



European Food Safety Authority

**DRAFT GUIDANCE DOCUMENT FOR THE RISK ASSESSMENT OF
GENETICALLY MODIFIED PLANTS AND DERIVED FOOD AND FEED**

April 2004

Prepared by the Scientific Panel on Genetically Modified Organisms of the European
Food Safety Authority

The European Food Safety Authority (EFSA) invites comments from interested parties.
Comments are to be submitted through the website of EFSA at the following URL:
<http://www.efsa.eu.int/cf/consultation.cfm>. The consultation period will be closed on
30 April 2004.

1 **DRAFT GUIDANCE DOCUMENT FOR THE RISK ASSESSMENT OF**
 2 **GENETICALLY MODIFIED PLANTS AND DERIVED FOOD AND FEED**

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4 **FOREWORD..... 3**

5 **TERMS OF REFERENCE..... 4**

6 **I. INTRODUCTION 4**

7 1. SCOPE OF THE DOCUMENT..... 4

8 2. LEGAL BACKGROUND FOR THE RISK ASSESSMENT OF GMOs, GM FOOD AND GM FEED AT COMMUNITY

9 LEVEL 5

10 **II. THE RISK ASSESSMENT STRATEGY 9**

11 1. DEFINING RISK ASSESSMENT..... 9

12 2. COMPARATIVE APPROACH..... 9

13 *Concept of familiarity..... 9*

14 *Concept of substantial equivalence..... 10*

15 3. ISSUES TO BE CONSIDERED.....10

16 4. GENERAL RECOMMENDATIONS11

17 5. FORTHCOMING DEVELOPMENTS 12

18 **III. INFORMATION REQUIRED IN APPLICATIONS CONCERNING RELEASES OF GENETICALLY**

19 **MODIFIED PLANTS (GYMNOSPERMAE AND ANGIOSPERMAE)..... 13**

20 A. GENERAL INFORMATION..... 13

21 B. INFORMATION RELATING TO (A) THE RECIPIENT OR (B) (WHERE APPROPRIATE) PARENTAL

22 PLANTS 13

23 C. INFORMATION RELATING TO THE GENETIC MODIFICATION 14

24 1. *Description of the methods used for the genetic modification..... 14*

25 2. *Nature and source of vector used..... 14*

26 3. *Size, source (name) of donor organism(s) and intended function of each constituent*

27 *fragment of the region intended for insertion..... 15*

28 D. INFORMATION RELATING TO THE GM PLANT 15

29 1. *Description of the trait(s) and characteristics which have been introduced or modified..*

30 15

31 2. *Information on the sequences actually inserted or deleted..... 15*

32 3. *Information on the expression of the insert..... 16*

33 4. *Information on how the GM plant differs from the recipient plant in: reproduction,*

34 *dissemination, survivability..... 17*

35 5. *Genetic stability of the insert and phenotypic stability of the GM plant..... 17*

36 6. *Any change to the ability of the GM plant to transfer genetic material to other*

37 *organisms 17*

38 7. *Information on any toxic, allergenic or other harmful effects on human or animal*

39 *health arising from the GM food/feed..... 18*

40 7.1 **Comparative assessment..... 18**

41 7.2 **Field trials..... 19**

42 7.3 **Selection of compounds for analysis..... 19**

43 7.4 **Agonomic traits..... 20**

44 7.5 **Product Specification 20**

45 7.6 **Effect of the production and processing 21**

46 7.7 **Anticipated intake/extent of use..... 21**

47 7.8 **Toxicology..... 21**

48 7.9 **Allergenicity 25**

49 7.10 **Nutritional assessment of GM food/feed 28**

50 7.11 **Post-market monitoring of GM food/feed 29**

51 8. *Mechanism of interaction between the GM plant and target organisms (if applicable)....*

52 30

53 9. *Potential changes in the interactions of the GM plant with the biotic environment*

54 *resulting from the genetic modification..... 30*

55 9.1 **Persistence and invasiveness 31**

1	9.2	Selective advantage or disadvantage.....	31
2	9.3	Potential for gene transfer	32
3	9.4	Interactions between the GM plant and target organisms	32
4	9.5	Interactions of the GM plant with non-target organisms.....	33
5	9.6	Effects on human health.....	33
6	9.7	Effects on animal health.....	33
7	9.8	Effects on biogeochemical processes	33
8	9.9	Impacts of the specific cultivation, management and harvesting techniques	34
9	10.	Potential interactions with the abiotic environment.....	35
10	11.	Environmental Monitoring Plan	35
11	11.1	General	35
12	11.2	Case-specific GM plant monitoring	36
13	11.3	General Surveillance of the impact of the GM plant.....	36
14	11.4	Parameters to be used in a monitoring plan.....	37
15	11.5	Implementing General Surveillance	37
16	11.6	Reporting the results of monitoring.....	38
17	IV.	REFERENCES	40
18	ANNEX I.....		45
19		EFSA GUIDANCE TO APPLICANTS ON THE PRESENTATION OF APPLICATIONS FOR THE REQUEST OF AUTHORISATION	
20		OF A GENETICALLY MODIFIED ORGANISM AND/OR DERIVED PRODUCTS.....	45
21	ANNEX II.....		49
22		SCOPE OF THE APPLICATION	49
23	ANNEX III		50
24		FORMAT OF TECHNICAL DOSSIERS	50
25	ANNEX IV		54
26		FORMAT OF THE SUMMARY OF APPLICATIONS FOR GENETICALLY MODIFIED PLANTS AND/OR DERIVED FOOD AND	
27		FEED	54
28			

1 FOREWORD

2

3 Genetic modification, genetic engineering or recombinant-DNA technology, first applied
4 in the 1970's, is one of the newest methods to introduce novel traits to micro-
5 organisms, plants and animals. Unlike other genetic improvement methods, the
6 application of this technology is strictly regulated. Before any genetically modified
7 organism (GMO) or product can be released into the EU market, it has to pass an
8 approval system in which the safety for humans, animals and the environment is
9 thoroughly assessed. The Regulation (EC) 1829/2003 on genetically modified food and
10 feed, which applies from April 18, 2004, provides that the European Food Safety
11 Authority (EFSA) shall publish detailed guidance to assist the applicant in the
12 preparation and presentation of the application for the authorisation of genetically
13 modified (GM) food and/or feed. The assessment of the genetic modification itself
14 complements, but does not replace, other requirements, as set in specific legislation
15 (e.g. seed or other plant-propagating materials), that a product has to fulfill in order to
16 be approved for the European market.

17 The present draft document provides detailed guidance for genetically modified plants
18 (GM plants) and food and/or feed containing, consisting of or produced from these
19 plants.

20 This document was compiled by the Scientific Panel on Genetically Modified Organisms
21 (GMO Panel) of EFSA, consisting of the following members:

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

27 The following *ad hoc* experts also contributed:

28 Gerhard Flachowsky (Panel on Additives and Products or Substances used in Animal
29 Feed), Tony Hardy (Panel on Plant Health, Plant Protection Products and their Residues),
30 Andreu Palou (Panel on Dietetic Products, Nutrition and Allergies) and Richard Phipps
31 (University of Reading, UK).

32 The draft document is published on the EFSA website for a 3-week period of public
33 consultation. On May 25, 2004, a stakeholder consultation will be held. The GMO Panel
34 will consider all comments relating to the risk assessment of GMOs before preparing a
35 revised guidance document. The GMO Panel will not consider issues related to risk
36 management of GMOs (traceability, labelling, coexistence). Political and socio-economic
37 issues are also outside the remit of the Panel. EFSA will regularly review this guidance in
38 the light of experience gained, technological progress and scientific developments. By
39 establishing a harmonised framework for risk assessment, this document should
40 provide useful guidance both for the applicants and for risk assessors. A thoroughly
41 prepared application and properly conducted risk assessment should facilitate the
42 scientific evaluation of the product.

43

44

1 TERMS OF REFERENCE

2 In accordance with Articles 5(8) and 17(8) of the Regulation (EC) N° 1829/2003 on
3 genetically modified food and feed, the European Commission has requested the
4 European Food Safety Authority (EFSA), in a letter dated 27 October 2003 (ref.
5 SANCO/D4/KM/cw/D/440551), to publish detailed guidance – before the date of
6 application of the Regulation on genetically modified (GM) food and feed which is 18
7 April 2004 – to assist the applicant in the preparation and the presentation of the
8 application for authorisation of GM food and/or feed.

9

10 I. INTRODUCTION

11 1. SCOPE OF THE DOCUMENT

12 This document provides guidance for the risk assessment of genetically modified (GM)
13 plants¹ and/or derived food and feed submitted within the framework of Regulation (EC)
14 No. 1829/2003 (EC, 2003a) on GM food and feed or Directive 2001/18/EC (EC, 2001a)
15 on the deliberate release into the environment of genetically modified organisms²
16 (GMOs). The guidance also applies to feed intended for animals which are not destined
17 for food production. When a product is likely to be used both for food and feed
18 purposes, the application should fulfil the authorisation criteria for both food and feed.
19 The applicant has the choice of applying for the environmental risk assessment to be
20 carried out at the same time as the safety assessment under the Regulation (EC)
21 1829/2003. The guidance document takes this into account and provides a framework
22 for the full risk assessment of the genetic modification.

23 More specifically, this document provides detailed guidance to assist the applicant³ in
24 the preparation and the presentation of the application, according to Articles 5(8) and
25 17(8) of Regulation (EC) No. 1829/2003. This guidance document addresses the
26 requirements of the Regulation (EC) No. 1829/2003 and is structured to meet the
27 requirements of Annex IIIB of Directive 2001/18/EC and Annex II of the same Directive.
28 Specific guidance on the presentation of the application can be found in the annexes to
29 this document. This guidance does not consider issues related to risk management
30 (traceability, labelling, coexistence).

31 This guidance document is an updated replacement of the ‘Guidance document for the
32 risk assessment of genetically modified plants and derived food and feed’ of 6-7 March
33 2003, prepared for the EU Scientific Steering Committee by the Joint Working Group on
34 Novel Foods and GMOs (EC, 2003d).

¹ In the context of this document “genetically modified plants” are defined as genetically modified higher plants, (Gymnospermae and Angiospermae) in line with Directive 2001/18/EC.

² Genetically modified organism means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination (Directive 2001/18/EC). Techniques of genetic modification include 1) recombinant DNA techniques involving the incorporation of the DNA molecules into a host in which they are capable of continued multiplication; 2) direct introduction of DNA by e.g. micro-injection; 3) cell/protoplast fusion or hybridisation by methods that do not occur naturally. Techniques not considered to result in genetic modification are *in vitro* fertilisation, natural transformation and polyploidy induction (for more details see Directive 2001/18/EC, Annex I A).

³ The term applicant is used hereafter as a generic reference to the official body submitting the application.

1 Food additives (Directive 89/107/EEC; EC, 1989), flavourings (Directive 88/388/EEC;
2 EC, 1988) and feed additives (Regulation (EC) No 1831/2003; EC, 2003c) containing, or
3 consisting of or produced from GM plants do not fall within the scope of this guidance
4 document.

5 This guidance does not cover the contained use (Directive 90/219/EEC; EC, 1990a) or
6 the deliberate release into the environment (Directive 2001/18/EC) of genetically
7 modified micro-organisms (GMMs), or the placing on the market of food and/or feed
8 consisting of, containing or produced from GMMs (Regulation (EC) No 1829/2003). For
9 food and feed containing or consisting of GMMs, a parallel guidance document is under
10 preparation by the GMO Panel. Similarly, guidance will be prepared for the safety
11 assessment of the genetic modification where substances, such as food additives
12 (Directive 89/107/EEC), flavourings (Directive 88/388/EEC) and feed additives
13 (Regulation (EC) No 1831/2003) contain, or consist of or are produced from GMOs that
14 fall within the scope of Regulation (EC) 1829/2003.

15 This guidance does not cover the deliberate release into the environment (Directive
16 2001/18/EC) of genetically modified animals, or the placing on the market of food
17 and/or feed consisting of, containing or produced from genetically modified animals
18 (Regulation (EC) No 1829/2003). Appropriate guidance will be prepared by the GMO
19 Panel in the future.

20 Additional guidance also needs to be developed for the environmental risk assessment
21 of GM plants used to produce medicinal products ('plant-made pharmaceuticals') for
22 human and veterinary use (Regulation (EEC) No 2309/93; EC, 1993) as well as other
23 non-food purposes (e.g. 'plant-made industrial compounds' and GM plants for phyto-
24 remediation) through biotechnology.

25 **2. LEGAL BACKGROUND FOR THE RISK ASSESSMENT OF GMOs, GM FOOD** 26 **AND GM FEED AT COMMUNITY LEVEL**

27 **Community food law (Regulation (EC) 178/2002)**

28 The Regulation (EC) 178/2002 (EC, 2002c) lays down the general principles of food law
29 and procedures in food safety. It defines food broadly, including animal feed and other
30 agricultural inputs at the level of primary production. The Community food law
31 establishes the European Food Safety Authority (EFSA) as an independent scientific
32 source of advice, information and risk communication, nevertheless stating that the link
33 between risk assessors and risk managers should be strengthened. The EFSA includes
34 Scientific Panels, for example the GMO Panel. The EFSA should provide a
35 comprehensive independent scientific view of the safety and other aspects of the whole
36 food and feed supply chains. The Community food law defines 'food' as any substance
37 or product, whether processed, partially processed or unprocessed, intended to be, or
38 reasonably expected to be ingested by humans. 'Food' includes drink and any substance
39 intentionally incorporated into the food during its manufacture, preparation or
40 treatment. 'Feed' means any substance or product, including additives, whether
41 processed, partially processed or unprocessed, intended to be used for oral feeding to
42 animals. The Community food law also defines 'risk', 'risk analysis', 'risk assessment',
43 'risk management' 'risk communication' and 'hazard'. Articles 14 and 15 of the
44 Community food law set the food and feed safety requirements, respectively.

45 **GM food and feed regulation (Regulation (EC) 1829/2003)**

1 Regulation (EC) 1829/2003 on genetically modified food and feed provides for the risk
2 assessment of GMOs and derived food and feed to be carried out by EFSA established
3 under the Regulation (EC) 178/2002 laying down the general principles and
4 requirements of food law and the procedures in matters of food safety (EC, 2002c).

5 Food products containing, consisting of or produced from GMOs were previously
6 regulated by Regulation (EC) 258/97 on Novel Foods and Novel Food Ingredients, which
7 has been amended by Regulation (EC) 1829/2003 from 18 April 2004. For feed
8 containing or consisting of GMOs, no specific Community legislation has been in place
9 prior to the entering into force of Regulation (EC) 1829/2003 and the safety of GM feed
10 has been assessed under Directive 2001/18/EC.

11 The scope of Regulation (EC) 1829/2003 is GMOs for food/feed use; food/feed
12 containing or consisting of GMOs; food/feed produced from GMOs; and food containing
13 ingredients produced from GMOs, (referred to as GM food/feed). The Regulation states
14 that GM food/feed must not (a) have adverse effects on human health, animal health or
15 the environment; (b) mislead the consumer/user; (c) differ from the food/feed which it
16 is intended to replace to such an extent that its normal consumption would be
17 nutritionally disadvantageous for the consumer/animals. In addition, GM feed must not
18 harm or mislead the consumer by impairing the distinctive features of the animal
19 products. Products will be authorised only when the applicant has adequately
20 demonstrated that they satisfy the requirements.

21 An application should contain the particulars as specified by Article 5 and Article 17 of
22 the Regulation. The Commission shall establish implementing rules for the application
23 of these Articles, including rules concerning the preparation and the presentation of the
24 application.

25 Under Regulation (EC) 1829/2003, an application for authorisation is sent to EFSA
26 through a national competent authority. From the receipt of a valid application, EFSA
27 will have a time limit of six months to carry out the safety assessment and to provide an
28 opinion. Such time limit will be extended whenever EFSA seeks supplementary
29 information from the applicant.

30 The other Member States and the Commission will be informed and EFSA will make the
31 application available to them.

32 EFSA is responsible for the scientific risk assessment that takes into account any risk to
33 human and animal health and, as the case may be, to the environment. However, if
34 EFSA is not in a position to realise all the workload, EFSA may ask the appropriate food
35 assessment body of a Member State to carry out an initial part of the safety assessment
36 of the food or feed in accordance with Article 36 of Regulation (EC) No 178/2002.

37 On the basis of the opinion of EFSA, the Commission will draft a proposal for granting or
38 refusing authorisation, which will be approved through qualified majority of the Member
39 States within a Regulatory Committee. Regulation (EC) 1829/2003 provides for a time
40 limit of a maximum of 10 years for the Community authorisation on GMOs for food
41 and/or feed use, food and/or feed containing or consisting of GMOs, as well as food
42 and/or feed produced from or by GMOs. The authorised product will have to comply with
43 the provisions of Regulation (EC) 1830/2003 concerning the traceability and labelling of
44 GMOs and the traceability of food and feed products produced from GMOs and
45 amending Directive 2001/18/EC (EC, 2003b). The authorised product shall be entered
46 in a Community register of genetically modified food and feed, which will be made
47 available to the public. Where appropriate and based on the conclusions of the risk
48 assessment, post-market monitoring requirements for the use of the genetically

1 modified foods for human consumption or for the use of genetically modified feeds for
2 animal consumption may be imposed.

3 **Deliberate release of GMOs (Directive 2001/18/EC)**

4 The principles regulating the deliberate release into the environment of GMOs are laid
5 down in Council Directive 2001/18/EC (EC, 2001a), which repeals Directive
6 90/220/EEC (EC, 1990b). This Directive puts in place a step-by-step approval process
7 made on a case-by-case assessment of the risk to human health and the environment
8 before any GMOs or products containing GMOs could be released into the environment,
9 or placed on the market. The Directive introduces a time limit for the authorisation,
10 which cannot be given for more than 10 years. Authorisations can be renewed on the
11 basis of an assessment of the results of the monitoring and of any new information
12 regarding the risks to human health and/or the environment. The Directive also
13 introduces the obligation to propose a monitoring plan in order to trace and identify any
14 direct or indirect, immediate, delayed or unforeseen effects on human health or the
15 environment of GMOs as or in products after they have been placed on the market.

16 Several supporting documents have been prepared to assist the applicant. Commission
17 Decision 2002/623/EC (EC, 2002a) establishes guidance notes on the objective,
18 elements, general principles and methodology of the environmental risk assessment
19 referred to in Annex II to Directive 2001/18/EC. Council Decision 2002/811/EC (EC,
20 2002b) establishes guidance notes supplementing Annex VII to the Directive. Council
21 Decision 2002/812/EC (EC, 2002e) establishes the summary information format. The
22 EU Scientific Steering Committee published on March 2003 the 'Guidance document for
23 the risk assessment of genetically modified plants and derived food and feed' prepared
24 by the Joint Working Group on Novel Foods and GMOs (EC, 2003d). The present
25 guidance document is an updated replacement of that guidance.

26 Under Directive 2001/18/EC, an applicant who intends to market a GMO must submit
27 an application to the competent authority of the Member State where the product is to
28 be placed on the market. The application must include a risk assessment. The principles
29 for the environmental risk assessment are laid down in Annex II of the Directive, and
30 also address aspects of human and animal health. Annex IIIB of the Directive has
31 details of the required information on which to base the risk assessment for higher
32 plants. If the national competent authority gives a favourable opinion on the GMO, this
33 Member State must inform the European Commission and other Member States. If no
34 objections are raised either by the Commission or by any other Member State, the
35 assessor Member State grants an authorisation and the product may then be marketed
36 throughout the Community. If, however, any objections are raised, a decision has to be
37 taken at Community level. If an objection relates to risks of the GMO to human health or
38 to the environment, the Commission must then consult the relevant Scientific
39 Committee (Art. 28 of Directive 2001/18/EC (EC, 2001a)), now represented by the
40 Scientific Panels of EFSA (Art. 22(5) and Art. 28 of Regulation (EC)178/2002 (EC,
41 2002c)).

42 **Interplay between Regulation (EC) 1829/2003 and Directive 2001/18/EC**

43 Under Regulation (EC) 1829/2003 and where the application concerns products
44 containing or consisting of a GMO, the applicant will have the choice of either supplying
45 an authorisation for the deliberate release into the environment already obtained under
46 part C of Directive 2001/18/EC, without prejudice to the conditions set by that
47 authorisation, or to submit the environmental risk assessment for review at the same
48 time as the safety assessment under Regulation (EC) 1829/2003. In the latter case, it
49 is necessary for the environmental risk evaluation to comply with the requirements

1 referred to in Directive 2001/18/EC and for the national competent authorities
2 designated in accordance with article 4 of Directive 2001/18/EC to be consulted by
3 EFSA. EFSA may also ask such competent authority to carry out an initial environmental
4 risk assessment. In the case of GMOs to be used as seeds or other plant-propagating
5 materials falling within the scope of Regulation (EC) 1829/2003, EFSA has the
6 obligation to delegate the environmental risk assessment to a national competent
7 authority. EFSA will conclude on the final assessment.

8 **GM seeds**

9 Regarding genetically modified seeds, Directive 98/95/EC (EC, 1998b) specifies that
10 those national authorities that have agreed to the use of a GM variety on their territory
11 must notify this acceptance to the European Commission. The Commission must
12 examine the information supplied by the Member State concerned and its compliance
13 with the provision of the Community seed legislation. If such is the case, the variety
14 concerned is included in the "Common Catalogue of varieties of Agricultural Plant
15 Species". The seed legislation requires that GM varieties must be authorised in
16 accordance with Directive 2001/18/EC. Risk assessment for a given GM plant
17 performed under Directive 2001/18/EC applies also to varieties derived by conventional
18 breeding methods from the line concerned. If the variety is intended for food or feed
19 crop production, it also must be authorised in accordance with Regulation (EC)
20 1829/2003 prior to inclusion in the Common Catalogue.

21 **Additives and flavourings for use in foodstuffs**

22 The authorisation of food additives is regulated by Directive 89/107/EC on the
23 approximation of laws of the Member States concerning food additives authorised for
24 use in foodstuffs intended for human consumption (EC, 1989). Flavourings are
25 regulated by Directive 88/388/EEC on the approximation of the laws of the Member
26 States relating to flavourings for use in foodstuffs and to source materials for their
27 production (EC, 1988). In addition to these authorisation procedures, food additives and
28 flavourings containing, consisting of or produced from GMOs also fall within the scope of
29 Regulation (EC) 1829/2003 for the safety assessment of the genetic modification.
30 Additives and flavourings for use in foodstuffs are however not covered by the scope of
31 this document.

32 **Products and additives used in animal nutrition**

33 Directive 82/471/EEC concerning certain products used in animal nutrition (EC, 1982)
34 provides for an approval procedure for feed materials produced using different
35 technologies that may pose risk to human or animal health and the environment.
36 However, feed materials containing, consisting of or produced from GMOs fall within the
37 scope of Regulation (EC) 1829/2003.

38 The placing on the market of feed additives is authorised by Directive 70/524/EEC
39 concerning additives in feedingstuffs (EC, 1970). From 18 October 2004, the provisions
40 of this Directive will be repealed by Regulation (EC) 1831/2003 on additives for use in
41 animal nutrition (EC, 2003c). In addition to this authorisation procedure, feed additives
42 containing, consisting of or produced from GMOs also have to undergo an authorisation
43 procedure provided for by Regulation (EC) 1829/2003 before they can be placed on the
44 market. However, feed additives are not covered by the scope of this document.

1 II. THE RISK ASSESSMENT STRATEGY

2 1. DEFINING RISK ASSESSMENT

3 Risk assessment can be defined as “a process of evaluation including the identification
4 of the attendant uncertainties, of the likelihood and severity of an adverse
5 effect(s)/event(s) occurring to man or the environment following exposure under defined
6 conditions to a risk source(s)” (EC, 2000a). A risk assessment comprises hazard
7 identification, hazard characterisation, exposure assessment and risk characterisation.
8 A hazard is the potential of an identified source to cause an adverse effect.

9 The sequential steps in risk assessment of GMOs identify characteristics which may
10 cause adverse effects, evaluate their potential consequence, assess the likelihood of
11 occurrence and estimate the risk posed by each identified characteristic of the GMOs
12 (EC, 2002a).

13 2. COMPARATIVE APPROACH

14 The risk assessment strategy for GMOs seeks to deploy appropriate methodologies and
15 approaches to compare the GMO and derived products with their non-GM counterparts.
16 The underlying assumption of this comparative assessment approach for GMOs is that
17 traditionally-cultivated crops have gained a history of safe use for the normal consumer
18 or animals as food or feed products. These crops can serve as a baseline for the
19 environmental and food/feed safety assessment of GMOs. To this end the concepts of
20 *familiarity* and *substantial equivalence* were developed by the OECD (OECD, 1993a;
21 OECD, 1993b) and further elaborated by WHO/FAO (WHO/FAO, 2000) for the
22 assessment of the environmental and food safety of GMOs, respectively. This
23 comparison is the *starting point* of the safety assessment which then focuses on the
24 environmental or food/feed safety and nutritional impact of any intended or unintended
25 differences identified.

26 It is obvious that the insertion of genes and other pieces of DNA from a donor organism
27 into the host will result in a plant that is not identical to the parent and therefore the risk
28 assessment in addition to focusing on intended modifications, concentrates on the
29 outcomes of the transformation process using appropriate comparators. Thus the safety
30 assessment of GMOs consists of two steps, i.e. a comparative analysis to identify
31 differences, followed by an assessment of the environmental and food/feed safety or
32 nutritional impact of the identified differences, including the intended differences.

33 **Concept of familiarity**

34 The concept of familiarity is based on the fact that most GMOs are developed from
35 organisms such as crop plants, the biology of which is well researched. In a risk/safety
36 assessment it is appropriate to draw on this previous knowledge and experience and to
37 use the non-GM crop as the comparator to the GM crop in order to highlight differences
38 associated with the transformation and the subsequent management of the GM crop.
39 Familiarity will also derive from the knowledge and experience available from
40 conducting a risk/safety analysis prior to scale-up of any new plant line or crop cultivar
41 in a particular environment (OECD, 1993a), and from previous applications for similar

1 constructs and traits in similar or different crops. The risk assessment should clearly
2 identify any differences between the GM and non-GM crop, including its management
3 and usage, and focus on the significance and implications of these differences.

4 **Concept of substantial equivalence**

5 The concept of substantial equivalence is based on the idea that an existing organism
6 used as food/feed with a history of safe use, can serve as a comparator when assessing
7 the safety of the genetically modified food/feed (OECD, 1993b; EC, 1997b). Application
8 of this concept, also denoted as comparative safety assessment (Kok and Kuiper,
9 2003), serves the purpose of identifying similarities and potential differences between
10 the GM crop-derived food/feed and the non-GM counterparts, which should
11 subsequently be assessed regarding their toxicological and nutritional impact on
12 humans and animals. The first step of the approach is the comparative analysis of the
13 molecular, agronomic and morphological characteristics of the organisms and derived
14 products in question, as well as their chemical composition. Such comparisons should
15 be made between GM and non-GM counterparts grown under the same regimes and
16 environmental conditions. The outcome of this comparative analysis will further
17 structure the second part of the safety assessment procedure, which may include
18 further specific toxicological and nutritional testing. This approach should provide
19 evidence whether or not the GM crop derived food/feed is as safe as the traditional
20 counterpart. Where no appropriate comparator can be identified, a comparative safety
21 assessment cannot be made and a comprehensive safety and nutritional assessment of
22 the GM crop derived food/feed *per se* should be carried out. For instance, this would be
23 the case where a trait or traits are introduced with the intention of modifying the
24 composition of the plant significantly.

25 **3. ISSUES TO BE CONSIDERED**

26 The risk assessment of GM plants and products should take account of the following:

- 27 – the characteristics of the donor and recipient organisms;
- 28 – the genes inserted;
- 29 – the expression of inserted genes;
- 30 – the potential consequences of the genetic modification;
- 31 – the potential environmental impact following a deliberate release;
- 32 – the potential toxicity and allergenicity of gene products, metabolites and the whole
33 GM plant;
- 34 – the compositional, nutritional, safety and agronomic characteristics;
- 35 – the influence of processing on the properties of the food or feed;
- 36 – the potential for changes in dietary intake;
- 37 – the potential for long-term nutritional impact.

1

2 Different outcomes of a genetic transformation event can be envisaged:

3

4 **Intended effects** are those that are targeted to occur from the introduction of the
5 gene(s) in question and which fulfil the original objectives of the genetic transformation
6 process. Alterations in the phenotype may be identified through a comparative analysis
7 of growth performance, yield, disease resistance etc. Intended alterations in the
8 composition of a GM organism compared to the parent, may be identified by
9 measurements of *single* compounds e.g. newly expressed proteins, macro and micro-
10 nutrients (*targeted* approach). Analytical detection methods used must meet specific
11 quality and validation criteria.

12

13 **Unintended effects** are considered to be consistent differences between the GM plant
14 and its appropriate control lines, which go beyond the primary expected effect(s) of
15 introducing the target gene(s). Unintended effect(s) could potentially be linked to
16 genetic rearrangements or metabolic perturbations. They may be evident in the
17 phenotype or composition of the GM plant when grown under the same conditions as
18 the controls. Unintended effects may be predicted or explained in terms of our current
19 knowledge of plant biology and metabolic pathway integration and interconnectivities. A
20 starting point in the identification of potential unintended effects is analysis of the
21 transgene flanking regions to establish whether the insertion has occurred within, or in
22 the proximity of, an endogenous gene. Furthermore a comparative and targeted
23 analysis should be carried out of single compounds in the GM organism and its
24 conventional counterpart and which represent components of important metabolic
25 pathways in the organism. The components will include macronutrients, micronutrients
26 and secondary metabolites as well as known anti-nutrients and toxins. Statistically
27 significant differences between parental and GM lines, which are not due to the
28 intended modification, may indicate the occurrence of unintended effects, and should
29 be assessed specifically with respect to their safety and nutritional impact.

30

31 **4. GENERAL RECOMMENDATIONS**

32 Risk assessment may be simplified if genes extraneous to the successful deployment of
33 the target transformation event are not present in the GM plant. Whenever possible,
34 applicants are encouraged to develop, for commercial release, those transgenic lines in
35 which only DNA essential to the modification of the trait in question is transferred to the
36 plant (ACRE, 2000).

37 The choice of a particular marker gene should be given careful consideration in view of
38 the amount of information required for risk assessment. At an early stage in the
39 development of GM plants some strategies are available which can be considered best
40 practice to reduce the potential identified risks and to avoid some unidentified risks in
41 the environment (ACRE, 2001a). The overall aim is to reduce environmental exposure
42 and the potential risks from the transgenes and their products. Three principle
43 approaches can be considered to achieve this:

44

- 1 – avoid or minimise the inclusion of superfluous transgenes or sequences;
- 2 – avoid or minimise superfluous expression of the transgene;
- 3 – avoid or minimise the dispersal of transgenes in the environment.

4

5 **5. FORTHCOMING DEVELOPMENTS**

6 To increase the chances of detecting unintended effects due to the genetic modification
7 of organisms, profiling technologies such as transcriptomics, proteomics and
8 metabolomics, extend the breadth of comparative analyses (EC, 2000b; Kuiper et al.,
9 2003; Cellini et al., 2004; ILSI USA monograph, 2004). The utility and applicability of
10 these technologies in the detection of altered gene and protein expression and
11 metabolite composition in GM plants has been under scrutiny in specific research
12 projects funded, for example, by EU FP5 (GMOCARE project⁴) and the UK Food
13 Standards Agency (GO2 research programme⁵). The applicability of metabolomic
14 techniques, such as gas chromatography coupled to mass spectrometry (GC-MS), and
15 off-line liquid chromatography (HPLC) coupled to nuclear magnetic resonance (NMR), for
16 the simultaneous analysis of a broad variety of metabolites in GM plants and their
17 conventional counterparts has been demonstrated. These non-targeted approaches may
18 be of particular relevance for GM food crops with specific metabolic pathways modified
19 e.g. those leading to enhanced nutritional profiles, obtained through the insertion of
20 single or multiple genes.

21 Further exploration of profiling approaches is needed with respect to the evaluation of
22 specificity and sensitivity. Profiling methods are not aimed at replacing conventional
23 analyses but may be useful to confirm and complete other data. The development of
24 appropriate profiling databases is strongly recommended.

25

26

27

28

⁴ <http://www.entransfood.com/RTDprojects/GMOCARE>

⁵ <http://www.foodstandards.gov.uk/science/research/NovelFoodsResearch/g02programme>

1 **III. INFORMATION REQUIRED IN APPLICATIONS CONCERNING**
2 **RELEASES OF GENETICALLY MODIFIED PLANTS**
3 **(GYMNOSPERMAE AND ANGIOSPERMAE)**

4

5 **A GENERAL INFORMATION**

6

- 7 1. Name and address of the applicant (company or institute)
- 8 2. Name, qualification and experience of the responsible scientist(s)
- 9 3. Title of the project
- 10 4. Scope of the application as defined in Annex II
- 11 5. Designation and specification of the GM plant and/or derived product
- 12 6. Where applicable, a detailed description of the method of production and
13 manufacturing

14

15 **B. INFORMATION RELATING TO (A) THE RECIPIENT OR (B) (WHERE**
16 **APPROPRIATE) PARENTAL PLANTS**

17

18 Applicants should provide information both on the organisms used as the DNA donor(s)
19 for genetic modification and the recipient organism. This information should include the
20 most recent taxonomic classification including the family, genus, species, subspecies,
21 cultivar/breeding line or strain. Taxonomic information could be used to identify the
22 need for specific analyses e.g. the known occurrence in the family of specific toxins
23 which are typically expressed at low levels in the unmodified recipient species, but
24 which may be unintentionally increased following the genetic modification process.
25 Information should be provided on all issues of potential concern, such as the presence
26 of natural toxins, allergens or virulence factors. Data should be provided on the previous
27 use of the donor and the recipient organism.

28 Information is required under the following headings:

29

- 30 1. Complete name; (a) family name, (b) genus, (c) species, (d) subspecies, (e)
31 cultivar/breeding line, (f) common name.
- 32 2. (a) Information concerning reproduction: (i) mode(s) of reproduction, (ii) specific
33 factors affecting reproduction, if any, (iii) generation time;
- 34 (b) Sexual compatibility with other cultivated or wild plant species.

- 1 3. Survivability; (a) ability to form structures for survival or dormancy, (b) specific
2 factors if any affecting survivability.
- 3 4. Dissemination; (a) ways and extent (for example and estimation of how viable
4 pollen and/or seeds declines with distance) of dissemination, (b) special factors
5 affecting dissemination, if any.
- 6 5. Geographical distribution and cultivation of the plant, including the distribution
7 in Europe of the compatible species.
- 8 6. In the case of a plant species not grown in the Member State(s), description of
9 the natural habitat of the plant, including information on natural predators,
10 parasites, competitors and symbionts.
- 11 7. Other potential interactions, relevant to the GM plant, of the plant with
12 organisms in the ecosystem where it is usually grown, or used elsewhere,
13 including information on toxic effects on humans, animals and other organisms.

14

15 **C. INFORMATION RELATING TO THE GENETIC MODIFICATION**

16

17 The requirements for molecular data are the same for applications under Directive
18 2001/18/EC for the placing on the market (Part C) and for the assessment of GM food
19 and GM feed.

20

21 **1. Description of the methods used for the genetic modification**

22 The transformation protocol should be described in detail and relevant references for
23 the transformation method should be provided. For *Agrobacterium*-mediated
24 transformation, the strain of *Agrobacterium* used during the transformation process
25 must be indicated, including information or references on how the Ti/Ri plasmid based
26 vector was disarmed. For transformation methods that involve the use of helper
27 plasmids, a detailed description of these plasmids should be given. If carrier DNA is
28 used in a transformation event, its source must be stated and a risk assessment
29 provided.

30

31 **2. Nature and source of vector used**

32 A physical and genetic map should detail the position of all coding and non-coding
33 sequences, origins of replication and transfer, and other plasmid elements together with
34 the applicant's selected restriction sites for the generation of probes, and the position
35 and nucleotide sequence of primers used in PCR analysis. A table identifying each
36 component, its size, its origin and its role should accompany the map.

1

2 **3. Size, source (name) of donor organism(s) and intended function of each**
3 **constituent fragment of the region intended for insertion**

4 The complete sequence of the DNA used in the transformation should be given. The
5 map/table should also indicate if there have been modifications that affect the amino
6 acid sequence of the product of the introduced gene. A risk assessment of these
7 changes needs to be provided.

8

9 **D. INFORMATION RELATING TO THE GM PLANT**

10

11 **1. Description of the trait(s) and characteristics which have been introduced**
12 **or modified**

13 A description of the trait and the changes that it makes to the plant phenotype is
14 required. Phenotypic modifications should be quantified in relation to the comparable
15 untransformed plant. The targets of the trait should be identified as well as the
16 sensitivity of non-targets. The purposes of the transformation and the uses of the GM
17 crop should be described together with changes in the crop composition, management,
18 cultivation, deployment, geographic range and end use.

19

20 **2. Information on the sequences actually inserted or deleted**

21 Applicants should provide information on:

22 (a) the copy number of all detectable inserts, both complete and partial

23 (b) in the case of deletion(s), size and function of the deleted region(s)

24 (c) chromosomal location(s) of insert(s) (nucleus, chloroplasts, mitochondria or
25 maintained in a non-integrated form) and methods for its determination. Inheritance
26 patterns following appropriate self- or cross- pollination should be used to confirm
27 that segregation is as predicted from the insert location. In the case of plastid
28 integration, the absence of insert DNA in the nuclear genome must be
29 demonstrated.

30 (d) the organisation of the inserted genetic material at the insertion site including
31 sequence data of the inserted material and of the flanking 5' and 3' regions.
32 Information on flanking sequences should be sufficient to allow identification of
33 potential chimeric ORFs⁶ generated at the junctions of the insert and the plant DNA.

⁶ open reading frames

1 Where DNA from mitochondria or chloroplasts flanks the insert, as can occur with
2 biolistic delivery methods, sequence data should extend to the nuclear genome of
3 the parent plant. PCR amplification of the flanking sequences both adjacent to and
4 across the insertion point in the parent plant could be used to demonstrate that this
5 has been achieved. Applicants should indicate where the sequence of the insert in
6 the plant does not match the sequence of the intended transformation event
7 (plasmid sequence) and provide a risk assessment on any changes observed. If a
8 chimeric ORF is identified from flanking sequence analysis then expression analysis
9 should be performed to determine if there is transcription. Homology analysis
10 should be conducted to establish the absence of any putative toxins or allergens
11 encoded by the identified chimeric ORF. However, potential effects arising from the
12 insertion cannot be characterised by molecular techniques alone but requires a
13 broader consideration including compositional and phenotypic analysis. This may be
14 particularly relevant where known ORFs or regulatory regions are disrupted by the
15 insertion event, but will require a case-by-case approach.

16 (e) all sequence information (in electronic format) including the location of primers
17 used for detection.

18 When events have been combined by the interbreeding of independent approved GM
19 lines or by re-transformation of an existing approved GM line, the need for further
20 molecular analysis will depend, on a case-by-case basis, on the nature of the genetic
21 modifications involved. However, copy number and sufficient data from Southern
22 hybridisations or PCR amplifications to demonstrate maintenance of insert structure is
23 a minimum requirement for molecular characterisation with such events. Stability of
24 copy number and insert size should be demonstrated where relevant. Further insert
25 sequencing may be required on a case by case basis.

26

27 **3. Information on the expression of the insert**

28 (a) Information on developmental expression of the insert during the life cycle of the
29 plant.

30 This type of information may be relevant to environmental safety aspects, whereas
31 analysis of the plant materials actually used for food/feed is considered more
32 relevant for human or animal safety assessment.
33

34 (b) Parts of the plant where the insert is expressed
35

36 Applicants should be aware that the information on the expression in the plant of
37 genetic elements from any part of the inserted DNA is required if a potential risk is
38 identified. Such requests may be made even where the gene is not under the control
39 of a plant promoter. Where tissue-specific promoters have been used, information
40 may be requested on expression of target genes in other plant parts relevant for risk
41 assessment. Evidence should be provided to indicate that expression of the inserted
42 gene(s) is as expected and stable in the tissues targeted.
43

44 (c) Expression of potential fusion proteins.
45

1
2 The potential creation of newly expressed fusion proteins should be investigated by
3 bioinformatic analysis and the demonstrated absence of any harmful fusion
4 proteins.

5 An investigation of newly expressed transcripts may be appropriate.

6
7 (d) Methods used for expression analysis

8
9 The methods used for the analysis of gene and protein expression must be provided.

10

11 **4. Information on how the GM plant differs from the recipient plant in:**
12 **reproduction, dissemination, survivability**

13 The applicant should identify whether the GM plant differs from the parental or near
14 isogenic non-GM plant in its biology. This should include information on biological
15 features that affect fitness and environmental sensitivity (e.g., multiplication, dormancy,
16 survivability, dispersal, outcrossing ability, stress tolerance, and sensitivity to specific
17 agents). The information provided should be linked to environmental risk assessment
18 including interaction with other organisms and the environment (sections 8, 9 and 10).

19

20 **5. Genetic stability of the insert and phenotypic stability of the GM plant**

21 Applicants should provide statistically analysed data, from a representative number of
22 generations (vegetative or generative propagation), to demonstrate the inheritance
23 pattern and stability of the trait(s) introduced (including the expression of corresponding
24 proteins under representative environmental conditions).

25

26 **6. Any change to the ability of the GM plant to transfer genetic material to**
27 **other organisms**

28 (a) Plant to bacteria gene transfer:

29 The transfer of genes from GM plants to bacteria is considered to be unlikely if no
30 homologous sequences are present (Nielsen et al., 1997). However, due to homologous
31 recombination, the risk of gene transfer and subsequent integration and expression
32 may be enhanced by the presence of bacterial sequences within the GM plant insert
33 DNA (Gebhard and Smalla, 1998) and thus this should be minimized. The inserted DNA
34 should be evaluated for possible enhancement of gene transfer potential (e.g. presence
35 of replication origins or genes/sequences that might enhance recombination). The
36 potential impact (consequences) of such an event should be evaluated in section 7 for
37 human and animal health and in section 9 for the environment.

1

2 (b) Plant to plant gene transfer:

3 The transfer of genes from GM plants to other sexually compatible plants is considered
4 to be a naturally occurring process under certain circumstances (Ellstrand et al., 1999),
5 However, the gene(s) inserted may modify the potential for plant to plant gene transfer
6 due to altered flower biology e.g. extended flowering period, attractiveness to
7 pollinators, change in fertility. Thus, a risk assessment should include an evaluation of
8 any new change in the biology of the GM plant that might increase or decrease the
9 potential for plant to plant gene transfer. The potential consequence arising from out-
10 crossing should be assessed in section 9.3.

11

12 **7. Information on any toxic, allergenic or other harmful effects on human or**
13 **animal health arising from the GM food/feed**

14 Genes inserted in a GM plant should be evaluated for their potential impact on human
15 and animal health. This evaluation should include the potential (albeit a rare
16 occurrence) for a plant to bacteria or plant to plant transfer event to take place. It
17 should also take into account any capacity for enhanced gene transfer reported in
18 section 6. Thus, on a case- by- case basis, specific experimental data on gene transfer
19 and its consequences may be required.

20

21 **7.1 Comparative assessment**

22

23 **Choice of the comparator**

24 In the case of vegetatively propagated crops, comparative analyses should include the
25 parental variety used to generate the transgenic lines. In the case of crops that
26 reproduce sexually, comparators would include appropriate non-GM lines of comparable
27 genetic background. Since many crops used to produce food and feed are developed
28 using back-crossing, it is important that in such cases, tests for morphological,
29 agronomical and chemical similarity use the most appropriate controls and do not
30 simply rely on comparisons with original parental material. For example, non-GM
31 parental lines may be used in the generation of the final product. In all cases, evaluation
32 of the extent of equivalence will be greatly enhanced by additional, valid comparisons,
33 with quality assessed data on the performance and composition of commercial varieties
34 of the crop species in question and which have a known history of safe use. Such data
35 could indicate that the GM lines fall within the variation reported for the species in
36 question.

37 Where events are combined by the interbreeding of GM lines, the appropriate
38 comparator will be the non-GM equivalent. Where this is not possible (e.g. in
39 vegetatively propagated crops) the GM parent lines are appropriate comparators.

40

1 **7.2 Field trials**

2
3 Protocols for field trials performed with genetically modified and control crops must be
4 specified and documented with respect to:

5
6 (a) *number of locations, growing seasons, geographical spreading and replicates;*

7 The basic set of data should be obtained from a comparison of the GM plant and an
8 appropriate control line grown in the same field under comparable conditions. This
9 comparison should normally cover more than one growing season and multiple
10 geographical locations representative of the various environments in which the GM
11 plants will be cultivated. The number of replicates at each location should reflect the
12 inherent variability of the plant.

13
14 (b) *statistical models for analysis, confidence intervals;*

15 Experimental design should be rigorous and analysis of data should be presented in a
16 clear format. Field trial data should be presented separately, and analysed statistically,
17 using appropriate statistical tools. A completely randomised design, for example, could
18 indicate whether the experimental factors (location, year, climatic conditions, plant
19 variety) interact with one another. The confidence intervals used for statistical analysis
20 should be specified (normally 95%, with possible adjustment according to the hazard of
21 the constituent to be compared).

22
23 (c) *the baseline used for consideration of natural variations.*

24 Quality assessed data demonstrating the natural range in component concentrations
25 found in non-GM counterparts should be provided to enable additional comparisons with
26 the GM plant in question. Data may be generated by the applicant and/or compiled
27 from the literature. The databases used for comparison should be specified. Special
28 attention must be paid to the comparability of the analytical methods used to create the
29 data. Ranges as well as mean values should be reported and considered.

30 Statistically significant differences in composition between the modified crop and its
31 traditional counterpart grown and harvested under the same conditions should trigger
32 further investigations as to the relationship between the identified difference and the
33 genetic modification process. Modifications that fall outside normal ranges of variation
34 will require further evaluation to determine any biological significance.

35

36 **7.3 Selection of compounds for analysis**

37
38 Analysis of the composition of the GM plant/food/feed is crucial when comparing the
39 product with its non-GM counterparts. Analysis should be carried out on the raw
40 agricultural commodity, such as grain, as this usually represents the main point of entry
41 of the material into the food/feed chain. Analysis of specific derived products should be
42 required only on a case-by-case basis and when justified scientifically.

43 In each case, key macro- and micro-nutrients, toxicants, anti-nutritional compounds, and
44 other constituents (including moisture and total ash) should be determined. Examples of

1 the key nutrients, anti-nutrients and toxicants characteristic for plant species and
2 information on the extent of natural variation are provided in OECD consensus
3 documents (a minimum list) which may provide further guidance for compositional
4 analysis to establish the extent of compositional equivalence (OECD a).

5 Key nutrients are those components that have a major impact on the diet, *i.e.* proteins,
6 carbohydrates, lipids/fats, fibre, vitamins and minerals. The vitamins and minerals
7 selected for analysis should be those which are present at levels which are nutritionally
8 significant and/or which make nutritionally significant contributions to the diet at the
9 levels at which the plant is consumed. The soil content of minerals might influence the
10 content in plants. The specific analyses required will depend on the plant species
11 examined, but should include a detailed assessment appropriate to the intention of the
12 genetic modification, the considered nutritional value and use of the plant. For example,
13 a fatty acid profile should be included for oil-rich plants (main individual saturated,
14 mono-unsaturated and poly-unsaturated fatty acids) and an amino acid profile
15 (individual protein amino acids and main non-protein amino acids) for plants used as an
16 important protein source. Measures of plant cell wall components are also required for
17 the vegetative parts of plants used for feed purposes.

18 Key toxicants are those compounds, inherently present, whose toxic potency and levels
19 may affect, adversely, human/animal health. The concentrations of such compounds
20 should be assessed according to plant species and the proposed use of the food/feed
21 product (Holm, 1998).

22 Similarly, anti-nutritional compounds, such as digestive enzyme inhibitors, and
23 important identified allergens should be studied. Compounds other than key nutrients,
24 key toxicants, and important anti-nutrients and allergens may be included in the
25 analyses on a case-by-case basis.

26 Knowledge of the introduced trait may trigger studies of specific compounds. For
27 example, if the introduction of a gene that confers herbicide tolerance is functionally
28 equivalent to an existing gene involved in aromatic amino acid synthesis, analysis of the
29 protein content and amino acid composition would be prudent.

30 If changes relative to the comparator and/or any commercial varieties included in field
31 trials are found, then any downstream metabolic and toxicological consequences should
32 be examined. Where appropriate, published ranges for parameters measured can be
33 taken into account.

34

35 **7.4 Agronomic traits**

36

37 Compositional analysis represents a key component of the risk assessment process.
38 However, unintended effects may also manifest themselves through, for example,
39 changes in susceptibility to important pests and diseases, through morphological and
40 developmental changes or through modified responses to agronomic and crop
41 management regimes.

42

43 **7.5 Product Specification**

44

1 Specification of the origin and the composition of the GM plant and GM food/feed is
2 needed to ensure the identity between the product tested/evaluated and the product to
3 be marketed. In the design of the specification, parameters most relevant for the
4 characterisation of the product from a safety and nutritional point of view should be
5 considered. Information on the availability of specified reference material should be
6 submitted.

7

8 **7.6 Effect of the production and processing**

9

10 For processed and/or preserved foods/feeds derived from GM sources the applicant
11 should assess whether or not the technologies applied are likely to modify the
12 characteristics of the GM product compared with its non GM counterpart. On a case -by-
13 case basis experimental data may be required. It is important to assess if, and to what
14 extent, the processing steps lead to the concentration or to the elimination,
15 denaturation and/or degradation of DNA and the newly expressed protein(s) in the final
16 product. Processing includes for example silage making, oilseed extraction, refining and
17 fermentation.

18

19 **7.7 Anticipated intake/extent of use**

20

21 An estimate of the expected intake is necessary for the safety evaluation of GM
22 food/feed and to evaluate nutritional significance. Information should be provided on
23 the intended function, the dietary role of the product, and the expected level of use.

24 Information on known or anticipated human exposure to other sources of analogous GM
25 food/feed and from other routes of exposure to new gene products and constituents,
26 including amount, frequency and other factors influencing exposure, should be provided.
27 On the basis of the available consumption data, the anticipated average and maximum
28 intake of the GM food/feed should be estimated. If possible, particular sections of the
29 population with an expected high exposure should be identified and this should be
30 considered within the risk assessment. Information should be provided on any expected
31 benefit and/or adverse reactions, as well as any scientific evidence on the efficacy of
32 the GM food/feed for the intended effect at the level proposed. Any assumptions made
33 in the exposure assessment should be described.

34 The concentrations of the new gene products and constituents produced, or modified by
35 the intended genetic modification (e.g. due to changes in metabolic pathways) in those
36 parts of the GM plant intended for food or feed use should be determined by appropriate
37 methods. Expected exposure to these constituents should be estimated taking into
38 account the influences of processing, storage and expected treatment of the food/feed
39 in question.

40

41 **7.8 Toxicology**

42

43 Toxicology studies evaluating risks to human and/or animal health complement each
44 other. Most studies recommended for the assessment of the safety of the GM food are
45 relevant for the assessment of GM feed. Testing methodologies are basically the same

1 and the same level of data quality is required. Should specific studies be required to
2 address the efficacy, nutritional value or wholesomeness of GM feed, e.g. long term
3 feeding trials on target species, the information gained could also be used for additional
4 assurance of the safety of the GMO in the case of human consumption.

5 The requirements of toxicological testing in the safety assessment of food/feed derived
6 from GM plants must be considered on a case-by-case basis and will be determined by
7 the outcome of the assessment of the differences identified between the GM product
8 and its conventional counterpart, including available information on intended changes.
9 Thus, the toxicological testing would not only include studies on newly expressed
10 proteins but also the consequences of any genetic modification (e.g. gene silencing or
11 over-expression of an endogenous gene). In principle, the safety assessment must
12 consider the presence of new proteins expressed as result of the genetic modification,
13 the potential presence of other new constituents and/or possible changes in the level of
14 natural constituents beyond normal variation. These potential deviations from the
15 conventional counterparts may require different toxicological approaches and varying
16 degrees of testing.

17 There may be circumstances, when the applicant considers that a decision on safety
18 can be taken without conducting some of the tests recommended in this chapter and/or
19 that other tests are more appropriate. In such cases the applicant must state the
20 reasons for not submitting the required studies or for carrying out studies other than
21 those mentioned below.

22 Those toxicological studies which are carried out should be conducted using
23 internationally agreed protocols. Test methods described by the OECD (OECD b) or in the
24 most up-to-date European Commission Directives on dangerous substances are
25 recommended (EC, 2002d). Use of any methods that differ from such protocols should
26 be justified. Studies should be carried out according to the principles of Good Laboratory
27 Practice (GLP) described in Council Directive 2004/10/EC (EC, 2004) and accompanied
28 by a statement of GLP-compliance.

29

30 *7.8.1 Safety evaluation of newly expressed proteins*

31
32 The studies required to investigate the toxicity of a newly expressed protein should be
33 selected on a case-by-case basis, depending on the knowledge available with respect to
34 the protein's source, function/activity and history of human/animal consumption. In the
35 case of proteins expressed in the GM plant where both the plant and the new proteins
36 have a history of safe consumption by humans and animals, specific toxicity testing
37 might not be required.

38 To demonstrate the safety of newly expressed proteins the following information is
39 needed:

40 A molecular and biochemical characterisation of the newly expressed protein including
41 the determination of the primary sequence and the molecular weight, studies on post-
42 translational modifications and a description of the function are needed. In the case of
43 newly expressed enzymes, information on the principal and subsidiary enzyme activities
44 is needed including the temperature and pH range for optimum activity, substrate
45 specificity, and possible reaction products.

46 A search for homology to proteins known to cause adverse effects, e.g. protein toxins,
47 should be conducted. A search for homology to proteins exerting a normal metabolic or

1 structural function can also contribute valuable information. The database(s) and the
2 methodology used to carry out the search should be specified.

3 The stability of the protein under conditions that represent processing, storage and
4 expected treatment of the food/feed in which it is present should be studied. The
5 influences of temperature and pH changes should normally be examined and potential
6 modification(s) of the proteins (e.g. denaturation) and/or stable protein fragments
7 generated through such treatments should be characterised.

8 Data concerning the resistance of the newly expressed protein to proteolytic enzymes
9 (e.g. pepsin) should be obtained, e.g. by *in vitro* investigations using appropriate and
10 standardised tests. Stable breakdown products should be characterized and evaluated
11 with regard to the hazards linked to their biological activity.

12 In the case of newly expressed proteins with an insufficient data base and, in particular,
13 if the available data suggest the existence of any cause for concern, specific toxicity
14 studies should be carried out.

15 Repeated dose toxicity studies should be performed, unless reliable information can be
16 provided which demonstrates the safety of the newly expressed protein (including its
17 mode of action) and that the protein is not structurally and functionally related to
18 proteins which have the potential to adversely affect human or animal health.

19 Normally a 28-day oral toxicity study with the newly expressed protein in rodents should
20 be performed according to OECD guideline 407 (OECD, 1995). Depending on the
21 outcome of the 28-days toxicity study, additional targeted investigations may be
22 required including investigation of the immunotoxicity.

23 If the applicant considers that a decision on safety can be taken without conducting a
24 repeated dosing study or that other tests are more appropriate, the applicant must state
25 the reasons for this.

26 It is essential that the tested protein is equivalent to the newly expressed protein as it is
27 expressed in the GM plant. If, due to the lack of sufficient amount of test materials (e.g.
28 plant proteins), a protein is used which was produced by micro-organisms, the structural
29 and functional equivalence of the microbial substitute to the newly expressed plant
30 protein must be demonstrated. For example, comparisons of the molecular weight, the
31 isoelectric point, amino acid sequence, post-translational modification, immunological
32 reactivity and, in the case of enzymes, the enzymatic activity, are needed to provide
33 evidence for the equivalence.

34

35 7.8.2 Testing of new constituents other than proteins

36

37 Identified new constituents other than proteins should be evaluated according to the
38 traditional toxicological approach on a case-by-case basis, which includes an
39 assessment of their toxic potency and occurrence in the GM food/feed. To establish
40 their safety, information analogous to that described in the "Guidance on submissions
41 for food additive evaluations by the Scientific Committee on Foods" (SCF, 2001) and
42 Directive 2001/79/EC (EC, 2001b) is needed. This implies the submission of
43 information on a core set of studies and the consideration of whether or not any other
44 type of study might also be appropriate. Normally, the core set includes information on
45 metabolism/toxicokinetics, sub-chronic toxicity, genotoxicity, chronic
46 toxicity/carcinogenicity and reproduction and developmental toxicity.

1

2 **7.8.3 Information on natural food and feed constituents**

3

4 Natural food and feed constituents comprise a large variety of substances: macro- and
5 micronutrients, secondary plant metabolites as well as natural toxicants and
6 antinutritional factors. If the content of such natural food constituents is increased
7 beyond the natural variation, a detailed safety assessment based on the knowledge of
8 the physiological function and/or toxic properties of these constituents should be
9 submitted. The result of this assessment would determine if, and to what extent,
10 toxicological tests are required. In case of constituents with a physiological or
11 biochemical function (macro- and micro-nutrients), an integrated toxicological and
12 nutritional evaluation is required (see section 7.10).

13

14 **7.8.4 Testing of the whole GM food/feed**

15

16 If the composition of the GM plant is modified substantially, or if there are any
17 indications for the potential occurrence of unintended effects, based on the preceding
18 molecular, compositional or phenotypic analysis, not only new constituents, but also the
19 whole GM food/feed should be tested.

20 The testing programme should include at least a 90-day toxicity study in rodents.
21 Special attention must be paid to the selection of doses and the avoidance of problems
22 of nutritional imbalance. At least two dose levels of the GM and parental test food
23 should be included in the diet. The highest dose level should be the maximum
24 achievable without causing nutritional imbalance, whilst the lowest level should
25 approximate the anticipated human intake. Stability of test diets and nutritional
26 equivalence between control and test diets are other important aspects to consider
27 (König et al., 2004).

28

29 To detect unintended effects it is recommended that comparative growth studies are
30 conducted with young rapidly growing animal species such as the broiler chick. Because
31 of their rapid weight gain, broilers are sensitive to the presence of certain toxic elements
32 in their feed. Studies of this type are, however, limited to those materials suitable for
33 inclusion in broiler diets and which can be nutritionally matched to a suitable control
34 diet. In a recent ILSI report (ILSI, 2004) the sensitivity of the model has, however, been
35 questioned.

36 The choice of the control diet in testing whole GM food/feed or components derived
37 from the GM crop that is compositionally different, should be based on the composition
38 of the traditional food/feed of ingredient which is intended to be substituted. For
39 instance in case of food/feed derived from GM crops that contain new or altered oils,
40 oils should be used as controls which are intended to be replaced. In case of whole GM
41 foods/feed or derived products that contain enhanced levels of specific biologically
42 active compound(s), the test design should include the GM food/feed or derived
43 product, the parent food/feed or derived product, and the GM test material spiked with
44 the enhanced active compound at relatively high dose levels that would induce a
45 biological effect. The latter control diet would be informative on whether specific matrix
46 effects may be expected and on the sensitivity of the test system. Whole feeding trials
47 may be paralleled by experiments in *in vitro* and *in vivo* systems from animal and/or
48 human origin, studying for instance gene expression profiles and/or potential

1 cytotoxicity of newly expressed proteins or metabolites (see for more information
2 SAFOTEST project⁷).

3 Additional toxicological studies may also be necessary, depending on the potential
4 exposure, the nature and extent of deviation from traditional counterparts and the
5 findings of the feeding study.

6 In the case of complex genetic modifications involving the transfer of multiple genes,
7 the potential risk(s) of possible interactions between the expressed proteins, new
8 metabolites and original plant constituents should be assessed. This is also applicable
9 to foods and feeds derived from GM plants obtained through traditional breeding of
10 parental GM lines (combined events). The outcome of the molecular analysis and
11 knowledge of the mode of action of the newly expressed proteins may provide
12 indications for possible synergistic interactions, as well as information on the response
13 to combined administration of proteins to target organisms and regarding effects on the
14 activity of target enzymes. Generally, feeding trials with this type of GM foods/feeds are
15 requested in order to assess the impact of consumption on human and animal health.

16 Any adverse effect(s) noted in individuals exposed to GM food/feed material as part of
17 their professional activities e.g. farming, seed processing should be submitted by the
18 applicant.

19

20 **7.9 Allergenicity**

21

22 Allergy is an adverse reaction which, by definition, is immune-mediated and particularly
23 involves IgE antibodies. It affects individuals who have a genetic predisposition (i.e.
24 atopic individuals). This section mainly deals with the risks to those individuals when
25 exposed to foods (and pollen) derived from GMOs with regard to sensitisation or to
26 elicitation of an allergic reaction.

27 The constituents that are responsible for allergenicity of foods as well as of pollens are
28 proteins. The specific allergy risk of GMOs is associated i) with exposure to newly
29 expressed protein(s) that can be present in edible parts of the plants or in the pollen.
30 This point is related to the biological source of the transgene and ii) with alterations to
31 the allergenicity of the whole plant and derived products e.g. due to over expression of
32 natural endogenous allergens as an unintended effect of the genetic modification. This
33 point is related to the biology of the host itself.

34

35 **7.9.1 Assessment of allergenicity of the newly expressed protein**

36

37 Allergenicity is not an intrinsic, fully predictable, property of a given protein but is a
38 biological activity requiring an interaction with individuals with a pre-disposed genetic
39 background. Allergenicity therefore depends upon the genetic diversity and variability in
40 atopic humans. Given this lack of complete predictability it is necessary to obtain, from
41 several steps in the risk assessment process, a cumulative body of evidence which
42 minimises any uncertainty with regard to the protein(s) in question.

⁷ <http://www.entransfood.com>

1 In line with the recommendations of the Codex *ad hoc* Intergovernmental Task Force on
2 Foods Derived from Biotechnology (Codex Alimentarius, 2003), an integrated, stepwise,
3 case-by-case approach, as described below, should be used in the assessment of
4 possible allergenicity of newly expressed proteins.

5 The source of the transgene must be carefully taken into consideration to make clear
6 whether or not it may encode for any allergen. Information should specify at what stage
7 of the development of the plant and in what organs of the plant the allergenic protein
8 may be expressed. When the introduced genetic material is obtained from wheat, rye,
9 barley, oats or related cereal grains, applicants should assess the newly expressed
10 proteins for a possible role in the elicitation of gluten-sensitive enteropathy or other
11 enteropathies which are not IgE mediated.

12 In every case the first step in the assessment should be a search for sequence
13 homologies and/or structural similarities between the expressed protein and known
14 allergens. Identification of potential linear IgE binding epitopes should be conducted by
15 a search for homologous peptidic fragments in the amino acid sequence of the protein.
16 The number of contiguous identical or chemically similar amino acid residues used in
17 the search setting should be based on a scientifically justified rationale in order to
18 minimise the potential for false negative or false positive results⁸. Using different
19 homology searching strategies based on the sequences available in relevant databases
20 may identify several scenarios. These include a high degree of homology, with or
21 without conservation of the allergenicity, or a low degree of homology with conservation
22 of allergenicity (Mills et al., 2003). To reduce the uncertainty of the conclusions that may
23 be drawn from the search of sequence homology alone, efforts should be encouraged to
24 improve the bioinformatic approach i) to improve and harmonize the algorithms that
25 are used by the different applicants and ii) to develop data bases which include
26 information on the three dimensional structure and function of known allergens and of
27 proteins belonging to protein families which include a high proportion of allergens.

28 The second step for assessing the potential that exposure to the newly expressed
29 proteins might elicit an allergic reaction in individuals already sensitised to cross
30 reactive proteins, is based on *in vitro* tests that measure the capacity of specific IgE
31 from serum of allergic patients to bind the test protein(s).

32 If the source of the introduced gene is considered allergenic, but no sequence homology
33 of the newly expressed protein to a known allergen is demonstrated, *specific* serum
34 screening of the expressed protein should then be undertaken with appropriate sera
35 from patients allergic to the source material using relevant validated immunochemical
36 tests. If positive IgE responses occur, the newly expressed protein may then be
37 considered very likely to be allergenic. If no IgE binding is observed, the newly expressed
38 protein should undergo pepsin resistance tests and additional testing as outlined below.

39 If the source is not known to be allergenic but if there are consistent indications of
40 sequence homology to a known allergen, the specific serum screening should be
41 conducted with sera from patients sensitised to this allergen in order to confirm or
42 exclude an IgE cross-reactivity between the newly expressed protein and this allergen.
43 The results of the screening are interpreted as above. The additional tests that should
44 be performed may include the following.

⁸ It is recognized that the 2001 WHO/FAO consultation suggested moving from 8 to 6 identical amino acid segment searches. The smaller the peptide sequence used in the stepwise comparison, the greater the likelihood of identifying false positives. Conversely, the larger the peptide sequence used the greater the likelihood of false negatives, thereby reducing the utility of the comparison.

1 *Pepsin resistance test.* Stability to digestion by proteolytic enzymes has long been
2 considered a characteristic of allergenic proteins. Although it has now been established
3 that no absolute correlation exists (Fu et al., 2002), resistance of proteins to pepsin
4 digestion is still proposed as an additional criterion to be considered in an overall risk
5 assessment. In the case that a rapid and extensive degradation of a protein in the
6 presence of pepsin is not confirmed under appropriate conditions, further analysis
7 should be conducted to determine the likelihood of the newly expressed protein being
8 allergenic. It will also be useful to compare intact, pepsin digested and heat denatured
9 proteins for IgE binding.

10 *Targeted serum screening.* As proposed in the FAO/WHO expert consultation
11 (WHO/FAO, 2001) targeted serum screening aims to assess the capacity of the newly
12 expressed protein to bind to IgE in sera of individuals with clinically-validated allergic
13 responses to categories of foods broadly related to the gene source.

14 Specific (as well as targeted) serum screening requires a sufficient number and
15 sufficient volumes of relevant sera from allergic humans. These might not always be
16 available either because the allergy is not frequent or for other reasons. The use of
17 existing models and the development and validation of new alternative models that can
18 substitute for and/or complement the use of human biological material for evidence of
19 cross reactivity and elicitation potency should be encouraged. These approaches would
20 include the search for T-cell epitopes, structural motifs, *in vitro* cell based assays using
21 animal or humanised-animal immune cells, etc. They also include appropriate *in vivo*
22 animal models.

23 Animal models are also essential for the assessment of the sensitising potential of
24 newly expressed proteins, i.e. their capacity to induce an allergic immune response with
25 the synthesis of specific IgE in individuals that have never been exposed to those
26 proteins nor to proteins that cross react with them. Several animal models are
27 developed and their use should be encouraged in order to increase the body of evidence
28 to support a conclusion.

29

30 *7.9.2 Assessment of allergenicity of the whole GM plant or crop*

31
32 If the host of the introduced gene is known to be allergenic, any potential change in the
33 allergenicity of the whole GM food should be tested by comparison of the allergen
34 repertoire with that of the conventional non-GM variety.

35 It should be pointed out that these approaches should be applied on a case-by-case
36 basis depending on the available information on the allergenic potential of the source
37 and/or the host.

38 Development of modern analytical tools including profiling techniques (see section II, 5)
39 is encouraged in association with human and animal serum or cell-based assays. These
40 are certainly promising and efficient tools which could be used to detect new proteins or
41 peptide fragments with allergenic potential in whole GM crops and in (processed) GM
42 foods.

43 The integrated process which is described above applies to the assessment of the
44 allergenicity of the edible components and the pollen of GM crops (i.e. covers both food
45 and respiratory allergy risk).

1 In addition, data on the prevalence of occupational allergy in workers or in farmers who
2 have significant exposure to GM plant and crops, or to the airborne allergens they may
3 contain, will provide useful information for the risk assessment process.

4 Regarding animal health, allergenicity is not a significant issue that needs to be
5 specifically addressed.

6

7 **7.10 Nutritional assessment of GM food/feed**

8

9 **7.10.1 Nutritional assessment of GM food**

10

11 The development of GM foods has the potential to improve the nutritional status of
12 individuals and populations and provide products with enhanced functionality. GM foods
13 also have the potential to introduce nutritional imbalances as a result of both expected
14 and unexpected alterations in nutrients and other food components.

15 The nutritional evaluation of GM foods should consider:

16 (a) nutrient composition (see compositional studies as described in section 2);

17 (b) biological efficacy of nutrient components in the foods;

18 (c) assessment of dietary intake and nutritional impact

19

20 When substantial equivalence to an existing food is demonstrated, the only further
21 nutritional assessment will deal with the impact of the introduction of the GM food on
22 general human dietary intake patterns. Information on the anticipated intake/extent of
23 use of the GM food will be required and the nutritional consequences should be
24 assessed at average and at extreme levels of daily intake. The influences of non-nutrient
25 components of the GM food should also be considered.

26 Specific additional requirements should be applied to those GM foods aimed at
27 modifying nutritional quality. In this case additional detailed studies on specific
28 biomolecules, tailored according to the genetic modification(s), would be required.

29 The introduction of a significant nutritional change in a food may require post-market
30 assessment to determine if the overall diet has been altered and to what degree (see
31 section 7.11).

32

33 **7.10.2 Nutritional assessment of GM feed**

34

35 Compositional analysis is the starting point and cornerstone for the nutritional
36 assessment of feed material. Consensus documents prepared by OECD (OECD a)
37 provide excellent guidance for the analyses needed and the analyses conducted should
38 be determined on a case-by-case basis and may vary depending on the introduced trait.
39 It should be noted that there are significant differences in composition of conventionally
40 bred varieties and thus the compositional analysis of GM crops must be assessed

1 against the background of natural variability in the conventional counterpart(s).
2 Attention is drawn to the crop composition database ILSI (2003b) as a key source for
3 such data and to ILSI (2004), which addresses the issue of nutritional assessment of
4 GM feeds.

5 Once compositional equivalence has been established in GM feeds modified for
6 agronomic input traits, nutritional equivalence can be assumed (Clark and
7 Ipharraguerre, 2001; Flachowsky and Aulrich, 2001), since routine long-term livestock
8 feeding studies generally add little to a nutritional assessment. In the case of crops
9 modified for agronomic input traits with combined events the need for long-term
10 feeding studies should be assessed on a case-by-case basis.

11 In the case of GM crops with improved nutritional characteristics, livestock feeding
12 studies with target species should be conducted on a case-by-case basis to study the
13 nutritional benefits that might be expected and to provide further safety assurance.
14 These studies should span either the growing and or finishing period to slaughter for
15 chickens, pigs, and cattle for fattening or a major part of a lactation cycle for dairy cows
16 and should be conducted according to internationally agreed standard protocols (ILSI,
17 2003a). For feedstuffs intended only for aquaculture, growth studies with fish species
18 such as carp or other typical herbivore fishes may be preferable to an extrapolation
19 from results obtained with land-animals.

20 Studies of this type are, however, limited to those materials suitable for inclusion in the
21 diets and which can be nutritionally matched to a suitable control diet.

22

23 When studies are conducted, the following guidelines are proposed:

24 (a) In the case of GM crops modified for improved bioavailability of nutrients, livestock
25 feeding studies with target species should be conducted to determine the
26 bioavailability of individual nutrients in the GM crop and a range of conventional
27 varieties.

28 (b) In the case of GM crops specifically modified with traits to enhance animal
29 performance through increased nutrient density (e.g. increased oil content) or an
30 enhanced level of a specific nutrient (e.g. lysine), an appropriate control diet using
31 its nearest genetic counterpart should be formulated by supplementing it with the
32 specific nutrient to the extent of the change effected in the GM crop. It is also
33 suggested that a number of other commercially relevant varieties should be
34 included in the study.

35 (c) In the case of co-products (e.g. oilseeds meals) from which the modified ingredient
36 has been extracted, these can be compared with those derived from an appropriate
37 counterpart and other commercial varieties on the basis that they are essentially
38 free from the modified component.

39 (d) In the case where nutritional components are to be deposited in food derived from
40 animals receiving GM feed resources specific tests for content should be conducted.

41

42 **7.11 Post-market monitoring of GM food/feed**

43

1 Where appropriate a Post Market Monitoring (PMM) programme should be performed
2 for GM food. PMM does not substitute for a thorough pre-marketing toxicological testing
3 programme but complements it in order to confirm the pre-market risk assessment. It
4 may increase the probability of detecting rare unintended effects. Therefore the PMM
5 for GM foods should be designed to generate reliable and validated flow of information
6 between the different stakeholders which may relate GM food consumption to any
7 (adverse) effect on health.

8 As pre-market risk assessment studies cannot fully reproduce the diversity of the
9 populations who will consume the marketed product, the possibility therefore remains
10 that unpredicted side effects may occur in some individuals of the population, such as
11 those with certain disease states (i.e. allergic individuals), those with particular
12 genetic/physiological characteristics or those who consume the products at high levels.
13 Indeed, risk assessment also relies on an estimate of exposure to the food, which is
14 variable and subject to uncertainty before the food is marketed. A PMM should
15 therefore address the following questions: i) is the product use as
16 predicted/recommended? ii) are known effects and side-effects as predicted? and iii)
17 does the product induce unexpected side effects? (Wal et al., 2003).

18 Given the practical difficulties in performing a PMM, it should be required only in
19 specific cases where there is no traditional comparator. Those cases could include GM
20 (functional) foods with altered nutritional composition and modified nutritional value
21 and/or with specific health claims. This could be the case for a GM food proposed as an
22 alternative or as a replacer to a traditional food. Because of its specific properties, the
23 intake of this GM food might be increased compared to the intake of the traditional
24 counterpart, which could result in a significant impact on the long term nutritional and
25 health status of some individuals of the population.

26 A similar approach could be developed for feed with improved nutritional
27 characteristics.

28

29 **8. Mechanism of interaction between the GM plant and target organisms (if**
30 **applicable)**

31 The applicant should describe the expression and mode of action of any new traits (for
32 example insect tolerance) present in the modified plant. There should be a reference to
33 sections B of this document where this information has already been given. The
34 potential environmental implications of, for example, the development of
35 resistance/tolerance by the target organisms are included in section 9.4 below.

36

37 **9. Potential changes in the interactions of the GM plant with the biotic**
38 **environment resulting from the genetic modification**

39 The evaluations of potential changes in the interactions between the GM plant and the
40 biotic environment (e.g. non-target organisms) are carried out on a case-by-case basis
41 taking into account the biology of the transformed plant and, where gene transfer might
42 occur, of any other recipient organisms, the characteristics and expression of the
43 introduced genetic material, the properties and consequences of the genetic

1 modification, the scale of release and gene transfer and the evaluation of any risk to the
2 receiving environment that might arise from the release of the GM plant.

3 Genes inserted in a GM plant should be evaluated for their potential impact on the
4 environment. This evaluation should include consideration of the consequences of low
5 frequencies of gene transfer to related and unrelated organisms, and take into account
6 any potential for enhanced gene transfer reported in section 6.

7

8 Possible interactions between the GM plant and its biotic environment include:

9 (a) effects on the population dynamics and genetic diversity of populations of species in
10 the receiving environment (plant, animal, microbe);

11 (b) altered susceptibility to pests and pathogens facilitating the dissemination of
12 infectious diseases and/or creating new reservoirs or vectors;

13 (c) compromising prophylactic or therapeutic medical, veterinary, or plant protection
14 treatments;

15 (d) effects on beneficial plant-microbial associations and biogeochemistry
16 (biogeochemical cycles), particularly on microbial-mediated carbon and nitrogen
17 recycling through changes in soil decomposition of organic material.

18

19 Data should be provided from field experiments in areas representative of those
20 geographical regions where the GM plant will be grown commercially in order to reflect
21 relevant meteorological, soil and agronomic conditions. Where data from field studies
22 on other continents are supplied, the applicant should submit a reasoned argument that
23 the data is applicable to European conditions.

24 Risk assessments should be carried out for each of the different environmental
25 compartments that are exposed to the GM plant. Whether any parts of it will remain in
26 the environment after harvest, will depend on the specific plant, its management
27 regime and agronomic practices.

28

29 **9.1 Persistence and invasiveness**

30

31 An assessment is required of the likelihood of the GM plant becoming more persistent
32 than the recipient or parental plants in agricultural habitats or more invasive in natural
33 habitats.

34 The applicant should refer to GM plant specific traits (see section D1), which may have
35 an impact on increased persistence and spread both in natural and cultivated areas.

36

37 **9.2 Selective advantage or disadvantage**

38

1 An assessment is required of any selective advantage or disadvantage conferred to the
2 GM plant.

3 The applicant should – if appropriate - refer to data collected from representative field
4 trials mentioned in section 7.2, if they have relevance to environmental interactions
5 concerning GM plant fitness. If no specific field data are provided, the applicant must
6 discuss any impact of selective advantage or disadvantage of the new trait(s) both in
7 natural and cultivated areas.

8

9 **9.3 Potential for gene transfer**

10

11 An assessment is required of the potential for gene transfer to the same or other
12 sexually compatible plant species under conditions of planting the GM plant and any
13 selective advantage or disadvantage conferred to those plant species.

14 The potential consequence arising from out-crossing to other plant cultivars should be
15 considered and assessed for environmental risk. This will vary with species. For
16 example, the release of GM oilseed rape raises the issue of gene transfer, since this
17 crop will readily cross-pollinate with nearby oilseed rape crops and may spontaneously
18 hybridise also with some wild relatives. In cases where gene transfer cannot be limited
19 between certain adjacent plants, the risk assessment should focus on the
20 consequences of cross-pollination. The potential consequence arising from out-crossing
21 to compatible wild species should be considered and assessed for environmental risk
22 (Saeglitz and Bartsch, 2002). This will depend on non-GM sexually compatible plants
23 being present in regions where the GM crops are being grown and which are available to
24 receive pollen and produce fertile hybrids. Selection pressure in non-crop habitats that is
25 required to maintain the selective advantage of any transferred trait should be
26 identified. For example, transferred herbicide tolerance may not be an advantageous
27 trait in habitats where the herbicide is not applied.

28 The applicant should also refer to information provided in sections 9.1, 9.2 and 10,
29 which may have an impact on increased persistence and spread both in natural and
30 cultivated areas of sexually compatible plants and their wild relatives. If appropriate, an
31 assessment of the potential impact of growing GM crops on wider biodiversity in the
32 crop ecosystem requires the combination of several different approaches (ACRE,
33 2001b).

34

35 **9.4 Interactions between the GM plant and target organisms**

36

37 An assessment is required of the potential immediate and/or delayed environmental
38 impact resulting from direct and indirect interactions between the GM plant and target
39 organisms, such as predators, parasitoids and pathogens (if applicable).

40 Data on the comparative susceptibility of the GM plant to pests and diseases compared
41 with that of the non-modified plants are useful indicators of effects together with
42 observations on agronomic performance during greenhouse and experimental field
43 trials. If appropriate, an assessment of the potential impact of growing GM crops on
44 wider biodiversity in the crop ecosystem requires the combination of several different
45 approaches (ACRE, 2001b), as considered further in section 9.5.

1

2 **9.5 Interactions of the GM plant with non-target organisms**

3

4 An assessment is required of the possible immediate and/or delayed environmental
5 impact resulting from direct and indirect interactions of the GM plant with non-target
6 organisms (also taking into account organisms which interact with target organisms),
7 including impact on population levels of competitors, herbivores, symbionts (where
8 applicable), predators, parasites and pathogens.

9 Impact should be assessed on non-target species in the crop ecosystem (which may
10 include pollinators, beneficial, predatory and phytophagous species), and, if appropriate,
11 the aquatic environment. Studies should be designed in order that sufficient statistical
12 power is obtained to detect possible effects on non-target organisms. Adequate
13 statistical power can be achieved from the proper control of variation and replication,
14 since power depends on sample size, the degree of random variation between
15 experimental units and the chosen significance of the tests. An appropriate approach
16 might be to select a desired level of statistical power and the size of effect to be
17 detected, collect preliminary data to estimate within-treatment variability and then to
18 calculate the required sample size for the proposed study. The duration of experiments
19 to assess the risks to non-target organisms should be sufficient to reflect the pattern
20 and duration of exposure that these organisms are likely to experience under field
21 conditions (Perry et al., 2003; Marvier, 2002). If appropriate, an assessment of the
22 potential impact of growing GM crops on wider biodiversity in the crop ecosystem
23 requires the combination of several different approaches (ACRE, 2001b).

24

25 **9.6 Effects on human health**

26

27 An assessment is required of the possible immediate and/or delayed effects on human
28 health resulting from potential direct and indirect interactions of the GM plant and
29 persons working with, coming into contact with or in the vicinity of the GM plant
30 release(s).

31 The applicant should refer to section 7, where this issue has already been addressed.

32

33 **9.7 Effects on animal health**

34

35 An assessment is required of the possible immediate and/or delayed effects on animal
36 health and consequences for the feed/food chain resulting from consumption of the GM
37 plant and any products derived from it, if it is intended to be used as animal feed.

38 The applicant should refer to section 7, where this issue has already been addressed.

39

40 **9.8 Effects on biogeochemical processes**

41

1 An assessment is required of the possible immediate and/or delayed effects on
2 biogeochemical processes resulting from potential direct and indirect interactions of the
3 GM plant and target and non-target organisms in the vicinity of the GM plant release(s).

4 The applicant should address, where appropriate, the potential impact on
5 biogeochemical processes, e.g. in relation to soil microbial communities. Examples are
6 CO₂-evolution, organic matter turnover, nitrogen fixation (Nannipieri et al., 2003). Soil
7 fertility strongly influences the growth and productivity of plants. As plant-associated
8 (rhizosphere) and soil microbial communities perform the vital biotransformation that
9 underpins soil fertility any negative impact(s) on microbial participants in this key
10 compartment would have to be carefully evaluated. This should be assessed on a case-
11 by-case basis with particular reference to the nature of the introduced trait and the
12 consequences of the genetic modification/alteration in the GM plant.

13 The risk assessment should aim to establish if direct or indirect effect(s) of the genetic
14 modification in the GM plant have any long-term or sustainable deleterious effect on the
15 recognised soil microbial communities and the associated functional activities that are
16 responsible for maintaining soil fertility and plant productivity. The assessment should
17 also address the fate of any (newly) expressed gene products and derivatives in those
18 environmental compartments where they are introduced and which result in exposure of
19 non-target organisms (e.g. in soil after the incorporation of plant material). Exposure
20 should also be estimated to relevant soil biota (e.g. earthworms, micro-organisms,
21 organic matter breakdown) in relation to the impact on decomposition processes. Risk
22 assessment should also include an analysis to determine if a shift occurs in populations
23 of deleterious organisms in the presence of the modified plant.

24

25 **9.9 Impacts of the specific cultivation, management and harvesting techniques**

26

27 An assessment is required of the possible immediate and/or delayed, direct and
28 indirect environmental impacts of the specific cultivation, management and harvesting
29 techniques used for the GM plant where these are different from those used for non-GM
30 plants.

31 If appropriate, an assessment of the potential impact of growing GM crops on wider
32 biodiversity in the crop ecosystem requires the combination of several different
33 approaches (ACRE, 2001b). The applicant should describe the appropriate commercial
34 management regimes for the GM crop including changes in applications of plant
35 protection products (pesticides and/or biocontrol agents), rotations and other plant
36 management measures for the GM plant where these are different from the equivalent
37 non-GM plant under representative conditions. The applicant should aim to assess the
38 direct and indirect, immediate and delayed effects, of the management of the GM plant.
39 This should include the biodiversity within the GM crop and adjacent non-crop habitats.

40 The extent of such studies will depend on the level of effect associated with a particular
41 GM plant and on the quality and availability of the literature that is relevant to the
42 particular risk assessment. For example, the published results of the UK's Farm Scale
43 Evaluations of genetically modified herbicide-tolerant crops (Squire et al., 2003) may
44 give information relevant to other herbicide-tolerant crops. However, it will be necessary
45 to compare the relative efficacy of different herbicides and their management
46 programmes on weed species in order to assess the impact of herbicide regimes on
47 biodiversity.

48

1 **10. Potential interactions with the abiotic environment**

2 The evaluations on potential changes in the interactions of the GM plant with the abiotic
3 environment should be carried out on a case-by-case basis taking into account the
4 biology of the recipient plant, the characteristics of the introduced genetic material, the
5 properties and consequences of the genetic modification, the scale of release and the
6 evaluation of any risk to the receiving abiotic environment that might arise from the
7 release of the GM plant.

8

9 Examples of possible interactions between the GM plant and its abiotic environment
10 are:

- 11 (a) alteration of climatic conditions (e.g. altered production of greenhouse gases),
- 12 (b) altered sensitivity or tolerance to climatic conditions (e.g. cold, heat, humidity),
- 13 (c) altered sensitivity or tolerance to abiotic fractions of soil (e.g. salinity, mineral
14 nutrients, mineral toxins),
- 15 (d) altered sensitivity or tolerance to gases (e.g. CO₂, oxygen, NH₄),
- 16 (e) alteration of mineralisation (e.g. root exudates changing the soil pH).

17

18 **11. Environmental Monitoring Plan**

19 **11.1 General**

20

21 Directive 2001/18/EC introduces an obligation for applicants to implement GMO
22 monitoring plans in order to identify any direct or indirect, immediate and/or delayed
23 adverse effects of GMOs, their products and their management to human health or the
24 environment, after the GMO has been placed on the market. Monitoring as detailed in
25 Articles 13, 19 and 20 of Directive 2001/18/EC and in this GM Food and Feed
26 Guidance Document refers to environmental monitoring, which takes place after the
27 granting of a consent to place a GMO on the market. Article 13(2)(e) of the Directive
28 requires applicants to submit a monitoring plan as part of their notifications. The
29 structure and content of this environmental monitoring plan should be in accordance
30 with the guidelines of Annex VII, Directive 2001/18/EC (strategy, method, analysis,
31 reporting; Wilhelm et al. 2003).

32 An environmental monitoring plan is required for applications where the natural or
33 cultivated environment will be exposed to GM plant propagules or GM plant products.
34 Applications concerning only food/feed or ingredients (for example, imported into but
35 not cultivated within the EU) will thus not normally be required to describe a detailed
36 environmental monitoring plan if the applicant has clearly shown that environmental
37 exposure is absent or will be at levels or in a form that does not present a risk to other
38 living organisms or the abiotic environment.

39 Monitoring can be defined as the systematic measurement of variables and processes
40 over time and assumes that there are specific reasons to collect such data, for example,

1 to ensure that certain standards or conditions are being met or to examine potential
2 changes with respect to certain baselines. Against this background, it is essential to
3 identify the type of effects or variables to be monitored, an appropriate time-period for
4 measurements and, importantly, the tools and systems to measure them. Monitoring
5 results may, however, be important in the development of further research.

6 The environmental monitoring of the GM plant will have two focuses: (1) the possible
7 effects of the GM plant, identified in the formal risk assessment procedure, and (2)
8 unforeseen effects. Where there is scientific evidence of a potential adverse effect
9 linked to the genetic modification, then case-specific monitoring should be carried out
10 after placing on the market, in order to confirm the assumptions of the risk assessment.
11 Consequently, case-specific monitoring is not obligatory and is only required to verify the
12 risk assessment, whereas a General Surveillance plan must be part of the application. A
13 published Guidance Note (2002/811/EG) (EC, 2002b) explicitly suggests that General
14 Surveillance should include long term monitoring, to allow for unexpected effects that
15 may occur after longer periods of environmental exposure.

16 Changes in the management and cultivation techniques of new GM crops may affect the
17 environment e.g. through changes in agrochemical usage. Directive 2001/18/EC
18 requires that the impacts of any such indirect effects, e.g. changes of cultivation
19 methods, should be addressed by the monitoring plan.

20 The ultimate goal of the environmental monitoring plan should be to determine whether
21 the data collected during case specific monitoring and General Surveillance identify
22 specific effects due to commercialisation of the GM plant which alter the balance
23 between the advantages of the introduction and any negative consequences, in both
24 managed and natural environments, compared with current farming practices or other
25 alternatives.

26

27 **11.2 Case-specific GM plant monitoring**

28

29 Guidance Note 2002/811/EC provides no clear differentiation between the monitoring
30 principles of either case-specific monitoring or general surveillance (Den Nijs and
31 Bartsch 2004). The main objective of case-specific monitoring is to determine the
32 significance of any adverse effects identified in the risk assessment (see chapters 8, 9
33 and 10). Case-specific monitoring should be targeted at those environmental factors
34 most likely to be adversely affected by the GM plant which were identified in the
35 environmental risk assessment. Such monitoring can be carried out at a limited number
36 of sites, where exposure is greatest and intensive recording and data collection can take
37 place. This specific and intensive, scientific measurement and data collection may often
38 have an experimental approach. The monitoring program design further depends on
39 levels of exposure in different geographical regions and other specific management
40 influences. The evaluation of risk should be based on Annex II of the Directive
41 (2001/18/EC).

42

43 **11.3 General Surveillance of the impact of the GM plant**

44

45 The objective of General Surveillance is to identify unforeseen adverse effects of the GM
46 plant or its use, on human health and the environment, that were not predicted in the
47 risk assessment. General Surveillance should be less experimental than case-specific

1 monitoring, largely based on routine observations and should be conducted over a wider
2 range of sites and environments with a range of parameters observed at a low intensity.
3 If unusual observations are reported, more focussed in-depth studies can be carried out.
4 Existing surveillance systems should be used where practical e.g. routine farm recording
5 systems, and any “abnormal” effects not usually occurring in similar situations with
6 conventional cropping should be recorded. However, direct comparison with non-GM
7 crop reference areas is not always necessary. Reference can be made to the historical
8 knowledge and experiences of the “observer” (e.g. farmers, inspectors, botanical
9 surveyors) in relation to the situation prior to the introduction of the GM plant.
10

11 General Surveillance should not be a substitute for general environmental monitoring by
12 Member States. The higher the ecological integration and scale (from the individual to a
13 population, from single farms to regions) the more difficult it is to distinguish potential
14 effects of GM plant from other factors. Initially, General Surveillance should focus on
15 each transgenic plant and type individually. Ultimately, when several GM plants have
16 been commercialised, the interactions between these GM plants and their management
17 regimes should be examined. Environmental monitoring at a regional level may be
18 considered primarily to be a governmental task and additional to the monitoring
19 requirements for the applicant following placing on the market. In the Directive
20 2001/18/EC, the possibility of additional surveillance by government authorities is
21 described in Item 44 of the Conciliation Committee. The applicant should be aware of
22 all relevant surveys and monitoring in areas where the GM plants will be grown and
23 should refer to the results of this monitoring in reports to the Competent Authority and
24 the Commission.

25

26 **11.4 Parameters to be used in a monitoring plan**

27

28 (a) **Background environmental data** e.g. soil parameters, climatic conditions, general
29 crop management data e.g. fertilisers, crop protection, crop rotations and previous
30 crop history should be collected to permit the assessment of the relevant
31 parameters listed under b):

32 (b) **GM plant-based parameters depending on the specific combination of**
33 **GMO/trait/environment:**

34 General surveillance methods will depend on the particular GM plant, trait and
35 environment combination. The key parameters to be observed should include
36 species/ecosystem biodiversity, soil functionality, sustainable agriculture, or plant
37 health. Indicators should be measurable, appropriate, adequate in terms of
38 statistical power, and comparable with existing baseline data.

39

40 **11.5 Implementing General Surveillance**

41

42 Existing surveillance systems

43 In conjunction with the exploitation plan for the GM plant, the applicant should define
44 the infrastructures that will be established and exploited in order to conduct General
45 Surveillance of regions where the GM plant is grown. The applicant should identify
46 existing surveillance systems which are already monitoring one or more of the relevant

1 parameters/elements. This should include arrangements for collecting and collating
2 data.

3 The applicant should also identify which additional surveys will be asked to contribute to
4 the General Surveillance (for example, public institutions, cultivation associations) in
5 Member States. Although detailed arrangements may not have been agreed at the time
6 of the application, the applicant should agree the formal procedures with the
7 Commission and Member States before commercial market introduction. For example,
8 when the GM cultivar is registered in the EU variety catalogue.

9

10 Involving Farmers/Growers of GM crops and suppliers of GM crop seeds

11 Applicants can obtain useful information directly from growers and seed suppliers of GM
12 crops and should involve them in supplying data on seed sales, areas sown, crop
13 management etc. Applicants should also be pro-active in developing reporting systems
14 so that farmers intending to purchase genetically modified seeds will be involved in
15 reporting unusual occurrences during and after the cultivation of the GM crop. The
16 applicant should describe the number of farmers/growers involved, the reporting
17 methods and the suitability of the data collected for statistical analysis.

18

19 Local Surveillance

20 Applicants may consider that an intensive local surveillance is more appropriate than a
21 more extensive General Surveillance described above. This would be particularly
22 appropriate when it is envisaged that there will be a phased or gradual introduction of
23 the GM crop into a limited number of regions in various EU Member States. This consists
24 of the systematic recording of a larger number of relevant parameters at a limited
25 number of locations where there is significant and repeated growing of the GM crop.
26 This might also be defined according to the extent of the cultivation of the GM crop, the
27 occurrence of targeted pest species or particular climatic/eco-regions. A "split field
28 design" (adjacent/parallel cultivation of GM and non-GM crop varieties under similar
29 management conditions) may be appropriate for local surveillance during the early
30 years of marketing release. However, the lack of availability of non-transgenic, isogenic
31 varieties and the lack of statistical power due to the small number of locations may
32 reduce the sensitivity of these experiments. The methods selected, the duration of the
33 monitoring and the extent or number of areas, will be determined by the specific case
34 and the parameters to be monitored.

35 Whilst the planning and conduct of local surveillance will be the applicant's
36 responsibility, it will be acceptable if the applicant involves public institutions in carrying
37 out some or all of the agreed work.

38

39 **11.6 Reporting the results of monitoring**

40

41 Following the placing on the market of a GMO, the applicant under Article 20(1) of the
42 Directive 2001/18/EC, has a legal obligation to ensure that monitoring and reporting
43 are carried out according to the conditions specified in the consent. The applicant is
44 responsible for submitting the monitoring reports to the Commission and the competent
45 authorities of the Member States. Information should also be made publicly available in

1 line with the requirements of Article 20(4) of the Directive. Applicants should describe
2 the methods, frequency and timing of reporting in their monitoring plan.

3 Although no time frame for reporting is specified in the Guidance Note (2002/811/EC),
4 reports should be submitted annually and summary reports covering longer periods in
5 which observations and data are collected should be submitted at appropriate intervals
6 during the monitoring period.

7 The monitoring report should include the results of any relevant monitoring by third
8 parties, including the farmers/growers, seed companies, independent surveyors, local,
9 regional and national environmental surveyors. In addition the applicant should
10 evaluate these results and incorporate full analysis and conclusions in the submitted
11 monitoring report.

12

13 **Flow of information on the cultivation of GM plants:**

14 Where GM plants are grown the following procedures should be complied with:

15 (a) All GM seeds must be labelled with the variety, and should also contain information
16 on the construct, the supplier's name and address, full instructions on any specific
17 cultivation requirements, and reporting procedures for any incidents, including the
18 address of the Consent Holder for the marketing of the seeds.

19 (b) The farmer/grower is required to declare the variety, sowing date, amount of
20 cultivated crops and exact geographic location to the national cultivation register
21 according to Dir. 2001/18/EG - Art 31 (3b).

22 (c) The farmer should record all relevant cropping and management data for that GM
23 crop and these data should be available for inspection.

24

25 **Flow of information in instances where GM plants are thought to have caused unusual**
26 **or adverse effects:**

27 If effects have been detected in areas where GM plants are grown or where there is a
28 suspicion that the GM plants may be associated with an incident, the following
29 procedures should be complied with:

30 (a) Farmers should follow the procedure agreed at the time of purchase of the GM
31 seeds and provide information to the seed supplier/Consent Holder of any unusual
32 observations without delay.

33 (b) The applicant should notify any relevant information immediately to the Member
34 State Competent Authority and to both the Commission and EFSA.

35 (c) If unusual effects are detected by external organisations (e.g. public institutions),
36 these must be communicated to the Consent Holder/ Seed supplier, the Member
37 State Competent Authority and to the Commission and EFSA immediately.

38 (d) The Consent Holder/Seed supplier must carry out a preliminary examination of the
39 report in order to verify whether a GM plant-related effect has really occurred and
40 within a defined period (e.g. one month or dependent on the event) and should

1 provide the Competent Authority with a report on the result of its preliminary
2 investigations, including an assessment of potential harm.

3 (e) Either directly upon receipt of the information or at the latest upon receipt of the
4 Consent Holder's report, the Competent Authority should decide whether further
5 authority action is required. If further action is required the Competent Authority
6 should inform the Commission of the reported observation and, together with the
7 applicant and professionally competent institutions or experts, should investigate
8 the causes and consequences of the reported incident. The Competent Authority
9 should submit a full report to the Commission and EFSA to include the extent of any
10 environmental damage, remedial measures taken, liability and recommendations
11 for the future use/management of the GM plant.

12

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1

2 **EFSA GUIDANCE TO APPLICANTS ON THE PRESENTATION OF APPLICATIONS FOR THE**
3 **REQUEST OF AUTHORISATION OF A GENETICALLY MODIFIED ORGANISM**
4 **AND/OR DERIVED PRODUCTS**

5

6 April 2004

7

8 **Introduction**

9

10 This annex provides guidance on the presentation of applications for the placing on the
11 market of genetically modified organisms (GMOs) and/or derived products introduced
12 under Community legislation (on *genetically modified (GM) food and feed*⁹ and on *the*
13 *deliberate release into the environment of GMOs*¹⁰) to be evaluated by the GMO panel of
14 EFSA. This annex will be regularly updated in view of the experience that EFSA and the
15 GMO panel will develop with the handling of GMO applications.

16

17 **Application for the authorisation of a GMO and/or derived product**

18

19 1. An application for the authorisation of a GMO and/or derived product submitted
20 within the framework of Regulation (EC) 1829/2003 should preferably be presented
21 in English and should consist of the following elements as specified by Articles 5
22 and 17 of that Regulation:

23

24 1.1. The technical dossier should be compiled according to the legislative
25 requirements and according to the format proposed in the EFSA guidance
26 document on GM plants and derived food and feed and as specified in Annex III.
27 Applications submitted within the framework of Directive 2001/18/EC, and for
28 which the GMO Panel has to be consulted according to Article 28 of the
29 Directive, should also be compiled according to this EFSA guidance document.

30 Each dossier should be a complete document containing all of the information
31 required for a full risk assessment of the product(s) in question. Assessors
32 should not be required to undertake any additional literature reviews, or
33 assemble, or process data to evaluate the dossiers.

⁹ Regulation (EC) No 1829/2003 on genetically modified food and feed, OJ L 268, 18.10.2003, p. 1.

¹⁰ Directive 2001/18/EC on the deliberate release into the environment of GMOs and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, p. 1

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To facilitate easy access of information in dossiers, information should be presented to conform with the format proposed in this document and a detailed index should be prepared. Continuous numbering of pages and appendices is required.

Care should be taken to ensure that all parts of the dossier are fully legible. Particular attention is drawn to the presentation of experimental data including tables, physical maps and blots. Statistical analysis of data should be provided and the statistical power tested whenever necessary. Note that summary data is not sufficient. Data presented in sections of the dossier should be clearly labelled whether in the form of tables, figures, photographs, analytical gels, etc. Such data can also be submitted electronically for clarity and to preserve the quality of the original data. In addition, the appropriate controls or reference points included should be clearly labelled and referenced.

Not all the points included in the guidance document will apply to every case. It is to be expected that individual applications will address only the particular subset of considerations which is appropriate to individual situations. The level of detail required in response to each subset of considerations is also likely to vary according the scope of the application.

Data provided in support of an application should be of at least the quality expected of data submitted to a peer-review journal. Particular attention should be paid to the sensitivity and specificity of methods employed and to the adequacy and appropriateness of controls.

- 1.2. The summary of the dossier shall be preferably presented in English in an easily comprehensible and legible form and follow the structure of the EFSA guidance on GM plants and derived food and feed as specified in Annex IV.
- 1.3. Where applicable, the information to be provided for the purpose of complying with Annex II to the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (hereinafter referred to as the "Cartagena Protocol").
- 1.4. Either an analysis, supported by appropriate information and data, showing that the characteristics of the food or feed are not different from those of its conventional counterpart, having regard to the accepted limits of natural variations for such characteristics and to the criteria specified in Article 13(2)(a) of Regulation (EC) 1829/2003, or a proposal for labelling the food in accordance with Article 13(2)(a) and (3) of Regulation (EC) 1829/2003;
- 1.5. Either a reasoned statement that the food or feed does not give rise to ethical or religious concerns, or a proposal for labelling it in accordance with Article 13(2)(b) of Regulation (EC) 1829/2003;
- 1.6. Where appropriate, the conditions for placing on the market the food(s) or feed(s) produced from it, including specific conditions for use and handling;

- 1 1.7. Methods for detection, sampling (including references to existing official or
2 standardised sampling methods) and identification of the transformation event
3 and, where applicable, for the detection and identification of the transformation
4 event in the food/feed and/or in foods/feeds produced from it in accordance
5 with the implementing rules¹¹ of Regulation (EC) No. 1829/2003;
6
- 7 1.8. Samples of the food or feed and their control samples, and information as to
8 the place where the reference material can be accessed shall be made
9 available to the Community Reference Laboratory (CRL) as specified in Article
10 32 of Regulation (EC) 1829/2003. A proof that the methods for detection and
11 sampling and the samples of the food and control samples were sent to the
12 CRL should be provided;
13
- 14 1.9. Where appropriate, a proposal for post-market monitoring regarding use of the
15 food for human consumption or the feed for animal consumption;
16
- 17 2. In the case of an application relating to a GMO for food or feed use, references to
18 “food” or “feed” shall be interpreted as referring to food or feed containing,
19 consisting of or produced from the GMO in respect of which an application is made.
- 20
- 21 3. In the case of GMOs or food or feed containing or consisting of GMOs, the
22 application shall fulfil the requirements of Directive 2001/18/EC. Where the placing
23 on the market of the GMO has been authorised under Part C of Directive
24 2001/18/EC, a copy of the authorisation decision shall be provided.
- 25
- 26 4. Where the application concerns a substance, the use and placing on the market of
27 which is subject, under other provisions of Community law, to its inclusion on a list
28 of substances registered or authorised to the exclusion of others, this must be
29 stated in the application and the status of the substance under the relevant
30 legislation must be indicated.
- 31
- 32 5. Where applications submitted in a Member State under other Community
33 legislation¹² are transformed into an application under Article 46 of Regulation (EC)
34 1829/2003, the original application shall be updated and revised according to the
35 requirements of Regulation (EC) 1829/2003 and to the EFSA guidance on GM
36 plants and derived food and feed. As the case may be, the initial assessment report

¹¹ Commission Regulation on detailed rules for the implementation of Regulation (EC) No. 1829/2003 of the European Parliament and of the Council as regards the application for the authorisation of new genetically modified food and feed, the notification of existing products and adventitious or technically unavoidable presence of genetically modified material which has benefited from a favourable risk evaluation (adopted on 25 February 2004, to be published in the Official Journal).

¹² Regulation concerning novel foods and novel food ingredients, OJ L 43, 14.2.1997, p. 1; Directive on the deliberate release into the environment of GMOs and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, p. 1; Directive concerning certain products used in animal nutrition, OJ L 213, 21.7.1982, p. 8; Directive concerning additives in feedingstuffs, OJ L 270, 14.12.1970, p. 1.

1 of the rapporteur Member State, as well as the response of the applicant to Member
2 States' questions shall be made available to EFSA. The questions/answers should
3 be grouped by subject (Molecular Characterisation, Food/Feed Safety, and
4 Environmental Risk Assessment), and where appropriate, refer to the page-number
5 in the dossier to easily trace-back the issue.

6

7 **Practical specifications**

8

9 Four paper copies and 25 copies in electronic format (CD-ROM) of the technical dossier
10 should be sent by registered post through the national Competent Authority
11 (1829/2003-applications) or through the Commission (2001/18/EC-applications) to the
12 scientific coordinator of the GMO-Panel:

13

14 European Food Safety Authority
15 Scientific Coordinator GMO panel
16 European Food Safety Authority
17 Provisional address:
18 Rue de Genève 10 (office G-10, 6/36)
19 B-1140 Brussels (Evere)
20 Belgium
21

22 The electronic version of the application should be certified as being identical to the one
23 on paper. Common electronic formats should be used, such as "MS Word" or "Adobe
24 Acrobat Reader". A print-out of the table of contents should accompany the CD-ROM,
25 clearly indicating the different files and where they can be found. Cross-references should
26 be made between the print-out and the electronic file names by describing the content
27 for each file name. The files should be searchable using the search facilities of standard
28 software packages.

29 Confidential business information should be clearly indicated and separated for the
30 other parts of the application. Confidential business information could for instance be
31 provided on a separate password protected CD-ROM (for which also 25 copies have to
32 be provided).

33 The application in itself can not be confidential. Sections considered as confidential by
34 the applicant should be kept to a minimum. Applicants are encouraged to make publicly
35 available a maximum of the information submitted, for example by posting on the
36 Internet the contents of the application.

37 The applicant should keep additional paper and electronic copies readily available in
38 cases EFSA (GMO-panel) would require them.

39 The application will be considered valid if it fulfils the requirements as specified in the
40 EFSA guidance document and accompanying annexes. Applications that are not
41 submitted in English will cause a delay in the assessment process.

1

2

SCOPE OF THE APPLICATION

3

4 The scope of the application shall cover one or more of the following categories:

5

6 **1 Food**

7 1.1 GM plants for all uses in food, including the use of the GM plant for
8 cultivation, import and processing

9 1.2 GM plants for all uses in food, including for import and processing only

10 1.3 Food containing or consisting of GM plants

11 1.4 Food produced from GM plants or containing ingredients produced from
12 GM plants

13

14 **2 Feed**

15 2.1 GM plants for all uses in feed, including the use of the GMO for
16 cultivation, import and processing

17 2.2 GM plants for all uses in feed, including for import and processing only

18 2.3 Feed containing or consisting of GM plants

19 2.4 Feed produced from GM plants

20

21 **3 GM plants for environmental release**

22 3.1 Import and processing

23 3.2 Cultivation in Europe

1

2

FORMAT OF TECHNICAL DOSSIERS

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6

INFORMATION REQUIRED IN APPLICATIONS CONCERNING RELEASES OF GENETICALLY MODIFIED PLANTS (GYMNOSPERMAE AND ANGIOSPERMAE)

7

8

A. GENERAL INFORMATION

9

10

1. Name and address of the applicant (company or institute)

11

2. Name, qualification and experience of the responsible scientist(s)

12

3. Title of the project

13

4. Scope of the application as defined in Annex II

14

5. Designation and specification of the GM plant and/or derived product

15

16

6. Where applicable, a detailed description of the method of production and manufacturing

17

18

19

B. INFORMATION RELATING TO (A) THE RECIPIENT OR (B) (WHERE APPROPRIATE) PARENTAL PLANTS

20

21

22

1. Complete name; (a) family name, (b) genus, (c) species, (d) subspecies, (e) cultivar/breeding line, (f) common name

23

24

2. (a) Information concerning reproduction: (i) mode(s) of reproduction, (ii) specific factors affecting reproduction, if any, (iii) generation time;

25

(b) Sexual compatibility with other cultivated or wild plant species.

26

27

3. Survivability; (a) ability to form structures for survival or dormancy, (b) specific factors if any affecting survivability.

28

29

30

4. Dissemination; (a) ways and extent (for example and estimation of how viable pollen and/or seeds declines with distance) of dissemination, (b) special factors affecting dissemination, if any.

31

32

5. Geographical distribution and cultivation of the plant, including the distribution in Europe of the compatible species.

- 1 6. In the case of a plant species not grown in the member state(s), description of
2 the natural habitat of the plant, including information on natural predators,
3 parasites, competitors and symbionts.
- 4 7. Other potential interactions, relevant to the GM plant, of the plant with
5 organisms in the ecosystem where it is usually grown, or used elsewhere,
6 including information on toxic effects on humans, animals and other organisms.

7

8 **C. INFORMATION RELATING TO THE GENETIC MODIFICATION**

9

- 10 1. Description of the methods used for the genetic modification
- 11 2. Nature and source of vector used
- 12 3. Size, source (name) of donor organism(s) and intended function of each
13 constituent fragment of the region intended for insertion

14

15 **D. INFORMATION RELATING TO THE GM PLANT**

16

- 17 1. Description of the trait(s) and characteristics which have been introduced or
18 modified
- 19 2. Information on the sequences actually inserted or deleted
- 20 (a) the copy number of all detectable inserts, both complete and partial
- 21 (b) in the case of deletion(s), size and function of the deleted region(s)
- 22 (c) chromosomal location(s) of insert(s) (nucleus, chloroplasts, mitochondria
23 or maintained in a non integrated form) and methods for its
24 determination.
- 25 (d) the organisation of the inserted genetic material at the insertion site
26 including sequence data of the inserted material and of the flanking 5'
27 and 3' regions.
- 28 (e) all sequence information (in electronic format) including the location of
29 primers used for detection.
- 30
- 31 3. Information on the expression of the insert
- 32 (a) Information on developmental expression of the insert during the life
33 cycle of the plant.
- 34 (b) Parts of the plant where the insert is expressed
- 35 (c) Expression of potential fusion proteins.
- 36 (d) Methods used for expression analysis

- 1
- 2 4. Information on how the GM plant differs from the recipient plant in:
3 reproduction, dissemination, survivability
- 4 5. Genetic stability of the insert and phenotypic stability of the GM plant
- 5 6. Any change to the ability of the GM plant to transfer genetic material to other
6 organisms
- 7 (a) Plant to bacteria gene transfer
- 8 (b) Plant to plant gene transfer
- 9 7. Information on any toxic, allergenic or other harmful effects on human or animal
10 health arising from the GM food/feed
- 11 7.1 Comparative assessment
- 12 7.2 Field trials
- 13 (c) number of locations, growing seasons, geographical spreading and
14 replicates
- 15 (d) statistical models for analysis, confidence intervals
- 16 (e) the baseline used for consideration of natural variations
- 17 7.3 Selection of compounds for analysis
- 18 7.4 Agronomic traits
- 19 7.5 Product Specification
- 20 7.6 Effect of the production and processing
- 21 7.7 Anticipated intake/extent of use
- 22 7.8 Toxicology
- 23 7.8.1 *Safety evaluation of newly expressed proteins*
- 24 7.8.2 *Testing of new constituents other than proteins*
- 25 7.8.3 *Information on natural food and feed constituents*
- 26 7.8.4 *Testing of the whole GM food/feed*
- 27 7.9 Allergenicity
- 28 7.9.1 *Assessment of allergenicity of the newly expressed protein*
- 29 7.9.2 *Assessment of allergenicity of the whole GM plant or crop*
- 30 7.10 Nutritional assessment of GM food/feed
- 31

- 1 **7.10.1 Nutritional assessment of GM food**
- 2 **7.10.2 Nutritional assessment of GM feed**
- 3 **7.11 Post-market monitoring of GM food/feed**
- 4
- 5 **8. Mechanism of interaction between the GM plant and target organisms (if**
- 6 **applicable)**
- 7 **9. Potential changes in the interactions of the GM plant with the biotic**
- 8 **environment resulting from the genetic modification**
- 9 **9.1 Persistence and invasiveness**
- 10 **9.2 Selective advantage or disadvantage**
- 11 **9.3 Potential for gene transfer**
- 12 **9.4 Interactions between the GM plant and target organisms**
- 13 **9.5 Interactions of the GM plant with non-target organisms**
- 14 **9.6 Effects on human health**
- 15 **9.7 Effects on animal health**
- 16 **9.8 Effects on biogeochemical processes**
- 17 **9.9 Impacts of the specific cultivation, management and harvesting techniques**
- 18
- 19 **10. Potential interactions with the abiotic environment**
- 20 **11. Environmental Monitoring Plan**
- 21 **11.1 General**
- 22 **11.2 Case-specific GM plant monitoring**
- 23 **11.3 General Surveillance of the impact of the GM plant**
- 24 **11.4 Parameters to be used in a monitoring plan**
- 25 **11.5 Implementing General Surveillance**
- 26 **11.6 Reporting the results of monitoring**

1

2 **FORMAT¹³ OF THE SUMMARY OF APPLICATIONS FOR GENETICALLY MODIFIED PLANTS**
3 **AND/OR DERIVED FOOD AND FEED**

4

5 According to Articles 5(3)(l) and 17(3)(l) of Regulation (EC) 1829/2003, the application
6 shall be accompanied by a summary of the dossier in a standardised form. This annex
7 specifies the format of such summary for genetically modified plants and/or derived
8 food and feed. Depending on the scope of the application, some of the specifications
9 may not be applicable. The summary shall be presented in an easily comprehensible
10 and legible form. It shall not contain parts which are considered to be confidential.

11

12 **A. GENERAL INFORMATION**

13

14 **1. Details of application**

a) Member State of application
b) Application number
c) Name of the product (commercial and other names)
d) Date of acknowledgement of valid application

15

16 **2. Applicant**

a) Name of applicant
b) Address of applicant
c) Name and address of the person established in the Community who is responsible for the placing on the market, whether it be the manufacturer, the importer or the distributor, if different from the applicant (Commission Decision 2004/204/EC Art 3(a)(ii))

17

18 **3. Scope of the application**

¹³ This format of summary is based on Part II of Council Decision 2002/812/EC of 3 October 2002 establishing pursuant to Directive 2001/18/EC of the European Parliament and of the Council the summary information format relating to the placing on the market of genetically modified organisms as or in products (Official Journal of the European Communities L280: 37-61), and is adapted according to the current guidance document.

- 1 Cultivation (Part C of Directive 2001/18/EC)
- 2 Import and processing (Part C of Directive 2001/18/EC)
- 3 Use as food/food ingredient (Regulation 1829/2003)
- 4 Use as feed/feed material (Regulation 1829/2003)

5

- 6 **4. Is the product being simultaneously notified within the framework of another**
 7 **regulation (e.g. Seed legislation)?**

Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, specify	

8

- 9 **5. Has the GM plant been notified under Part B of Directive 2001/18/EC and/or**
 10 **Directive 90/220/EEC?**

Yes <input type="checkbox"/>	No <input type="checkbox"/>
If no, refer to risk analysis data on the basis of the elements of Part B of Directive 2001/18/EC	

11

- 12 **6. Has the GM plant or derived products been previously notified for marketing in**
 13 **the Community under Part C of Directive 2001/18/EC or Regulation (EC)**
 14 **258/97?**

Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, specify	

15

- 16 **7. Has the product been notified in a third country either previously or**
 17 **simultaneously?**

Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, specify	

18

- 19 **8. General description of the product**

a) Name of the recipient or parental plant and the intended function of the genetic modification
b) Types of products planned to be placed on the market according to the authorisation applied for
c) Intended use of the product and types of users

d) Specific instructions and/or recommendations for use, storage and handling, including mandatory restrictions proposed as a condition of the authorisation applied for
e) Any proposed packaging requirements
f) Any proposed labelling requirements in addition to those required by Community law (Annex IV of Directive 2001/18/EC; Regulation 1829/2003 art. 13 and 25)
g) Unique identifier for the GM plant (Regulation (EC) 65/2004; does not apply to applications concerning only food and feed produced from GM plants, or containing ingredients produced from GM plants)
h) If applicable, geographical areas within the EU to which the product is intended to be confined under the terms of the authorisation applied for. Any type of environment to which the product is unsuited

1

2 **9. Measures suggested by the applicant to take in case of unintended release or**
 3 **misuse as well as measures for disposal and treatment**

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4

5 **B. INFORMATION RELATING TO (A) THE RECIPIENT OR (B) (WHERE APPROPRIATE)**
 6 **PARENTAL PLANTS**

7

8 **1. Complete name**

a) Family name
b) Genus
c) Species
d) Subspecies
e) Cultivar/breeding line
f) Common name

9

10 **2 a. Information concerning reproduction**

(i) Mode(s) of reproduction

(ii) Specific factors affecting reproduction
(iii) Generation time

1

2 **2 b. Sexual compatibility with other cultivated or wild plant species**

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3

4 **3. Survivability**

a) Ability to form structures for survival or dormancy
b) Specific factors affecting survivability

5

6 **4. Dissemination**

a) Ways and extent of dissemination
b) Specific factors affecting dissemination

7

8 **5. Geographical distribution and cultivation of the plant, including the distribution**
9 **in Europe of the compatible species**

--

10

11 **6. In the case of plant species not normally grown in the Member State(s),**
12 **description of the natural habitat of the plant, including information on natural**
13 **predators, parasites, competitors and symbionts**

[Empty box]

1

2 **7. Other potential interactions, relevant to the GM plant, of the plant with**
3 **organisms in the ecosystem where it is usually grown, or used elsewhere,**
4 **including information on toxic effects on humans, animals and other**
5 **organisms**

[Empty box]

6

7

8 **C. INFORMATION RELATING TO THE GENETIC MODIFICATION**

9

10 **1. Description of the methods used for the genetic modification**

[Empty box]

11

12 **2. Nature and source of the vector used**

[Empty box]

13

14 **3. Size, source (name) of donor organism(s) and intended function of each**
15 **constituent fragment of the region intended for insertion**

[Empty box]

16

17 **D. INFORMATION RELATING TO THE GM PLANT**

18

19 **1. Description of the trait(s) and characteristics which have been introduced or**
20 **modified**

--

1

2 **2. Information on the sequences actually inserted or deleted**

a) The copy number of all detectable inserts, both complete and partial
b) In case of deletion(s), size and function of the deleted region(s)
c) Chromosomal location(s) of insert(s) (nucleus, chloroplasts, mitochondria, or maintained in a non-integrated form), and methods for its determination
d) The organisation of the inserted genetic material at the insertion site

3

4 **3. Information on the expression of the insert**

a) Information on developmental expression of the insert during the life cycle of the plant
b) Parts of the plant where the insert is expressed

5

6 **4. Information on how the GM plant differs from the recipient plant in**

a) Reproduction
b) Dissemination
c) Survivability
d) Other differences

1

2 **5. Genetic stability of the insert and phenotypic stability of the GM plant**

--

3

4 **6. Any change to the ability of the GM plant to transfer genetic material to other**
5 **organisms**

a) Plant to bacteria gene transfer
b) Plant to plant gene transfer

6

7 **7. Information on any toxic, allergenic or other harmful effects on human or**
8 **animal health arising from the GM food/feed**

9

10 **7.1 Comparative assessment**

Choice of the comparator

11 **7.2 Field trials**

a) number of locations, growing seasons, geographical spreading and replicates
b) the baseline used for consideration of natural variations

12 **7.3 Selection of compounds for analysis**

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13 **7.4 Agronomic traits**

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1 **7.5 Product specification**

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2 **7.6 Effect of the production and processing**

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3 **7.7 Anticipated Intake/extent of use**

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4 **7.8 Toxicology**

7.8.1 Safety evaluation of newly expressed proteins

7.8.2 Testing of new constituents other than proteins

7.8.3 Information on natural food and feed constituents

7.8.4 Testing of the whole GM food/feed

5 **7.9 Allergenicity**

7.9.1 Assessment of allergenicity of the newly expressed protein

7.9.2 Assessment of allergenicity of the whole GM plant or crop

6 **7.10 Nutritional assessment of GM food/feed**

7.10.1 Nutritional assessment of GM food

7.10.2 Nutritional assessment of GM feed

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1 **7.11 Post-market monitoring of GM food/feed**

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2

3 **8. Mechanism of interaction between the GM plant and target organisms (if**
4 **applicable)**

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5

6 **9. Potential changes in the interactions of the GM plant with the biotic**
7 **environment resulting from the genetic modification**

9.1 Persistence and invasiveness
9.2 Selective advantage or disadvantage
9.3 Potential for gene transfer
9.4 Interactions between the GM plant and target organisms
9.5 Interactions of the GM plant with non-target organisms
9.6 Effects on human health
9.7 Effects on animal health
9.8 Effects on biogeochemical processes
9.9 Impacts of the specific cultivation, management and harvesting techniques

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1

2 **10. Potential interactions with the abiotic environment**

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3

4 **11. Environmental monitoring plan** (not if application concerns only food and feed
5 produced from GM plants, or containing ingredients produced from GM plants)

11.1 General (risk assessment, background information)
11.2 Case-specific GM plant monitoring (approach, strategy, method and analysis)
11.3 General surveillance of the impact of the GM plant (approach, strategy, method and analysis)
11.4 Reporting the results of monitoring

6

7 **12. Detection and event-specific identification techniques for the GM plant**

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8

9 **E. INFORMATION RELATING TO PREVIOUS RELEASES OF THE GM PLANT AND/OR**
10 **DERIVED PRODUCTS**

11

12 **1. History of previous releases of the GM plant notified under Part B of the**
13 **Directive 2001/18/EC and under Part B of Directive 90/220/EEC by the same**
14 **notifier**

a) Notification number

b) Conclusions of post-release monitoring
c) Results of the release in respect to any risk to human health and the environment (submitted to the Competent Authority according to Article 10 of Directive 2001/18/EC)

1

2 **2. History of previous releases of the GM plant carried out outside the Community**
 3 **by the same notifier**

a) Release country
b) Authority overseeing the release
c) Release site
d) Aim of the release
e) Duration of the release
f) Aim of post-releases monitoring
g) Duration of post-releases monitoring
h) Conclusions of post-release monitoring
i) Results of the release in respect to any risk to human health and the environment

4

5 **3. Links (some of these links may be accessible only to the competent authorities**
 6 **of the Member States, to the Commission and to EFSA):**

a) Status/process of approval
b) Assessment Report of the Competent Authority (Directive 2001/18/EC)
c) EFSA opinion
d) Commission Register (Commission Decision 2004/204/EC¹⁴)
e) Molecular Register of the Community Reference Laboratory/Joint Research Centre
f) Biosafety Clearing-House (Council Decision 2002/628/EC¹⁵)
g) Summary Notification Information Format (SNIF) (Council Decision 2002/812/EC)

1

2

¹⁴ Commission Decision of 23 February 2004 laying down detailed arrangements for the operation of the registers for recording information on genetic modifications in GMOs, provided for in Directive 2001/18/EC of the European Parliament and of the Council. Official Journal of the European Communities L 65: 20 – 22.

¹⁵ Council Decision of 25 June 2002 concerning the conclusion, on behalf of the European Community, of the Cartagena Protocol on Biosafety. Official Journal of the European Communities L 201: 48 – 49.