms for non-food or non-feed products with the food and feed chain[7];
- To critically review the present international (US[8], Canada[9] and other) guidelines targeted for applications within the scope of the self-tasking activity;
- To establish communication between EFSA and EMEA (European Agency for the Evaluation of Medicinal Products, now European Medicines Agency) for clarification

[7] The scope of the mandate was enlarged to GM plants in general used for non-food or non-feed purposes.

[8] Documents available at FDA website http://www.fda.gov/cder/Guidance/index.htm (FDA/USDA, 2002) and APHIS website http://www.aphis.usda.gov/biotechnology/submissions.shtml (USFR, 2003, APHIS/BRS, 2007)

[9] Documents available at CFIA website http://www.inspection.gc.ca/english/plaveg/bio/mf/molecule.shtml (CFIA, 2001, CFIA, 2004, CFIA, 2005, CFIA, 2006)

of the interplay between Council Regulation (EEC) 2309/93 (as amended)[10] and Directive 2001/18/EC and its implications for the assessment of the products falling into the scope of both legislations;

- To develop additional guidance (supplementing the Guidance Document for the risk assessment of GM plants and derived food and feed) to help applicants in the risk assessment of GM plants used as production platforms for non-food or non-feed products and the preparation and presentation of the dossier;
- To evaluate feedback from an online stakeholder consultation organised by EFSA;
- To elaborate the effectiveness of biological/physical confinement strategies for GM plants used as production platforms for non-food or non-feed products.

ACKNOWLEDGEMENTS

The European Food Safety Authority and its GMO Panel wish to thank the hearing experts Paul Christou and Uwe Sonnewald; and Alexis Nolte (EMEA).

[10] Repealed by Regulation (EC) No 726/2004 (EC, 2004)

OPINION

1. Scope

Applications for the deliberate release into the environment through cultivation in the field or import of GM plants destined to be placed on the market for non-food or non-feed purposes under Part C of the Directive 2001/18/EC, fall within the scope of this Opinion. The use of GMOs under contained conditions[11] as laid down in Directive 90/219/EEC or in field trials under Part B of Directive 2001/18/EC do not fall within the remit of EFSA and therefore is outside the scope of this Opinion. However, most of the risk assessment strategies presented in this Opinion may also be valid for contained use or field trials applications, to be evaluated and managed by the Competent Authorities of the Member States.

The expression "risk assessment" as used in the present Opinion on Guidance for risk assessment refers to the environmental risk assessment as described in Directive 2001/18/EC Annex II, to look at effects on human health and the environment, including *inter alia* flora and fauna, the food and feed chain, biological diversity and animal health.

EFSA as a scientific risk assessment body issues guidance for applicants on how to prepare and present their risk assessment for the safety of human and animal health and the environment. Management issues related to the environmental release of GMOs in EU, such as standard operating procedures, equipment and storage, site security, monitoring, personnel training programs, isolation from reproductively compatible plants, post harvest monitoring and land-use restriction, reports to the regulators, premises inspections and compliance, are within the remit of the Competent Authorities of the Member States and the European Commission.

Within the context of the Opinion, the expression "for non-food or non-feed purposes" means destined for purposes other than food or feed use, where "food" is any substance or product, whether processed or unprocessed, intended to be, or reasonably expected to be ingested by humans; and "feed" is any substance or product, including additives, whether processed, partially processed or unprocessed, intended to be used for oral feeding to animals (Articles 2 and 3 of Regulation (EC) No 178/2002).

The scope of this Opinion does not cover GM plants to be used as or in medicinal products (see section 2.3.1), but it may be applicable to GM plants that produce medicinal products by molecular farming.

Any type of exposure to the GM plant or plant parts, as covered in this Opinion, excludes any type of exposure as a consequence of medication. For instance, oral exposure as covered in this Opinion excludes oral medication as this is covered in a specific legal framework such as Directive 2001/83/EC and the risk assessment follows the centralised procedure by EMEA.

[11] Confinement measures (as further discussed in section 5.2 of this document) are not to be confused with contained use of GMOs.

The mission of EFSA is to provide scientific advice and scientific and technical support for the Community's legislation and policies in all fields which have a direct or indirect impact on food and feed safety, including environmental aspects (see Article 22 (3) of Regulation (EC) No 178/2002, (EC, 2002)). Accordingly, products derived from GM plants used for non-food or non-feed purposes are covered by this Opinion provided they have a direct or indirect impact on food and feed safety, including environmental aspects.

The Opinion is applicable to GM plants for non-food or non-feed purposes which will be cultivated or imported in the EU. Derived products for non-food or non-feed purposes would not be regulated under Part C of Directive 2001/18/EC as the Directive is applicable to genetically modified organisms wherein organisms means any biological entity capable of replication or of transferring genetic material, nor under Regulation (EC) No 1829/2003 applicable for GM food and feed. Therefore, the present Opinion does not cover processed GM products that are imported for non-food or non-feed uses in the EU, since they are not regulated under the EU GMO legislation and therefore do not fall in the remit of EFSA.

The processing for industrial uses of edible GM crops, such as the ones already approved in the EU under Directive 2001/18/EC and/or Regulation (EC) No 1829/2003 or currently under assessment by EFSA, is also out of scope of this Opinion.

The risk assessment criteria for genetically modified plants containing stacked transformation events is considered in the Guidance Document. Stacked transformation events for non-food or non-feed purposes are also within the scope of this Opinion.

2. Legal Background

The EU Regulations, Directives and Decisions published in the Official Journal of the European Communities establish the procedures to be followed in seeking approval for GMOs as well as the requirements for the applications and are, therefore, always the primary source of advice.

In cases in which a GM plant is used as the source of a product, the applicant should follow the specific legislation and the corresponding guidelines, if available, when preparing an application to market that product. To facilitate the assessment of the genetic modification, the applicant should follow the relevant parts of the Guidance Document and the present Opinion of EFSA.

In reference to section I.2 of the Guidance Document, giving a detailed overview of the legal background for GM plants and the role of EFSA for the risk assessment of GMOs, the following community legislation is of particular relevance for the risk assessment of GM plants for non-food or non-feed purposes by EFSA.

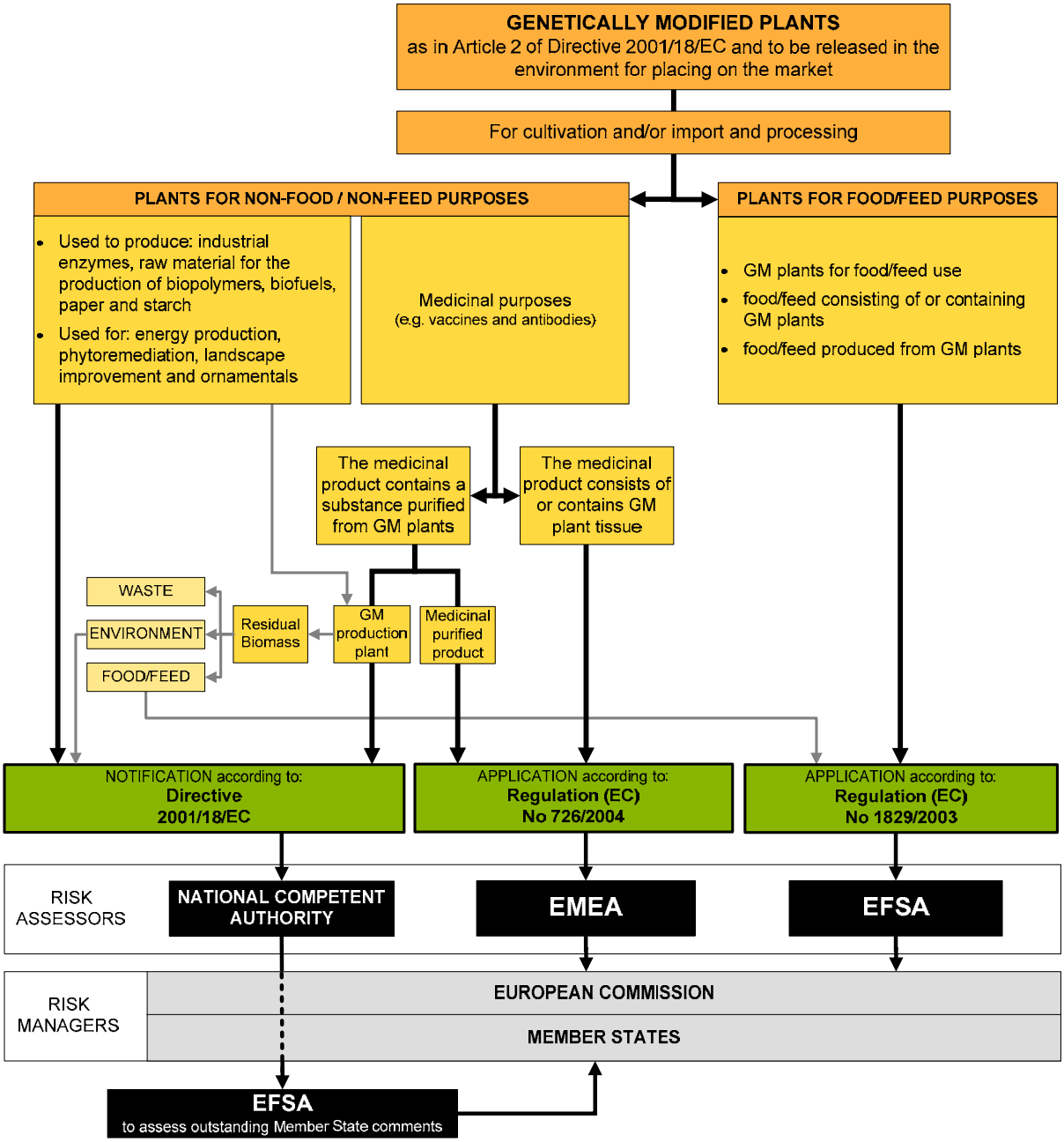

Figure 1 Regulatory flowchart

This flowchart gives a schematic overview of the interplay between the intended uses of a GM plant and the respective EU legislation applicable. The flowchart also gives an overview of the regulatory bodies that are involved in scientific risk assessment and the ones that are responsible for risk management and decisions on authorisations.

2.1. Deliberate release of GMOs (Directive 2001/18/EC)

The placing on the market of GMOs as or in products is dealt with by Directive 2001/18/EC Part C (EC, 2001a). Applicants prepare the risk assessment dossier for the GM plant and associated production systems and products, regarding the safety of human and animal health and environment, and submit this technical dossier in one of the EU Member States. That EU Member State carries out the risk assessment for human and animal health and the environment. If during the authorisation process of the GM product, objections on the risk assessment are raised and maintained by another Member State, then the Commission may consult EFSA for an independent risk assessment for human and animal health and the environment. Under Directive 2001/18/EC (Article 28.1) EFSA is consulted only on the maintained objections of the Member States, and is not supposed to carry out a full environmental risk assessment. However, on its own initiative the Authority considers it important to conduct a full environmental risk assessment according to the standards as laid down in the Guidance Document.

2.2. GM food and feed (Regulation (EC) No 1829/2003)

The placing on the market of a GMO for food and feed use[12] as well as food and feed containing, consisting of or produced from a GMO are subject to Regulation (EC) No 1829/2003 (EC, 2003b). The presence of a GM plant/plant parts in the food and feed chain is subject to an authorisation under this regulation and based on a safety assessment to be carried out by EFSA. Therefore, when the unmodified plant to be used for non-food or non-feed purposes is a plant traditionally used for the production of food or feed, such authorisation under Regulation (EC) No 1829/2003 is to be considered.

The Guidance Document further explains the interaction of EU regulations in cases of overlapping scope, *e.g.* GM products used as food supplements, food additives or feed additives.

2.3. Medicinal products for human and veterinary use (Regulation (EC) No 726/2004)

The general legal framework for medicinal products in the European Union are Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use and Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. In addition, medicinal products which consist of or contain GM plant material or which contain substances manufactured using genetically modified plants fall within the scope of the Annex to Regulation (EC) No 726/2004 (EC, 2004)[13] and may only be placed on the market within the European Union if a marketing authorisation is granted by the European Commission following evaluation by the European

[12] See Article 2 of Regulation (EC) No 1829/2003 for the definition of GMOs for food use or for feed use.

[13] Repealing Council Regulation (EEC) No 2309/93 (EC, 1993).

Medicines Agency (EMEA) in accordance with the "Centralised Procedure" as defined in this Regulation.

Two situations are further explained here below:

2.3.1. The medicinal product consists of or contains GM plant tissue[14]

Any proposal to market a medicinal product which consists of or contains GM plant tissue should be evaluated in relation to its potential for falling within the scope of the definition of a GMO (Article 2 of Directive 2001/18/EC). In such cases, the exemption of Article 12 of Directive 2001/18/EC would apply, meaning that the environmental risk assessment in accordance with Directive 2001/18/EC for the placing on the market of the medicinal product is required as part of the marketing authorisation application for the medicinal product and is assessed by the EMEA scientific committees in accordance with Articles 6 (2) and 31 (2) of Regulation (EC) No 726/2004. For their Opinion, the Committee for human medicinal products (CHMP) and the Committee for veterinary medicinal products (CVMP) shall respect the environmental safety requirements laid down by Directive 2001/18/EC and carry out the necessary consultations of bodies that the Community or Member States have set up in accordance with Directive 2001/18/EC. Since GM plants as or in medicinal products are specifically excluded from Directive 2001/18/EC, they are not within the remit of EFSA, but within the remit of EMEA. Therefore, the scope of this Opinion does not cover GM plants, or plant parts, to be used as or in medicinal products. However, in accordance with Directive 2001/18/EC, some of the principles developed in the Guidance Document as well as in this Opinion may be applicable to the environmental risk assessment of these GM plants.

2.3.2. The medicinal product contains a substance purified from a GM plant

In accordance with the applicable legislation as outlined above, the medicinal product that contains a substance purified from a GM[15] plant, *e.g.* a purified metabolite or recombinant protein (*e.g.* a purified monoclonal antibody), requires an authorisation under Regulation (EC) No 726/2004. For the development of such products, in addition to other relevant guidance available for medicinal products, the "Guideline on the quality of biological active substances produced by stable expression in higher plants" (EMEA, 2008) should be taken into account. This Guideline of EMEA provides guidance on approaches to achieve satisfactory quality of biological active substances contained in the medicinal product. It does not address the risk assessment with regard to the safety of GM plants used for non-food or non-feed purposes for human and animal health and the environment.

The placing on the market of a GM plant, containing the above substance to be purified from said GM plant and to be used as a medicinal product, needs a separate authorisation from the European Commission under Articles 12-24 (Part C) of Directive 2001/18/EC. During the field trial stage (Articles 6-11 (Part B) of Directive 2001/18/EC), in accordance with Article 6 (9) of the Directive 2001/18/EC, Member States shall ensure that no material derived from GMOs is placed on the market, unless in accordance with Part C of the Directive. On the

[14] Under the terminology "GM plant tissue", is most generally, but not restrictively, understood transgene-bearing plant tissue, the latter terminology being used by EMEA.

[15] As defined by Article 2 of Directive 2001/18/EC

other hand, products derived from GM plants released under Part B, can be used for research purposes and clinical trials.

It should be noted that the quality, safety and efficacy of medicinal products purified from GM plants are to be evaluated by EMEA or non-EU equivalents (for products to be marketed outside the EU), and are not within the scope of this Opinion or of the Guidance Document. Hence, for GM plants producing a substance to be used as or in a medicinal product, the risk assessment of the GM plant with regard to the safety for humans and animals, as discussed in this Opinion, is not an evaluation of the safety of the medicinal product for the patients and animals intended to be treated but is relevant to the safety of the general population or livestock or wildlife that may come into contact with the GM plant containing the substance to be used as or in medicinal products.

2.3.3. Advice to applicants on the legal routes to follow and risk assessments to carry out

In line with a WHO report (WHO, 2005) on the regulatory evaluation of candidate human vaccines from plants, EFSA and EMEA support the idea that an innovator wishing to bring a plant-derived medicinal product to the market should consult closely with regulatory authorities to ensure that all appropriate regulatory steps are undertaken.

The EMEA may be consulted on aspects relevant to the development of medicinal products manufactured using GM plant production systems. The EMEA may also be consulted on environmental aspects for medicinal products consisting of or containing material from GM plants (see section 2.3.1). The EMEA also offers scientific advice for medicinal products for human and veterinary use, irrespective of whether the medicinal product is eligible for the centralised procedure or not.

EFSA has provided for applicants a detailed Guidance Document for the risk assessment of GM plants and derived food and feed (EFSA, 2008b). This Guidance Document describes the data requirements and risk assessment criteria to assist the applicant in the preparation and presentation of the GM plant application. This Guidance Document with the practical templates for submission of dossiers, together with this Opinion that considers additional elements for the risk assessment of plants for non-food or non-feed purposes, is to be taken into account by future applicants. EFSA herewith advises applicants/regulators to read this Opinion in parallel with the Guidance Document. As from its adoption, the present Opinion shall be used by the EFSA GMO panel when applications for GM plants developed for non-food or non-feed purposes are evaluated by EFSA.

When a notification under Directive 2001/18/EC is to be evaluated by EFSA, it is expected that the necessary data for the environmental risk assessment (including aspects of human and animal health) are all provided in a comprehensive technical dossier submitted to EFSA. In case the GM plant is used to produce a medicinal product, it is expected that this technical dossier includes relevant data as expected in a marketing authorisation application (MAA) as submitted to EMEA. Possible deviations from this requirement have to be scientifically substantiated by the applicant.

3. Risk assessment strategies for GM plants used for non-food or non-feed purposes

As is the current Guidance Document, also this Opinion is a generic Opinion to cover the wide range of possible GM plants for non-food or non-feed purposes and without pre-empting the case-by-case risk assessment of particular applications.

3.1. General considerations for the risk assessment

Comparative approach

The GMO Panel investigated whether or not the general principles and considerations for the risk assessment of GM plants used for non-food or non-feed purposes require a different approach compared with the risk assessment commonly used for GM plants developed for food or feed.

The risk assessment strategy for GM plants seeks to deploy appropriate methods and approaches to compare the GM plant and derived products with their non-GM comparators. The underlying assumption of this comparative risk assessment approach for GM plants is that *traditionally cultivated crops for consumption as food* have a history of safe use[16] for the average consumer or animals and familiarity for the environment. These crops can serve as a baseline for the food/feed safety and environmental risk assessment of GM plants and their derived food/feed (Concept of familiarity, Concept of Substantial Equivalence, Comparative Assessment, see the Guidance Document section II.2).

By applying the comparative approach, the risk assessment of GM plants focuses on the identification of differences between the GM and its non-GM comparators. These differences are subsequently assessed for their potential impact on human and animal health and the environment. If a concern is identified, the specific information necessary for the risk assessment should be determined on a case-by-case basis. For *plants not cultivated traditionally for consumption as food and not having a history of safe use*, these general considerations for the risk assessment equally apply.

In some instances *extensive genetic modifications*, *e.g.* by insertion of multiple inserts, may have been required in the GM plant to obtain the intended property for non-food or non-feed purposes. This may have led to substantial - but targeted and intended - changes in the original metabolism and composition of the GM plant. Since possibly also unintended changes in the metabolism and composition may have occurred, evaluation is to be considered in a case specific manner and with respect to potential impact on human and animal health and the environment. The GMO Panel considers that the vast majority of the basic biology of the GM plant and the non-GM comparator will remain the same. Therefore a certain level of

[16] For consumption as food (Codex Alimentarius, 2003).

comparison with a non-GM comparator will always be appropriate even in instances where the genetic modification was extensive. In any case it is required that the applicant provides sufficient scientific data regarding the level of impact of the genetic modification on the main biological characteristics of the recipient plant.

The EFSA GMO Panel considers that for GM plants used for non-food or non-feed purposes the comparative approach is valid, but will need to be applied carefully.

Outline of the risk assessment

The risk assessment for plants used for non-food or non-feed purposes follows the four integrative risk assessment steps (see the Guidance Document section II.4, *i.e.* (1) identification and characterisation of a risk source capable of causing adverse effects (*i.e.* hazard identification), (2) a quantitative evaluation of the nature of the adverse effects including, where possible, a dose response assessment (*i.e.* hazard characterisation), (3) exposure assessment and (4) assessment of the probability of occurrence and severity of adverse effects in a given population or environment (*i.e.* risk characterisation).

The risk assessment prior to the environmental release of GM plants used for non-food or non-feed purposes should be focussed on the evaluation of the specific characteristics of these plants. The potential risks of such plants will vary, depending on a range of factors, but will largely depend on (i) the function/biological activity and potential toxicological properties of the substance(s) produced in the GM plant (for example some of these plants may be modified to produce novel compounds which are biologically active in humans, in livestock animals or in wildlife/non-target organisms); (ii) the number and type of humans, livestock animals or wildlife/non-target organisms that may be exposed to such plants; and (iii) the source, route, level, frequency and duration of such exposure. The outcome of the risk assessments may vary depending on the specific protein, the protein expression and exposure scenarios. It follows that a case-by-case risk assessment is recommended (Shama and Peterson, 2008a, Shama and Peterson, 2008b).

For GM plants used for non-food or non-feed purposes the assessment for the potential impact of the differences identified in the comparative analysis is particularly important with regard to accidental intake by humans, livestock and wildlife animals, the exposure of farmers and workers handling the GM plants, and the exposure of people living in the vicinity and of passers.

In addition, the risk assessment of plants used for non-food or non-feed purposes has to take into account the confinement measures when applied. To allow for a quantitative risk assessment, this is to be integrated in a two step risk assessment. In a first step, risks for human and animal health and the environment of the GMO need to be assessed based on an exposure assessment without the consideration of the confinement measures and in a second step, taking account of the confinement measures as proposed and applied by the applicant. This two-step approach is essential for assessing overall risk for human and animal health and the environment. In this way the effect of failure of the proposed confinement measures can be estimated in a transparent manner.

The sections below follow the structure of the Guidance Document, although some of the headings have been modified: The issues to be considered for risk assessment of GM plants used for non-food or non-feed purposes are grouped into the sections (1) Molecular characterisation, (2) Safety for humans and animals and (3) Safety for the environment. While the Guidance Document applies for GM plants used for non-food or non-feed purposes, the present Opinion describes only the issues that differ or that need special attention for GM plants for non-food or non-feed purposes.

3.2. Molecular characterisation

The GMO panel considers that the main principles and risk assessment criteria for molecular characterisation[17] in the Guidance Document (sections III C1-C3, D1-D6) are to be followed for all GM plants used for non-food or non-feed purposes. Even in case of non-food/feed GM crops or food/feed GM crops used for non-food or non-feed purposes, EFSA will take into account accidental intake by humans, livestock and wildlife animals, the exposure of farmers and workers handling the GM plants, and the exposure of people living in the vicinity and of passers. This type of molecular information is necessary in order to evaluate potential unintended effects in the GM plant and risks for human and animal health and the environment posed by the GM plant or plant parts (*e.g.* pollen).

For medicinal products

For GM plants producing a substance to be used as or in a medicinal product, it should be noted that the molecular characterisation as described in the relevant sections of the Guidance Document is for evaluating the genetic modification of the GM plant, and not to evaluate the quality, safety and efficacy of the medicinal product derived from the GM plant as this would be performed by EMEA (see section 2.3.2).

3.3. Safety for humans and animals

The risk assessment of GM plants used for non-food or non-feed purposes with respect to human and animal exposure and the information on potential toxic, allergenic or other harmful effects on human or animal health arising from the GM plant (see the Guidance Document section III.D.7) is described in this section.

The strategy for risk assessment regarding human and animal safety focuses on (i) the characteristics of the newly expressed protein(s); (ii) the characteristics of new constituent(s) other than protein(s) and/or possible changes in the level of constituents occurring naturally in the respective unmodified plant species; (iii) the characteristics of the whole GM plant.

The focus of the evaluation for human and animal safety is on the risks resulting from oral exposure through accidental intake (through inadvertent entry in the food and feed chain via

17 Detection method, sampling method and reference materials are outside EFSA's remit, but are important issues for risk management. The type and format of information for these issues is assessed by the Community Reference Laboratory for GM Food and Feed, under the responsibility of the European Commission.

admixture or gene flow or through accidental consumption in the field) of the GM plants/plant parts used for non-food or non-feed purposes by humans and animals.

The availability of appropriate non-GM plant comparators is important when performing the comparative risk assessment (see the Guidance Document for the choice of the comparator, section III D 7.1.1).

3.3.1. Analysis of the composition and agronomic and phenotypic characteristics of the GM plant

Compositional analyses have to be carried out to determine the expression level of (i) the newly expressed protein(s) and (ii) the new constituent(s) other than protein(s) and/or possible changes in the level of constituents occurring naturally in the respective unmodified plant species; as well as (iii) to identify and quantify possible unintended changes in the composition of the whole GM plant. This type of information is necessary in order to evaluate potential risks of exposure of humans, animals and organisms in the biotic environment to the GM plant or plant parts.

For identification of intended and unintended alterations in the GM plant, the strategies should be followed as recommended in the Guidance Document sections II.2 and III D 7. Analyses should be carried out using established and validated analytical methods according to appropriate quality standards.

The extent of the compositional and agronomic analyses for GM plants used for non-food or non-feed purposes (*i.e.* the type and number of components and agronomic and phenotypic parameters to be compared) may vary, taking the nature of the plant, the possible non-food or non-feed use and the nature of the genetic modification of the plant into account. The selection of compounds must follow an interdisciplinary approach and should be based on expert knowledge.

3.3.2. Product specification and effect of processing

The information requirements regarding product specification and the effect of processing are described in the Guidance Document section III D 7.1.3 and should be provided by the applicant as appropriate.

Applicants are asked for any relevant product specification data that they have obtained to fulfil other legal obligations, *e.g.* under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

3.3.3. Exposure assessment (Anticipated intake/extent of use)

The exposure assessment considering sources, routes, levels, frequency and duration of exposure is an essential element in the risk assessment process (see 3.1 and the Guidance Document section II.4.1.3). It is recommended that the exposure assessment is carried out in parallel to the hazard identification because the information on exposure is needed in order to determine the requirements of the safety testing.

Exposure can result directly from the GM plant or from gene flow of the transgene(s) into other plants outside the field. The environmental risk assessment includes the assessment of the possibility of gene flow. Risk assessment taking into account all potential exposure routes

described below is necessary regardless of whether the exposures result directly from the GM plant or from gene flow. This should also be considered in the exposure/risk assessment with and without taking into account the confinement measures to be applied.

For GM plants used for non-food or non-feed purposes accidental intake by humans, livestock and wildlife animals, the exposure of farmers and workers handling the GM plants, and the exposure of people living in the vicinity and of passers should be taken into account.

The present Opinion covers import and processing as well as cultivation of GM plants used for non-food or non-feed purposes. The routes of exposure as described below are to be considered for each GM plant case, whether cultivated in Europe or imported. For imported GM plants, it is considered that all risk assessment criteria and potential exposure routes must be addressed by the applicant. However, appropriate justification may be given why specific routes of exposure (and thus specific toxicity and allergenicity testing, see 3.3.4) are considered less relevant or irrelevant, for example in the case of cut flowers imported for ornamental use.

Efficacy of confinement strategies

As part of the applicant's risk assessment, the applicant must describe in detail the type(s) of confinement measure(s) and provide sufficient scientific data on the efficiency and effectiveness of the confinement strategy.

To allow for a quantitative risk assessment, the applicant must apply a two step risk assessment. In a first step, risks for human and animal health and the environment of the GMO need to be assessed based on an exposure assessment without the consideration of the confinement measures and in a second step, taking account of the confinement measures as proposed and applied by the applicant. In this way the effect of failure of the proposed confinement measures can be estimated in a transparent manner.

It is thus in the second step of the risk assessment that the applicant must provide information on the potential remaining sources and routes of exposure, the level of exposure, the frequency of such exposure and duration of exposure, depending on the type and efficacy of the confinement strategies proposed and applied.

Hypothetical exposure scenarios could make use of measurements made on reference crops, or derived from research or evaluation reports on previous GM plant (field) trials, in order to generate data on for example the potential intake of the GM plant and the newly expressed protein(s).

3.3.3.1. Oral exposure and general considerations on the use of food/feed plants

For GM plants used for food/feed production, exposure is linked to the anticipated intake and the extent of the intended use of the plant/plant parts (Guidance Document section III D 7.5).

Regarding the source, route, level, frequency and duration of exposure to GM plants/plant parts used for non-food or non-feed purposes, it is important to note that there is no chronic oral exposure to be expected since these plants are not intended for food or feed use.

However, when a food/feed plant is used, accidental intake via inadvertent entry of the GM plant/plant part into the regular food and feed chain (through admixture or gene flow) cannot

be completely ruled out. In addition, accidental intake through unintentional consumption of the GM plants/plant parts in the field by humans, livestock or wildlife animals may occur.

Therefore and as mentioned above, the GMO Panel considers that for the safety assessment of GM plants developed for non-food or non-feed purposes under Directive 2001/18/EC, accidental oral exposure should be considered and that this is to be addressed during the risk assessment.

When a non-food/feed plant is used, it is expected that the oral exposure for humans or livestock animals will in most cases be accidental (if occurring at all) in the meaning of unintentional, infrequent and/or of relatively short duration. It should be noted that this does not exclude the possibility for the EFSA GMO Panel to require the applicant to do oral toxicity tests on a case-by-case basis. For wildlife animals, however, the potential that certain species feed on the type of plant species in question is to be determined and it is expected that oral exposure will be relevant in most cases, regardless if the GM plant is a food/feed crop or a non-food/feed crop. This potential for oral exposure of wildlife and the potential impact of such exposure have to be described under the environmental risk assessment (see section 3.4.3 on non-target organisms) and should refer to the sections under safety for humans and livestock animals where the necessary toxicological studies are performed.

Even if confinement measures have been adopted to avoid oral exposure, an assessment of the risks resulting from oral exposure through the above routes is required for food/feed plants as well as for non-food/feed plants.

General considerations on the use of food/feed plants for non-food or non-feed purposes

In this Opinion, the EFSA GMO Panel considered the use of various food/feed plants (reviewed in Sparrow et al. (2007), *e.g.* maize, rice, barley, oilseed rape, soybean, potato, banana, tomato) for the development of GM plants for non-food or non-feed purposes and whether there are scientific reasons to exclude such uses.

While obviously plants that are traditionally cultivated for food or feed purposes are more likely to enter the food and feed chain, the use of non-food/feed plants would not pose the same (extent of) problems of admixture or gene flow in the food and feed chain. On the other hand, certain plants, and especially non-food/feed plant species, may evoke new aspects of risk assessment (such as for instance an increased risk of spreading in the environment) since most of them are less domesticated and there is less experience with their cultivation.

3.3.3.2. Dermal, ocular and inhalatory exposure

In accordance with Directive 2001/18/EC, the risks for farmers and workers handling the GM plants also have to be assessed. According to the Guidance Document, this assessment is to be incorporated under the environmental section, with a link to the sections under safety for human health where relevant tests are performed. To address these risks, the applicant has to assess potential dermal, ocular and inhalatory exposure as applicable. For instance, in the case of GM plants which produce pollen, an assessment of the inhalatory exposure to pollen and, where applicable, any new constituents expressed therein will be required.

For farmers and workers handling the GM plants, the exposure assessment and risk assessment should take into account current work conditions for farmers and workers who produce or process non-GM counterpart products (comparative approach).

For people living in the vicinity and passers, the dermal, ocular and inhalatory exposure as a consequence of skin and eye contact with or inhalation of plant material, pollen or dust is also to be addressed.

Specific data on the potential dermal, ocular and inhalatory exposure routes to the GM plant material should be required on a case-by-case basis, *i.e.*, if a specific hazard was identified based on the characterization of the GM plant.

It is expected that the procedures applied during cultivation, harvest, transport and storage of the plants/plant parts as well as the methods used to obtain relevant products, differ widely between different production systems. Therefore, as a prerequisite for the exposure assessment, a detailed description of the production systems applied is required. These descriptions should focus on the identification of critical steps where skin and eye contact and/or inhalation of plant material could occur as well as the level, frequency and duration of exposure during the production systems. The measures intended to minimise the exposure of farmers and workers handling the GM plants, and the exposure of people living in the vicinity and of passers should be described and the expected impact of these measures should be assessed.

3.3.4. Toxicology

According to the Guidance Document section III D 7.2, the requirements of toxicological testing of GM plants used for non-food or non-feed purposes are to be considered on a case-by-case basis and will be determined by the outcome of the assessment of the differences identified between the GM plant and derived food/feed products and their conventional counterparts in the comparative analysis of composition, agronomic and phenotypic traits. The risk assessment must consider the presence of new proteins expressed as a result of the genetic modification, the presence of other new constituents and/or possible changes in the level of constituents occurring naturally in the respective unmodified plant species (according to the Guidance Document section III D 7.2).

Deviations from the normal testing program may be possible if scientifically justified. For example, in the case of GM plants containing a substance(s) with pronounced biological activity, the risk assessment should be tailored accordingly. On the other hand, extension of the testing program may be required on a case-by-case basis.

If the GM plant used for non-food or non-feed purposes is obtained by genetic modification of a plant species which is traditionally used for food or feed, its presence in the food and feed chain would require authorisation under Regulation (EC) No 1829/2003 and in such cases the Guidance Document applies.

If the unmodified plant is not traditionally used for food or feed, or closely related to food and feed plants into which gene flow is possible, in principle the Guidance Document also applies. In most cases exposure to the GM plants used for non-food or non-feed purposes is expected for humans and livestock animals to be accidental (if occurring at all) in the meaning of unintentional, infrequent and/or of relatively short duration (see section 3.3.3). Therefore in these cases the EFSA GMO Panel considers that toxicological assessment should primarily focus on acute and/or short term exposure. However, to cover for wildlife exposure (*e.g.* if

specific animals graze on the plant species), longer-term exposure is to be addressed in the risk assessment.

Moreover data on potential genotoxicity, metabolism and toxicokinetics should be generated when required on a case-by-case basis.

3.3.4.1. Toxicological testing of newly expressed proteins

According to the Guidance Document (section III D 7.2.2) the toxicological testing program for newly expressed proteins should be selected on a case-by-case basis depending on the protein's source, function/activity and history of human/animal consumption. The general strategy as well as the recommendations outlined in the Guidance Document are also considered appropriate with regard to the testing of newly expressed proteins in GM plants used for non-food or non-feed purposes.

Possible post-translational modifications, such as glycosylation, should be assessed in accordance with the requirements as mentioned in section III D 7.2.2 of the Guidance Document.

Proteins or peptides to be used as or in medicinal products

Those proteins or peptides which are newly expressed in the GM plant and which are intended to be used in medicinal products may have a wide variety of different pharmacological and immunological activities in humans or animals, sometimes at relatively low doses. In the case of proteins or peptides to be used in medicinal products for human use, studies on toxicokinetics/pharmacokinetics, toxicological studies *in vitro* and *in vivo* as well as clinical trials are normally required (see Annex I of Directive 2001/83/EC (EC, 2001b) as amended by Directive 2003/63/EC (EC, 2003a) for dossier requirements for medicinal products). It can be expected that the results of the studies required for the evaluation of the non-clinical and clinical safety of the medicinal product are relevant for the evaluation of the GM plant containing the respective protein(s). Therefore a summary of the studies and the results as expected to be submitted to EMEA in a marketing authorisation application (MAA) should be provided by the applicant to EFSA as appropriate. In particular, the examples of studies as mentioned in Table 1 are considered to be of potential relevance for the assessment of the GM plants containing the respective protein(s). Possible deviations from this requirement have to be scientifically substantiated by the applicant. On a case-by-case basis, additional information may be required.

However, in some cases (*e.g.* when the product is a protein) the information available on the medicinal product may not be sufficient for the evaluation of the protein(s) when present in GM plants/plant parts, which generally has to consider oral, dermal, ocular and inhalatory exposure. For example, the route of administration used in the pharmacokinetic and/or toxicological studies of the medicinal product may not be relevant or not sufficient for the evaluation of the GM plant containing the protein. If the protein is intended to be used in medicinal products and was thus only tested via the oral route, additional studies using the dermal and/or inhalatory route of administration may be necessary. Furthermore, the protein used in these studies may not be regarded as equivalent to the protein present in the GM plant and therefore, additional toxicological information may be required on a case-by-case basis.

Table 1. **Examples from the Common Technical Document (CTD) of EMEA.**

While Annex I of Directive 2001/83/EC describes in a comprehensive way the information required by EMEA for the risk assessment of medicinal products for human use and isolated from a plant, the following examples are considered of potential relevance when assessing the GM plant producing that medicinal product.

1. Pharmacological data	1.1 Primary pharmacology
	1.2 Secondary pharmacology
	1.3 Safety pharmacology
2. Pharmacokinetic data	
3. Toxicological data, including toxicokinetics for each study	3.1 Single dose toxicity in two species (rodent and non-rodent)
	3.2 Repeated dose toxicity including immunotoxicity in two species (rodent and non-rodent)
	3.3 Genotoxicity (two tests *in vitro* and one *in vivo*)
	3.4 Carcinogenicity
	3.5 Reproductive and developmental toxicity including 3.5.1 fertility 3.5.2 teratogenicity 3.5.3 development 3.5.4 juvenile study
	3.6 Local tolerance where appropriate
	3.7 Skin sensitization, including phototoxicity testing
	3.8 Mechanistic studies supporting all toxicity studies
4. Phase I Clinical trials in human using the intended route of administration	

In addition, once a medicinal product is authorised, the pharmacovigilance system ensures that the safety of the medicinal product in patients is constantly monitored and the holder of

the marketing authorisation for the medicinal product shall inform the European Commission, the National Competent Authority under Directive 2001/18/EC and EFSA of any adverse reactions relevant to the risk assessment of the GM plant comprising the medicinal product.

Furthermore, no specific assessment of allergenicity (apart from skin sensitisation) is foreseen in the EMEA preclinical evaluation as outlined in Annex I of Directive 2001/83/EC, except for observations during the clinical trials. However, for plant derived products the requirements of that module may have to be adapted for individual products and include other tests. Any information as expected for the assessments performed by EMEA should be included in the GM plant application as appropriate. Emerging signals for allergenicity from safety clinical data or post market monitoring should be provided when available.

3.3.4.2. Testing of new constituents other than proteins and/or possible changes in the level of constituents occurring naturally in the respective unmodified plant species

For the selection of a test scheme it is irrelevant whether the new constituent is completely new or if it occurs naturally in the respective unmodified plant species.

For GM plants and derived food and feed, identified new constituents other than proteins should be evaluated according to the Guidance Document (section III D 7.2.3). According to the Guidance Document, testing of natural food and feed constituents is only applicable in instances where the content of such natural food and feed constituents is altered beyond the natural variation.

To establish the safety of new constituents having no history of safe use, information analogous to that described in the "Guidance on submissions for food additive evaluations by the Scientific Committee on Foods" (SC, 2001) and Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives (EC, 2008) shall be provided. This implies the submission of information on a core set of studies and the consideration of whether or not any other type of study might also be appropriate. Normally, the core set includes information on metabolism/toxicokinetics, sub-chronic toxicity, genotoxicity, chronic toxicity, carcinogenicity and reproduction and developmental toxicity.

Since there is no chronic oral exposure to be expected for GM plants used for non-food or non-feed purposes because these plants are not intended for food or feed use, nor expected to be widely distributed in the environment (see section 3.3.3 on exposure), and since the intake of such plants/plant parts is accidental in the meaning of unintentional, infrequent and/or of relatively short duration, the GMO Panel is of the opinion that it is justified to deviate from the above recommendations for food and feed plants, in that the toxicological information should primarily be obtained from acute and/or short-term repeated-dose testing. The risk assessment should also consider the presence of precursors and intermediates which might occur in the plant on a case-by-case basis.

For some non-food or non-feed purposes, for example for phytoremediation, there is no purified product. In general, safety tests should not be required on purified substances (proteins as well as other constituents) if these do not exist as purified substances in the final product. The Authority reserves the right to require such tests on a case-by-case basis.

For medicinal products

For non-protein constituents that are intended to be used in medicinal products, comprehensive pharmacological and toxicological information will be provided to EMEA for the evaluation of the marketing application of such products. This information is expected to be relevant for the risk assessment of the GM plant containing the new constituent(s). Therefore a summary of these studies and the results as expected to be submitted in a marketing authorisation application (MAA) to EMEA should be provided by the applicant of the GM plant to EFSA as appropriate. On a case-by-case basis, additional information may be required (see also 3.3.4.1).

3.3.4.3. Toxicological testing of the whole GM plant

It is important to note that chronic oral exposure of humans and animals to GM plants not intended for food or feed use is not anticipated. As stated above in section 3.3.4 oral exposure as a consequence of (i) accidental intake via inadvertent entry of GM plants/plant parts into the regular food and feed chain (through admixture or gene flow), or (ii) accidental intake through accidental consumption of GM plants/plant parts in the field by humans, livestock or wildlife animals, cannot be excluded and is to be taken into account. Therefore, the Guidance Document section III D 7.2. on the testing of whole GM food/feed as well as the Report of the EFSA GMO Panel Working Group on Animal Feeding Trials (EFSA, 2008a) are considered of relevance with regard to the testing of the whole GM plants used for non-food or non-feed purposes. This means that the results from molecular characterization, compositional and agronomical analysis, together with information on the toxicological profile and allergenic potential of newly expressed proteins and other plant constituents, and information on potential exposure routes and patterns, should be evaluated before any decision is made on further testing of the whole GM plant/plant parts. In general further testing of whole GM plants used for non-food or non-feed purposes in animals is not recommended and should be evaluated with respect to added value.

Genotoxicity has to be considered on a case-by-case basis and justification for carrying out genotoxicity testing would be necessary. As an example, the expression of particular antigens in plants could require genotoxicity testing. Genotoxicity would be tested with plant extract. Also the potential difficulties in the test should be described.

A comprehensive set of *in vitro* and *in vivo* tests is available to study potential toxicity resulting from skin, eye and inhalatory exposure. The studies required should be determined on a case-by-case basis depending on the expected route of exposure, the characteristics of the plant and the changes resulting from the genetic modification. For example, the Local Lymph Node Assay (LLNA) using mice or the Guinea Pig Maximisation Test (OECD Guidelines 429 (OECD, 2002) and 406 (OECD, 1992)) may be required to test extracts from GM plants for their potential to induce skin sensitization. Internationally agreed protocols to test for skin and eye irritation/corrosion as well as for acute and repeated dose dermal and inhalation toxicity are also available (OECD Guidelines for the Testing of Chemicals).

3.3.5. Allergenicity

It is considered that the case-by-case risk assessment for allergenicity of GM plants for non-food or non-feed purposes should cover at least one of the two possible hypotheses, namely

(1) that the plant and/or one of the products produced herein is already known as allergenic, or alternatively (2) that the plant and/or one of the products produced herein is not known to be allergenic.

In the first case, when the plant used for non-food or non-feed purposes, and/or one of the products produced herein, is known to be allergenic, the risk of an allergic reaction should be managed by reducing exposure of humans and animals through suitable confinement measures (see section 5.2).

In the second case the Guidance Document section D III 7.3 is applicable and to be followed. Respiratory exposure (*e.g.* via pollen) may need particular attention. Regarding the assessment of allergenicity of the newly expressed proteins, a strategy is applied which is in accordance with the recommendations of the Codex *ad hoc* Intergovernmental Task Force on Foods Derived from Biotechnology (Codex Alimentarius, 2003). In addition, the potential allergenicity of the whole GM plant is to be assessed.

For medicinal products

For newly expressed proteins that are medicinal products and assessed by EMEA, emerging signals for allergenicity from safety clinical data or post market monitoring should be provided when available (see section 3.3.4.1).

3.3.6. Nutritional assessment

Nutritional assessment is connected to intended intake of food and feed, not accidental intake, and therefore is not an issue for GM plants used for non-food or non-feed purposes.

3.4. Safety for the environment

The environmental risk assessment is described in sections III D 4, 8, 9, 10 of the Guidance Document. The Guidance Document considers the direct and indirect effects of GM plants on the environment.

These sections of the Guidance Document as a whole represent the different potential routes of exposure to the environment that have to be taken into account and these sections inform the applicant of the data requirements needed to address these routes of exposure and their potential impact on the environment. For cultivation applications, this would include for example gene flow, interactions with non-target organisms and plant exudates in the soil leading to exposure of soil microorganisms and other soil biota. Placing on the market under Part C of the Directive 2001/18/EC also covers import and processing. Accordingly, environmental exposure as a result of transport and handling (loss and spillage) are also to be addressed. GM plants used for non-food or non-feed purposes should be assessed in the same way as described in the Guidance Document, though some characteristics, such as interaction with target organisms (as would be the case for insect resistant GM plants), may not be relevant.

As mentioned in section 3.1, the applicant has to perform environmental risk assessment initially (in a first step) without taking the confinement measures into account, and in a second step with taking the confinement measures into account.

Further to the description of the environmental risk assessment criteria as in the Guidance Document, the following sections indicate which aspects need special consideration when assessing GM plants used for non-food or non-feed purposes.

3.4.1. Persistence, invasiveness, selective advantage or disadvantage

Persistence, invasiveness, selective advantage or disadvantage should be assessed as in the Guidance Document. Further consideration may be necessary in some cases. For example, plants for bioremediation may have enhanced ability to establish and spread on contaminated land which provides an ecological niche for naturally occurring specialised plants (*e.g.* rare metal tolerant flora). It will be important to determine whether they also have advantages in other niches and a tendency to displace other plant species.

Regarding GM plants that produce bio-active or biocidal substances, for instance pharmaceuticals, that are stable or that can be considered to have a long persistence in the environment, particular attention should be directed to accumulation and effects in the environment of such substances and their metabolites.

3.4.2. Potential for gene transfer

Further to the potential oral exposure through gene flow in the food and feed chain, an equally important matter is the environmental exposure as a consequence of gene flow to related plants within the environment that can cross with the GM plant (food/feed plants or non-food/feed plants). This gene flow and its potential consequences for plants within the environment need to be addressed during the risk assessment, even if confinement measures

have been adopted to prevent gene flow into wild plants. The EFSA GMO Panel considers it unlikely that biological and/or physical confinement measures will prevent all gene flow and so the consequences of low levels of gene flow for human and animal health and the environment will need to be considered as described in the Guidance Document and this Opinion. This means that in a first step an environmental risk assessment is to be performed without the proposed confinement measure to avoid admixture or gene flow. In a second step, an assessment is expected taking the confinement measure into account, including an assessment of the effectiveness of confinement measures in controlling admixture or gene flow.

The Guidance Document section III D 9.3 is applicable to cover the environmental risk assessment criteria that should be applied by the applicant to assess the potential for gene transfer of plants for non-food or non-feed purposes. So far, for GM plants used for food or feed purposes, gene flow and its consequences are not identified as a hazard for human and animal health and the environment. However for GM plants used for non-food or non-feed purposes, there might be some new potential risks associated and hence, the consequences of potential gene transfer may need further consideration. The following two paragraphs describe how this should be done.

Potential for gene transfer and consequences for human and animal health

After determination of potential for gene flow from the GM plant used for non-food or non-feed purposes and potential exposure of humans and animals, the potential consequences of this gene flow to human and animal health through oral, dermal, ocular or inhalatory exposure to these GM plants should be assessed as described in section 3.3.

Potential for gene transfer and consequences for the environment

After determination of potential gene flow from the GM plant used for non-food or non-feed purposes, the potential consequences for the environment should be assessed as described in the Guidance Document (section III D 9.3).

In cases where gene flow from GM plants used for non-food or non-feed purposes may result in adverse effects for human and animal health and the environment, the use (import and processing or standard operating procedures for cultivation) of such GM plants should be accompanied by measures to restrict gene flow. For example, as a result of the identification of hazard, *i.e.* that potential gene flow and its consequences can pose a danger, biological and/or physical confinement measures (see section 5.2) might be proposed by the applicant to reduce gene flow. It is unlikely that biological and/or physical confinement measures will prevent all gene flow and so the consequences of low levels of gene flow for human and animal health and the environment will need to be considered as described in the Guidance Document and this Opinion. Applicants are requested to fully describe the confinement strategy to limit human and animal and environmental exposure through gene flow and to assess the efficacy of the confinement measures. The proposed confinement measures should be related to any hazard identified. The risk assessment should scientifically evaluate the effectiveness of physical and biological confinement measures in order to quantify levels of exposure and estimate the magnitude of risks.

3.4.3. Interactions of the GM plant with non-target organisms

The Guidance Document section III D 9.5 covers the assessment of the possible immediate and/or delayed environmental impact resulting from the direct or indirect interactions of the GM plant with non-target organisms, including herbivores. These include the wildlife animals for which it needs to be determined which species feed on the type of plant species used. The potential impact of the oral exposure of such wildlife species has to be described under the environmental risk assessment and when necessary should refer to the sections under human and animal safety where relevant tests are described.

3.4.4. Effect on human health - Worker safety

In line with other legislative requirements on worker safety[18], in the framework of GMO risk assessment under Directive 2001/18/EC, information has to be provided on the possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GM plant and persons working, coming into contact or being in the vicinity of the GM plant release (see Annex II D.2.6 of the Directive). This is covered in section III D 9.6 of the Guidance Document, referring back to section III D.7, where the necessary studies to address human and animal safety are described.

3.4.5. Release of residual biomass into the environment

When the GM plant used for non-food or non-feed purposes is developed to produce a substance, the residual biomass after removal of the intended substance can be (1) processed and treated as waste, (2) deliberately released in the environment for further (non-food and non-feed) use or (3) used for food or feed.

In the first case, necessary information regarding the processing of plant wastes should be included in the application. Process and treatment of plant wastes after removal of the substance should be carried out according to the nature of the expressed compounds and the related safety measurements. In this respect it has to be considered if such waste could be classified as hazardous depending on the nature and extent of residual active ingredients.

In the second case, the environmental risk assessment should cover the deliberate release into the environment and the Guidance Document applies. When the residual biomass after extraction of the relevant product for example remains in the environment or is re-released into the environment (*e.g.* as fertilizer), the environmental risk assessment of the release into the environment of the biomass should take the processing (including extraction and possible presence of solvent/extraction buffers) into account when applicable. The assessment should also include whether or not the exposure is altered when compared to the whole GM plant and how the handling of the residual biomass is covered by Good Manufacturing Practice (*e.g.* Regulation (EC) No 2023/2006 (EC, 2006)) and WHO (WHO, 2003)). As stated in the Guidance Document, the receiving environment has to be considered. When more and more

[18] The European Union has a substantial body of legislation on the safety and health of workers at work, the basic text of which is Directive 89/391/EEC (EC, 1989). This defines the employer as the person responsible for the health and safety of workers in every aspect relating to their work. It also makes worker information, training, consultation and participation the focal point of the preventive policies to be implemented, in accordance with a risk assessment which must be carried out within a company. Such a workplace assessment principally comprises a risk assessment as well as the development and implementation of adequate measures against these risks.

GM plants will be adopted, the receiving environment may also include other approved events.

In the third case, when an intended (as opposed to accidental) route exists for the GM plant, or its residual biomass (any plant parts or their processed products (*e.g.* side streams)), to enter the food and feed chain, the risk assessment should follow the requirements laid down in Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (see section 2.2), and the risk assessment will need to consider the advice given in both this Opinion and in the Guidance Document. This will be the case even if the primary purpose of the GM plant is for non-food or non-feed applications. If any plant parts or processed products of the GM plant developed for non-food or non-feed purposes are to be used as food or feed, an application to place such GM plant parts or processed products on the market should be submitted under Regulation (EC) No 1829/2003 using the so called one key - one door approach.

With regard to the effects of processing of a plant material (GM or non-GM), the following should be noted. In cases where solvents are used during the extraction process, these solvents should be authorised and used in accordance with Council Directive 88/344/EEC of 13 June 1988 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients (EC, 1988). The evaluation of potential risks involved in such extraction is not within the scope of GMO regulations. However, where the extraction or processing method is relevant to the safety assessment of residual biomass of the GM plant intended to be used as food or feed or released into the environment, relevant information should be provided for the risk assessment of the GM residual biomass.

4. Post-Market Environmental Monitoring

Though Post-Market Environmental Monitoring (PMEM) is related to risk management, the EFSA GMO Panel gives its opinion on the scientific quality of the monitoring plans provided by the applicants. The GMO Panel considers that the main principles and scientific criteria for PMEM in the Guidance Document (see section III D 11) are appropriate and sufficient for GM plants used for non-food or non-feed purposes. The following points may require special attention.

As stated in section 3.4.2, environmental hazards that are identified in the Environmental Risk Assessment may trigger the need for specific confinement methods. The monitoring plan may also need to include monitoring of the effectiveness of the confinement measures as well as monitoring of anticipated and unanticipated risks. If there are reasonable doubts on reliability of confinement, then specific inspections may be needed to either confirm or control the reliability of the confinement measures (see section 5). In the present Opinion a two step risk assessment is requested, wherein in a first step, risks for human or animal health and the environment of the GMO need to be assessed based on an exposure assessment without the consideration of the confinement measures and in a second step, with taking account of the confinement measures as proposed and applied by the applicant. In this way the effect of

failure of the proposed confinement measures and/or the need for case-specific monitoring can be estimated in a transparent manner.

Case-specific monitoring and general surveillance should be conducted as for other GM plants. Attention is drawn to the section III D 11.4.1.1. of the Guidance Document describing the approach and principles for GM plants intended for import and processing only. Attention is also drawn particularly to the fact that in the case of imported GM products containing viable propagating material, general surveillance plans should consider the implications of substantial loss, spillage or unanticipated establishment and spread of GM plants.

Case-specific monitoring is required on a case-by-case basis including monitoring of viable genetically modified plants that may cause hazards for human or animal health or the environment, and cases where environmental exposure is controlled by biological or physical confinement of uncertain reliability. Case-specific monitoring therefore needs to address the efficiency of the confinement measures. It also needs to consider, on a case-by-case basis, the potential impacts on biota at risk in the receiving environment if a critical level of exposure is likely.

5. The interplay between risk assessment and risk management

5.1. Standard production protocols and Stewardship

The use of GM plants for non-food or non-feed purposes, for example the production of novel compounds, expands the role of crop plants. The target products could have adverse effects when in contact with humans, animals or the environment, or when consumed by humans or animals. Where new potential GM plant risks are identified, the plants are likely to require more specific risk management conditions, such as methods of production stewardship, defined confinement measures, safety thresholds and inspections. In view of this, specific confinement methods and standard protocols for plant production may need to be defined as part of the plant production method. Furthermore, standard production protocols (SPP) are also likely to form a fundamental part of the production of medicinal products which must achieve a high level of batch to batch consistency as a part of medicinal product regulation and approval. Though there are non-controllable variables under open field conditions (*e.g.* weather conditions, pathogens, soil quality), it may be useful and necessary to define in detail the methods of initial seed production and maintenance, the confinement measures, isolation distances, agronomic management, usage of fertilizer and segregation methods for the products from harvest to final market.

Hence, for some applications of GM plants used for non-food or non-feed purposes, it is likely that the technical dossier submitted for regulatory approval will also be accompanied by a defined production protocol (as described above) that will help to inform the risk assessment of the GM plant in the context of its intended use. It will also be important to have this information to enable an assessment of the whole production process of the medicinal

product, and to facilitate the work of risk managers[19] deciding, where appropriate, on thresholds, tolerance of admixture, labeling *etc.*

It is also important to note that this situation is not new, or necessarily a consequence of genetic modification. Experience with traditional non-GM plants that produce industrial compounds (*e.g.* high erucic acid oilseed rape) demonstrates that such industrial plants may require closely defined production protocols and confinement measures. For industrial or medicinal GM plants it will be useful to draw on the extensive experience of stewardship practices widely used within the European Community.

Standard production protocols may also involve tagging of such plants with a generic non-food/feed GM plant-specific DNA sequence identifier (NOFI), apart from an event-specific marker, preferably being devoid of open reading frame. This risk management tool would support the consumer's choice by enabling event-specific DNA detection and facilitate mandatory product labelling, on one hand, and prevention from entry into the food and feed chain by confinement, on the other. Furthermore, a NOFI will greatly support molecular detection and quantification of accidentally appearing non-food/feed GM plants or some (processed) residual parts thereof in food or feed, especially when a considerable number of diverse crops are reached.

5.2. Confinement strategies

The assessment of the efficacy of confinement strategies (physical or biological) is an important component for assessing exposure levels and quantifying risks and is also an important aspect of the case-specific monitoring (risk management). The risk assessment of some GM industrial plants may indicate that these plants have potential adverse effects on human and animal health and the environment, so that appropriate confinement strategies will need to be applied in order to obtain approval to commercialise these plants. If there are reasonable doubts on reliability of confinement of GM plants for which hazards for human or animal health and the environment have been identified in the risk assessment, then specific inspections may need to be put in place to either confirm or control the reliability of the confinement measures during cultivation.

Given the high diversity of molecules that could be produced in GM plants, many different scenarios of such GM plants used for non-food or non-feed purposes, based on the hazard and the potential exposure, can be envisaged. In each scenario the applicant should describe the link between (1) the acceptable level of exposure due to admixture or gene flow or due to the production of a (potentially toxic or otherwise bioactive) compound and (2) the confinement requirements and further control measures necessary to reduce exposure of humans or animals and the environment. It is envisaged that the links between unacceptable level of exposure

[19] In Europe risk management is separated from risk assessment. The risk assessor (Member States risk assessment bodies or Competent Authorities and EFSA and/or EMEA), carries out the risk assessment of the GM plant based on the information provided in the technical dossier prepared by the applicant. The nature of the potential risks resulting from the deliberate release of the GM plant into the environment must be described in the dossier and evaluated by the risk assessor. The risk assessment Opinions of EFSA are forwarded to the European Commission and to the Member States Competent Authorities. These are the risk managers making decisions for or against market approval, based on the scientific risk assessment and taking account of other information. In deciding on whether or not a product should be marketed, the risk manager may also define conditions for the production and marketing of the GM product, including confinement requirements and inspection needs.

and confinement are described in detail on a case-by-case basis for each GM plant. By way of illustration only, three such scenarios are here provided.

1. No confinement might be necessary when the risk for human and animal health and the environment is negligible (*i.e.* where the level of exposure could be acceptable). Admixture with food or feed plants (*e.g.* via admixture or gene flow) does not raise concern with respect to food or feed safety and environmental risk.

2. Partial confinement could be necessary for example through gene use restriction technology, the use of only non-food or non-feed plants, the use of separation markers, or isolated production areas (thus where exposure would have to be reduced). In these cases, low frequencies of GMO could be tolerated in the food and feed chain or the environment as they do not raise concern with respect to food/feed safety and environmental risk. The acceptable admixture with food and feed plants is case-specific, as are further requirements for the PMEM.

3. Where exposure would have to be avoided, high biological and/or geographical confinement or isolation of the cultivated GM plant[20] will be necessary to prevent adverse effects on human and animal health and the environment. No admixture of GMO into food or feed plants (*e.g.* via admixture or gene flow) or in the environment outside the cultivation site can be tolerated from a safety perspective. It could be considered that this scenario requires case-specific monitoring as part of PMEM and inspection measures.

The applicant has to provide information and argumentation as outlined above and how confinement will be implemented. To assess the reliability of confinement (and how the effectiveness of confinement will be monitored) the following should be taken into account. The effectiveness of confinement measures may be influenced by external factors such as abiotic and biotic conditions. The applicant therefore should provide data that allow the assessment of confinement measures under all environmental conditions envisaged taking worst-case scenarios into account. In this regard it may be necessary and useful for the applicant to narrow the geographical area in which he seeks permission for the product.

The applicant should also provide detailed emergency plans for the case that confinement measures fail.

Confinement strategies, applicable to all GM plants used for the production of non-food or non-feed products, may be based on many different biological principles. An overview of such techniques is given in the DEFRA report "Technologies for Biological Containment of GM and Non-GM Crops" (Dunwell and Ford, 2005). New technologies are being explored in the EU research project Transcontainer[21]. Due to the wide variety of containment techniques and the amount of time required to assess all techniques at this stage, the present Opinion

[20] As the present Opinion covers applications under Directive 2001/18/EC, this means still outside "Contained use" under Directive 90/219/EEC.

[21] http://www.transcontainer.wur.nl/NL/

does not elaborate further on the effectiveness of individual biological/physical confinement strategies for genetically modified plants used for non-food or non-feed purposes[22].

In the present Opinion for plants used for non-food or non-feed purposes, biological confinement strategies are discussed in so far as they are intended to keep the GM plant material separate for safety reasons. These confinement measures are not to be confused with co-existence measures, which are intended to keep GM plants separated from non-GM plants for strictly economical reasons and to guarantee free choice for the consumer.

The geographic area foreseen for a specific management system will probably be very small. Therefore, the impact of the management should be estimated locally, *e.g.* if measures like soil sterilising or removal of all cross-compatible wild species are foreseen in the cultivation areas.

In light of the above, applicants should describe for each GM product the details and rationale for the proposed physical and biological confinement strategy, where applicable. The proposal should specify the methodology used and its effectiveness in reducing or preventing accidental intake or gene flow into the environment. Methods of enforcing monitoring and emergency measures for restricting gene flow should also be described. Regarding GM plants used for non-food or non-feed purposes that produce bio-active substances that are stable, or persist for a long time in the environment, it should be considered whether the confinement should also prevent or reduce herbivory and leakage through drainage or sewage.

[22] The fact that EFSA does not assess the effectiveness of individual confinement measures at present, is not hampering this general risk assessment Opinion. EFSA shall collect the necessary expertise and knowledge at the time when GM plant applications for non-food or non-feed purposes will be submitted and assessed.

STAKEHOLDER CONSULTATIONS AND PUBLIC CONSULTATION

A draft Opinion was adopted by the EFSA GMO Panel on 22 November 2007 and submitted to the European Commission for legal consultation and to the EMEA for commenting. After incorporation of input from the European Commission and EMEA, an amended draft opinion was adopted on 16 April 2008. EFSA is open to input from all Stakeholders amongst which are (1) biotech and pharma industry, seed and food retailers, agricultural organisations, (2) research institutes and the Member States, (3) the broader public or individual scientists and (4) organisations such as environmental NGOs and EU consumer groups. To seek a wider input into the presented Opinion, the amended draft was published on the EFSA website from 16 June 2008 until 16 September 2008 for a 12-week period of public consultation for comments and additional recommendations. EFSA wishes to thank the following organisations that contributed to this work and gave their recommendations and views, comments and suggestions.

Table 2. **Organisations who provided comments to this Opinion during the public online consultation**

Country	Organisation
AUT	Florigene
AUT	Austrian Ministry of Health, Family and Youth, Dep. IV/B/9
BEL	Scientific Institute of Public Health
BEL	EuropaBio
BEL	International Life Sciences Institute (ILSI) Europe International Non-Profit Organization
DEU	Federal Agency for Nature Conservation (BfN)
DEU	Federal Institute for Risk Assessment
DNK	National Food Institute
FIN	Ministry of Social Affairs and health
FRA	Institut National de la Recherche Agronomique (INRA)
GBR	Government Chemist
GBR	Department for Environment, Food and Rural Affairs (DEFRA)/ACRE
GBR	Greenpeace
IRL	Food Safety Authority of Ireland
MLT	The Maltese Biosafety Coordinating Committee
NLD	Ministry of the Environment, Ministry of Agriculture, Nature and Food Quality, Ministry of Health
NOR	Norwegian Scientific Committee for Food Safety
SVN	Slovenian Scientific Committee for the Deliberate Release of GMOs into the Environment and Placing Product on the Market (SCDR)
SWE	National Food Administration
SWE	Swedish Board of Agriculture
USA	Biotechnology Industry Organization

CONCLUSIONS AND RECOMMENDATIONS

An increasing number of GM plants are being developed for a wide range of non-food or non-feed purposes. Some are developed to manufacture non-food or non-feed products such as medicinal or industrial products, others for purposes of energy production, phytoremediation, landscape improvement and ornamentals.

EFSA has provided for applicants a detailed Guidance Document for the risk assessment of GM plants and derived food and feed. This Guidance Document describes the data requirements and risk assessment criteria to assist the applicant in the preparation and presentation of the GM plant application. Based on risk assessment experience and new advancements in science, EFSA regularly updates its Guidance Document. The GMO Panel decided that additional guidance needed to be developed for the environmental risk assessment of GM plants used for non-food or non-feed purposes to supplement the Guidance Document.

Issues for the assessment of GM plants used for non-food or non-feed purposes that would need special attention or may have more/less stringent requirements compared with the risk assessment requirements for GM plants for food and feed purposes have been identified. The wide range of possible GM plants for non-food or non-feed purposes is covered in this Opinion without pre-empting the case-by-case risk assessment of particular applications.

The Guidance Document with the templates for submission of dossiers, together with this Opinion that considers additional elements for the risk assessment of plants for non-food or non-feed purposes, is to be taken into account by future applicants. EFSA herewith advises applicants/regulators to read this Opinion in parallel with the Guidance Document. A regulatory flowchart is provided showing the interplay between the intended uses of a GM plant and the respective EU legislation applicable. The flowchart also gives an overview of the regulatory bodies that are involved in scientific risk assessment and the ones that are responsible for risk management and decisions on authorisations.

When a notification under Directive 2001/18/EC is to be evaluated by EFSA, it is expected that the necessary data for the environmental risk assessment (including aspects of human and animal health) are all provided in a comprehensive technical dossier submitted to EFSA. In case the GM plant is used to produce a medicinal product, it is expected that this technical dossier includes relevant data as expected in a marketing authorisation application as submitted to EMEA. Possible deviations from this requirement have to be scientifically substantiated by the applicant. EFSA and EMEA support the idea that an innovator wishing to bring a plant-derived medicinal product to the market should consult closely with regulatory authorities to ensure that all appropriate regulatory steps are undertaken.

The EFSA GMO Panel considers that for GM plants used for non-food or non-feed purposes the comparative approach is valid, but will need to be applied carefully. For these plants, the assessment of the potential impact of the differences identified in the comparative analysis is particularly important with regard to accidental intake by humans, livestock and wildlife animals, the exposure of farmers and workers handling the GM plants, and the exposure of passers and of people living in the vicinity.

The focus of the evaluation for human and animal safety is on the risks resulting from oral exposure through accidental intake (through inadvertent entry in the food and feed chain via admixture or gene flow or through accidental consumption in the field) of the GM plants/plant parts used for non-food or non-feed purposes by humans and animals.

The risk assessment for plants used for non-food or non-feed purposes has to take into account the confinement measures when applied. To allow for a quantitative risk assessment, this is to be integrated in a two-step risk assessment. In a first step, risks for human and animal health and the environment of the GMO need to be assessed based on an exposure assessment without the consideration of the confinement measures and in a second step, confinement measures as proposed and applied by the applicant should be taken into account.

The use of GM plants for non-food or non-feed purposes, for example the production of novel compounds, expands the role of crop plants. The target products could have adverse effects when in contact with humans, animals or the environment, or when consumed by humans or animals. Where new potential GM plant risks are identified, the plants are likely to require more specific risk management conditions, such as methods of production stewardship, defined confinement measures, safety thresholds and inspections.

To assess the reliability of confinement (and how the effectiveness of confinement will be monitored) the following should be taken into account. The effectiveness of confinement measures may be influenced by external factors such as abiotic and biotic conditions. The applicant therefore should provide data that allow the assessment of confinement measures under all environmental conditions envisaged taking worst-case scenarios into account. In this regard it may be necessary and useful for the applicant to narrow the geographical area in which he seeks permission for the product.

Applicants should describe for each GM product the details and rationale for the proposed physical and biological confinement strategy, where applicable. The proposal should specify the methodology used and its effectiveness in reducing accidental intake or preventing gene flow into the environment. Methods of enforcing monitoring and emergency measures for restricting gene flow should also be described. Regarding non-food or non-feed GM plants that produce bio-active substances that are stable, or that persist for a long term in the environment, it should be considered whether the confinement should also prevent or reduce herbivory and leakage through drainage or sewage.

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GLOSSARY / ABBREVIATIONS

CFIA	Canadian Food Inspection Agency
CHMP	Committee for human medicinal products
CTD	Common Technical Document
CVMP	Committee for veterinary medicinal products
DEFRA	Department for Environment, Food and Rural Affairs (United Kingdom)
EC	European Commission
EEC	European Economic Community
EFSA	European Food Safety Authority
e.g.	*exempli gratia*, meaning “for example”
EMEA	European Medicines Agency
etc.	*et cetera*, meaning "and other things"
EU	European Union
FDA	Food and Drug Administration (United States)
GM	Genetically Modified
GMO	Genetically Modified Organism
i.e.	*Id est*, meaning “that is”
MAA	Marketing Authorisation Application
NGO	Non-Governmental Organisation
No	Number
OECD	Organisation for Economic Co-operation and Development
PMEM	Post-Market Environmental Monitoring
PMI	Plant-Made Industrial compound
PMP	Plant-made Medicinal Product
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SC	Scientific Committee (of the EC)
SPP	Standard Production Protocols
US	United States of America
WHO	World Health Organization