参考資料２

ＥＵ　遺伝子組換え微生物及びそれを利用した食品・飼料のリスク評価のためのガイダンスドキュメント（抜粋）

GUIDANCE DOCUMENT OF THE SCIENTIFIC PANEL ON GENETICALLY MODIFIED ORGANISMS FOR THE RISK ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS AND THEIR DERIVED PRODUCTS INTENDED FOR FOOD AND FEED USE

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（EFSA 欧州食品安全機関ホームページから）

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GUIDANCE DOCUMENT OF THE SCIENTIFIC PANEL ON GENETICALLY MODIFIED ORGANISMS FOR THE RISK ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS AND THEIR DERIVED PRODUCTS INTENDED FOR FOOD AND FEED USE

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About EFSA

The European Food Safety Authority (EFSA) was established and funded by the European Community as an independent agency in 2002 following a series of food scares that caused the European public to voice concerns about food safety and the ability of regulatory authorities to fully protect consumers.

In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides objective scientific advice on all matters with a direct or indirect impact on food and feed safety, including animal health and welfare and plant protection. EFSA is also consulted on nutrition in relation to Community legislation.
EFSA's work falls into two areas: risk assessment and risk communication. In particular, EFSA's risk assessments provide risk managers (EU institutions with political accountability, *i.e.* the European Commission, European Parliament and Council) with a sound scientific basis for defining policy-driven legislative or regulatory measures required to ensure a high level of consumer protection with regard to food and feed safety.

EFSA communicates to the public in an open and transparent way on all matters within its remit.

Collection and analysis of scientific data, identification of emerging risks and scientific support to the Commission, particularly in case of a food crisis, are also part of EFSA's mandate, as laid down in the founding Regulation (EC) No 178/2002 of 28 January 2002.

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Summary

The Scientific Panel on Genetically Modified Organisms (GMO Panel) adopted its guidance document for the risk assessment of genetically modified microorganisms (GMMs) and their derived products intended for food and feed use on 17 May 2006. The European Food Safety Authority (EFSA) and the GMO Panel have published the guidance on the EFSA web site for public consultation prior to the final adoption of this document.

This document provides guidance for the scientific risk assessment of genetically modified microorganisms (GMMs) and their derived products intended for food and feed use. In particular, it provides detailed guidance to assist in the preparation and presentation of applications to market GMMs and their products for food and/or feed use, according to Regulation (EC) 1829/2003 (EC, 2003a). In addition, this document provides guidance for the risk assessment of food and feed produced using GMMs, irrespective of whether they fall in the scope of Regulation (EC) 1829/2003 or not. Issues related to risk management of GMOs (traceability, labelling) are outside the scope of the guidance document.

Guidance for the preparation of applications is given throughout the different chapters of the document. The first chapter of the guidance document clarifies the scope of the document. Chapter II describes the overall risk assessment strategy and the regulatory background for the risk assessment of GMOs, GM food and feed at Community level. Chapter III describes the issues to be considered when carrying out a comprehensive risk characterisation. These include general information, information relating to the recipient, the donor(s), the genetic modification and the final GMM, as well as information relating to the GM product. It also includes information on modification of the genetic traits or phenotypic characteristics of the GMM and evaluation of food/feed safety aspects of the GMM and/or derived products. Data on composition, toxicity, allergenicity, nutritional value and environmental impact provide, on a case-by-case basis, the cornerstones of the risk assessment process. The characterisation of risk may give rise to the need for further specific activities including post-market monitoring of the GM food/feed and/or for the environmental monitoring of GM microorganism. A table (Table 1.) summarising the risk assessment requirements for the different GMM groups is also provided. Finally, Chapter IV summarises the overall risk characterisation process.

Guidance for the presentation of applications can be found in the Annexes to the guidance document. These include details on the key component parts of the application, on the format of technical dossiers and on the summary of applications. There are also specifications on the submission of samples of GM microorganisms and derived product to DG Joint Research Centre.

Key words: GMOs, GM microorganisms, GM food, GM feed, guidance, applications, Regulation (EC) 1829/2003, Directive 2001/18/EC, food safety, feed safety, environment.

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Foreword

Genetic modification, genetic engineering or recombinant-DNA technology, first applied in the 1970's, is one of the newest methods to introduce novel traits to microorganisms, plants and animals. Unlike other methods, the application of this technology is strictly regulated. Before any genetically modified organism (GMO) or derived product can be placed on the EU market, it has to pass an approval system in which the safety for humans, animals and the environment is thoroughly assessed. In line with the provisions of Regulation (EC) 1829/2003 on genetically modified food and feed, which applies from April 18, 2004, the Commission has asked the European Food Safety Authority (EFSA) to publish detailed guidance to assist the applicant in the preparation and presentation of the application for the authorisation of genetically modified (GM) food and/or feed. A first guidance document for the risk assessment of genetically modified plants and derived food and feed has already been published by EFSA (EFSA, 2004b).

The present document provides detailed guidance for the assessment of genetically modified microorganisms (GM microorganisms) and their derived products intended for food and feed use. This guidance complements, but does not replace, other requirements, as set out in specific legislation, that a product has to fulfil in order to be approved for the European market.

This document was compiled by the Scientific Panel on Genetically Modified Organisms (GMO Panel) of EFSA, consisting of the following members:
Christer Andersson, Detlef Bartsch, Hans-Joerg Buhk, Howard Davies, Marc De Loose, Michael Gasson, Niels Hendriksen, John Heritage, Sirpa Kärenlampi, Ilona Kryspin-Sørensen, Harry Kuiper, Marco Nuti, Fergal O'Gara, Pere Puigdomenech, George Sakellaris, Joachim Schiemann, Willem Seinen, Angela Sessitsch, Jeremy Sweet, Jan Dick van Elsas and Jean-Michel Wal.

The following *ad hoc* experts also contributed:

Bevan Moseley, Ingolf F. Nes and Paul Ross.

The draft document was published on the EFSA website in July 2005 for a two and a half month period of public consultation. The GMO Panel considered all comments relating to the risk assessment of GMOs before preparing its revised guidance document. The GMO Panel did not consider issues related to risk management of GMOs (traceability, labelling). Political and socio-economic issues are also outside the remit of the Panel. The guidance document was adopted by the GMO Panel on 17 May 2006. The GMO Panel will regularly review this guidance in the light of experience gained, technological progress and scientific developments. By establishing a harmonised framework for risk assessment, this document should provide useful guidance both for applicants and risk assessors.

Terms of reference

In accordance with Articles 5(8) and 17(8) of the Regulation (EC) 1829/2003 (EC, 2003a) on genetically modified food and feed, in a letter dated 27 October 2003, the European Commission has requested the European Food Safety Authority (EFSA), to publish detailed guidance to assist applicants[2] in the preparation and presentation of applications for the authorisation of GM food and/or feed (ref. SANCO/D4/KM/cw/D/440551(2003)).

A guidance document for the risk assessment of GM plants and derived food and feed has already been published by EFSA (EFSA, 2004b).

In addition, the Commission requested EFSA, in a letter dated 1 February 2005, to provide guidance on the scientific information necessary for the risk assessment for food and feed produced using GMMs, irrespective of whether they fall in the scope of Regulation (EC) 1829/2003 or not (ref. SANCO/D4/KN/cw/D/440010 (2005)). The guidance should cover both food/feed and food/feed ingredients produced using GMMs as well as substances such as additives, vitamins and flavourings produced by GMMs.

Mandate of EFSA and the GMO Panel

Consistent with Regulation (EC) 178/2002 (EC, 2002c), EFSA is mandated to provide scientific advice and scientific technical support for the Community's legislation and policies in all fields that have a direct or indirect impact on food and feed safety. EFSA is required to provide independent information on all matters within these fields and communicate on risks. EFSA shall contribute to a high level of protection of human life and health. It shall take account of animal health and welfare and also plant health and the environment. This responsibility is placed in the context of the operation of the internal market.

The Scientific Panel on Genetically Modified Organisms, hereafter referred to as the GMO Panel, deals with questions on GMOs as defined in Directive 2001/18/EC (EC, 2001a), including plants, microorganisms and animals, relating to their deliberate release into the environment and their use in genetically modified food and feed including their derived products (EC, 2001a; EC, 2003a; EFSA, 2002).

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

I. INTRODUCTION

1. Scope of the document

This document provides guidance for the scientific risk assessment of genetically modified microorganisms (GMMs)[3] and their derived products intended for food and feed use. In particular, it provides detailed guidance to assist in the preparation and presentation of applications to market GMMs and their products for food and/or feed use, according to Articles 5(8) and 17(8) of Regulation (EC) 1829/2003 (EC, 2003a). In addition, this document provides guidance for the risk assessment of food and feed produced using GMMs, irrespective of whether they fall in the scope of Regulation (EC) 1829/2003 or not.

Not all requirements of the guidance document may be applicable for all products.

For the purpose of this guidance document, the types of genetically modified microorganisms (GMMs) covered include both prokaryotes and eukaryotes[4]. This document does not cover the use of tissue cultures of plant or animal cells[5], nor does it cover issues related to risk management (traceability, labelling, etc.). Socioeconomic and ethical issues are also outside the scope of this guidance. This guidance does not cover the contained use of GMMs (Directive 90/219 EEC; EC, 1990, Directive 98/81/EC; EC, 1998), nor does the guidance cover the deliberate release into the environment of GMMs for any other purpose than for the placing on the market (Directive 2001/18/EC). This exclusion covers releases for experimental purposes and for research; such releases fall under Part B of Directive 2001/18/EC. A separate guidance document has been produced for the risk assessment of genetically modified plants and derived food and feed (EFSA, 2004b).

This document provides guidance on:

1) the drawing up of Annex IIIA of the Directive 2001/18/EC (EC, 2001a) on the deliberate release into the environment of genetically modified organisms (GMOs),

2) the preparation of an environmental risk assessment as stated in Annex II paragraph D.1, and

3) the establishment of an environmental monitoring plan according to Annex VII of that Directive.

This guidance is without prejudice to the supplementary guidance notes 2002/623/EC (EC, 2002a) and 2002/811/EC (EC, 2002b) established within the framework of Directive 2001/18/EC.

The document addresses the requirements of Regulation (EC) 1829/2003 and is structured essentially according to the requirements set out in Articles 5(5) and 17(5) of the Regulation (EC) 1829/2003, *i.e.* taking into account Annexes IIIA, IID1 and VII of Directive 2001/18/EC. This guidance also takes into account all relevant parts of the Directives 90/219 EEC and 98/81/EC on the contained use of GMMs (EC, 1990; EC, 1998).

3 - Genetically modified organisms are defined in Directive 2001/18 (EC) (EC, 2001a) as organisms in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.
4 - Prokaryotic microorganisms include archaea and eubacteria. Eukaryotic microorganisms include yeasts, filamentous fungi, protozoa and microalgae (Heritage et al., 1996).
5 - Directive 98/81/EC defines microorganisms as "any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, animal and plant cells in culture".

Food additives (Directive 89/107/EEC; EC, 1989), flavourings (Directive 88/388/EEC; EC, 1988) and feed additives (Regulation (EC) No 1831/2003; EC, 2003b) and certain products used in animal nutrition (Directive 82/471/EEC; EC, 1982) containing, consisting of, or produced from GMMs, fall under Regulation 1829/2003 and therefore also fall within the scope of this guidance document.
As regards the use of GMMs as plant protection products, bioremediation agents, biofertilisers or phytostimulators, these applications will fall into the wider scope of the Directive 2001/18/EC, and further guidance in this area will be developed. Although this document focuses on GMMs and derived food and feed, the principles of risk assessment of GMMs intended for other applications when products are likely to enter the food or feed chains, is unlikely to differ significantly with respect to their presence in food or feed.

In general, a risk assessment of the GMM includes the nature of the genetic modification and the presence of the GMM and its derivatives, including DNA, in the final food or feed product. GMMs used for food and feed purpose can be differentiated on the basis of their use in i) GMMs deliberately released into the environment, according to Directive 2001/18/EC, and used as food or feed or contained in food or feed; ii) GMMs deliberately released into the environment, according to Directive 2001/18/EC, and used for the production of food or feed; iii) GMMs used for the production of food or feed under 'contained use' according to conditions defined in Directive 90/219/EEC (EC, 1990).

For uses as in i) and ii), a full risk assessment according to Regulation (EC) 1829/2003 in combination with Directive 2001/18/EC is required and is covered by this guidance. With regard to uses as in iii), *i.e.* GMMs used for food or feed production under containment, this guidance covers the assessment of the final product to be used as food or feed for the placing in the market, while taking into account the characteristics of the GMM, but does not cover the production process as such that is performed under containment according to Directive 90/219/EEC.

In cases of GM food or feed produced under containment the applicant should submit not only the information relevant to Regulation (EC) 1829/2003 but should also make available the risk assessment undertaken in compliance with Directive 90/219/EEC and the implemented national legislation, thereby covering the assessment of the GMM itself and taking account of the genetic modification and the gene products derived therefrom. There may be circumstances in which the DNA as such introduced into a GMM gives cause for concern and in this case it needs to be subjected to risk assessment. Data on the absence of DNA need to be very robust in such instances. Indeed, given that no method will give absolute proof that DNA is absent, there is a case to undertake a specific safety assessment based on the minimal level of DNA that might be detected.

II. THE RISK ASSESSMENT STRATEGY

The risk assessment strategy is the driving force and justification for the information requirements.

1. Risk assessment

Risk assessment is "a process of evaluation including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect(s)/event(s) occurring to humans or the environment following exposure under defined conditions to a risk source(s)" (EC, 2000a). A risk assessment comprises hazard identification, hazard characterisation, exposure assessment and risk characterisation. A hazard is the potential of an identified source to cause an adverse effect.

The sequential steps in risk assessment of GMOs identify characteristics that may cause adverse effects, evaluate their potential consequences, assess the likelihood of occurrence and estimate the risk posed by each identified characteristic of the GMOs.

1.1. Hazard identification

In hazard identification, potential adverse effects (hazards) are identified on the basis of knowledge about the characteristics of the recipient microorganism, knowledge about the function that the introduced traits have in the donor organism, knowledge about the way the newly acquired traits interact with the physiology of the recipient microorganism, and the anticipated interaction of the GMO with the receiving environment.

1.2. Hazard characterisation

Hazard characterisation involves an assessment of the consequences of exposure to a hazard. It involves the qualitative or, whenever possible, quantitative description of the nature of the hazard and their respective attendant uncertainties. It may also be described as determining the potential severity of adverse effects following exposure to a hazard.

1.3. Exposure assessment

Exposure assessment determines the probability and the likely levels of exposure in the human population.

1.4. Risk characterisation

Risk characterisation is the qualitative or, whenever possible, quantitative estimate of the probability of occurrence and severity of adverse effect(s) or event(s) in a given population under defined conditions based on hazard identification, hazard characterisation and exposure assessment (SSC, 2000), including the attendant uncertainties. Chapter IV describes how this step should be carried out and gives examples of issues to be addressed.

"Qualified Presumption of Safety" (QPS)

In a recent Opinion (EFSA, 2005), the Scientific Committee of EFSA took steps towards the establishment of a generic approach to the safety assessment by EFSA of microorganisms used in food and feed and the production of food or feed additives.

This proposes the introduction of the concept of the "Qualified Presumption of Safety" (QPS), which is intended to be applied to selected groups of microorganisms. This opinion specifically excludes microorganisms developed using recombinant DNA technology for strain improvement, since these are covered by separate existing legislation (Regulation (EC) 1829/2003). The EFSA Scientific Colloquium on QPS (EFSA, 2004c) addressed the status of GMMs, with particular reference to self-cloning. It was concluded that in such cases, there appears to be no scientific basis for the exclusion of self-cloned GMMs from a QPS risk assessment in the future. A list of QPS organisms is being established and will increase in time.

2. Risk assessment of the GMMs and derived products for human and animal health

GMMs and their products intended for human and animal consumption form a broad spectrum ranging from a single compound used in food or feed at one end to pure cultures of viable GMMs at the other end. Amino acids or vitamins that have been purified by crystallisation would represent examples at one end of this spectrum and cultures of probiotic microorganisms or dairy starters at the other extreme. In the middle of the spectrum lie both products of genetically modified microorganisms, such as dairy products, in which the viable GMMs persist and products in which it is not expected the presence of viable GMMs but where traces of the transgenic event may persist, for example crude enzyme preparations produced by the lysis of microbial cells. Three groups of GMMs or derived food and feed may be distinguished:

Group 1: Single compounds or defined mixtures of compounds derived from GMMs (*e.g.* amino acids, vitamins, pure enzymes);

Group 2: Complex products derived from GMMs but not containing viable GMMs nor unit length of any cloned (foreign) open reading frames (*e.g.* lysed cell extracts, some feed enzymes, wine, some beers, etc.);

Group 3: GMMs and products containing viable GMMs or genetically intact cloned (foreign) DNA (*e.g.* live or heat killed starter cultures and probiotic cultures, some beers, cheeses, yoghurts, etc.).

Foods and feeds consisting of or containing single compounds or defined mixtures obtained from a GMM require a different assessment from foods and feeds containing either viable or non-viable GMMs. The level of scrutiny and the focus of the assessment will also differ for food and feed consisting of or containing single compounds or defined mixtures of chemically purified and defined compounds derived from GMMs compared with other food and feed produced using GMMs in which no purification process has been carried out but which do not contain viable GMM cells. The most intense scrutiny is reserved for products containing viable GMMs, whether as a component of a food or feed or as a pure culture used, for example, as a probiotic or as starter culture in the food industry (Table 1). Only limited information focusing on the production system is required to perform a risk assessment on single compounds. When GMMs are not recoverable from a product but where purification of the product is limited, information required for risk assessment will be more extensive than for single products. It will be necessary to understand the processes by which the GMM

6 - *Self-cloning, as defined by Directive 98/81/EC (EC, 1998), consists in the removal of nucleic acid sequences from a cell of an organism which may or may not be followed by reinsertion of all or part of that nucleic acid (or a synthetic equivalent) with or without prior enzymic or mechanical steps, into cells of the same species or into cells of phylogenetically closely related species which can exchange genetic material by natural physiological processes where the resulting microorganism is unlikely to cause disease to humans, animals or plants.*

has been inactivated in the product and the degree to which traces of the transgenic event may be detected in the product. When live GMMs persist in a product, the most extensive information will be required to permit a scientific risk assessment.

In the case of food or feed consisting of or containing GMMs obtained by self-cloning[6], applicants should address all of the requirements needed for the risk assessment of GMMs and derived food or feed as described in this document. A restricted information set might be sufficient for risk assessment when food and feed are derived from self-cloned GMMs but not containing viable GMMs. In such cases, however, the assessment should be performed on a case-by-case basis. In cases in which self-cloning has been performed using different strains of the same or closely related species, information on the history of use and on the safety of the species should be provided. Species that are recognised to have strains that are pathogenic should be evaluated for this trait.

The level of scrutiny of the risk assessment depends on the history of use of the recipient and donor strains (depending on the sequences to be cloned) as well as of the modification itself. The risk assessment of GMMs will be simplified when the qualified presumption of safety (QPS) of microorganisms in the food and feed chains has been introduced. In particular, the risk assessment will need only to focus on relevant information not available in the QPS qualification in cases when the parental or recipient and the donor strains have been granted the status of QPS or if they belong to a taxonomic group with QPS status for the same end-use.

3. Comparative approach

The risk assessment strategy for GMMs seeks to deploy appropriate methods and approaches to focus not only on intended modifications, but also on the potential unintended (unexpected) outcomes of the genetic modification process itself. The strategy adopted in this guidance document is based on comparison of the GMM or GM food or feed with its conventional counterpart. The comparative approach is based on the concept that a conventional counterpart with a history of safe use can serve as a baseline for the environmental and food and feed risk assessment of a particular GMM. For this, the concepts of “familiarity” and “substantial equivalence” were developed by the OECD (OECD, 1993a & OECD, 1993b) and further elaborated by ILSI (ILSI, 1999) and WHO/FAO (WHO/FAO, 2001b). The purpose of the risk assessment is to identify new or altered hazards relative to the conventional counterpart. The comparison should be considered as the first step of the risk assessment. In the second step, the environmental and food or feed safety or nutritional impact of the identified differences, whether intended or unintended, should be assessed.

Concepts of “familiarity” and “body of knowledge”

The concept of “familiarity” refers to the fact that most GMMs to be used for food or feed purposes belong to well-characterised microbial species. This “familiarity” allows the risk assessor to draw on previous knowledge and experience with the introduction of similar microorganisms into food and the environment. “Familiarity” will also derive from the knowledge and experience available from the risk/safety analysis conducted prior to the scale-up of the microorganism in a particular environment (OECD, 1993a). The concept of “history of safe use” was described in detail by ILSI (ILSI, 1999) and was discussed further at the EFSA Scientific Colloquium on QPS (EFSA, 2004c), when the term “body of knowledge” was proposed as a replacement for “familiarity”. Neither of these concepts as such represents a reasonable certainty of no harm. It is the nature

and content of the body of knowledge that may or may not lead to such a conclusion. If the parental microorganism has been granted the proposed status of QPS for the same production conditions and final use as it is intended in the application, all the information on the history of safe use has already been assessed.

Concept of substantial equivalence

The concept of "substantial equivalence" is based on the rationale that an existing microorganism with a history of safe use as food or feed can serve as a comparator when assessing the safety of GM food and feed (OECD, 1993b). Application of this concept, also referred to as comparative risk assessment (Kok and Kuiper, 2003), serves to identify similarities and, in particular, differences between the GMM or derived food or feed and its conventional counterpart. The differences should then be assessed for their toxicological and/or nutritional impact on humans and animals. In some cases, a GM strain that has already been through a risk assessment and been approved for marketing in the EU could serve as the comparator if it has been shown to have a good safety record.

The application of the concept of substantial equivalence is not a risk assessment per se, but it structures the risk assessment process. The first step in the risk assessment is thus the comparative analysis of the molecular characteristics of the microorganism including, when relevant, its metabolic products. The comparisons should be made between microorganisms grown or used under the same conditions, if possible. The outcome of the comparative analysis will give further guidance to the second part of the risk assessment procedure, which may include specific toxicological and, when relevant, nutritional testing. The outcome should be the comparative safety of the GM food or feed and the traditional counterpart. When no appropriate comparator can be identified, a more straightforward risk and nutritional assessment of the GM food or feed should be carried out. This would be the case, for instance, when a trait or traits are introduced into a microorganism with the intention of significantly modifying the composition of the food or feed.

Intended and unintended effects

Intended effects are those that are targeted to occur due to the introduction or inactivation of gene(s) or DNA sequences, and that fulfil the objectives of the genetic modification. Intended alterations in the composition of a GMM compared with the parent may be identified by measurements of single compounds like newly expressed proteins, and the intended impact on metabolic flux (a targeted approach).

Unintended effects are consistent phenotypical differences between the GMM and its otherwise isogenic comparator that goes beyond the primary expected effect(s) of introducing or inactivating the target gene(s). Unintended effects may be predicted or explained in terms of current knowledge of microbiology and of the integration of metabolic pathways. Unintended effect(s) could also be due to genetic rearrangements. Insertion of new DNA sequences may lead to changes in the expression of particular genes in the recipient genome, metabolic perturbations and pleiotropic effects. It may also result in the synthesis of new fusion proteins. A starting point in the identification of potential unintended effects is the sequence analysis of regions flanking the insertion site to establish whether the insertion has occurred within, or in the proximity of, an endogenous gene. Sequence analysis should extend to identifying whether the introduced DNA interrupts a transcriptional unit, *e.g.* a polycistronic operon as well as whether it causes the synthesis of a fusion protein. In addition, pulsed field gel electrophoresis (PFGE) could be employed to generate restricted genomic DNA fingerprints to assess whether any gross genomic change has occurred. In microorganisms in which the genome sequence is available,

microarray technology and proteomics may be used to identify significant alterations in gene order and gene expression. A comparative and targeted analysis should be carried out of single compounds in the GMM and its conventional counterpart, which represent components of relevant metabolic and physiological pathways in the organism. If the GMM comprises a significant part of the diet, or leads to changes of intake of such GM food to certain sub-populations (children, the elderly, etc.) these components should include macronutrients, micronutrients and primary and secondary metabolites as well as known anti-nutrients but also whole GMMs (probiotics, starter cultures, etc.). The presence of known toxins, when relevant, should be analysed. Statistically significant differences between the GMM and its comparator that are not due to the intended modification may indicate the occurrence of unintended effects. These should be assessed specifically with respect to their safety and, when relevant, nutritional impact.

Considering the high level of gene mobility and the plasticity of microbial genomes, particular attention should be paid to the evaluation of differences in gene expression between the GMM and its conventional counterpart. This is particularly important when the genetic modification of the GMM is located on a multi-copy plasmid. In addition, the presence of naturally occurring changes or rearrangements within the genome of closely related strains in natural microbial populations should be considered as this provides a baseline of natural changes. Thus, scientific evidences should be provided in order to attribute the identified differences to the genetic modification event.

4. Environmental risk assessment and monitoring

The risk of adverse effects on the environment caused by a GMM depends on whether the GMM has access to and can survive in the natural environment. Therefore, an assessment of the ability of the GMM to survive and persist and spread in the environment is always needed. In this context, comparison with a conventional counterpart under the same conditions of use should be considered, when applicable. Further, the receiving environments for the GMM need to be identified. If material containing DNA from the GMM may gain access to the open environment, the possibility of gene transfer and selection of the transgene sequences should be assessed and the consequences evaluated.

For GMMs that have the potential to survive, persist and spread in the environment to which they may gain access it is necessary to identify and assess effects linked to the genetic modification that may result in adverse effects in any receiving environment on a case-by-case basis. The following points should be addressed when appropriate:

- the potential for survival and persistence in the receiving environment and any selective advantage that may be offered: in the case of selective advantage, its nature should be identified along with any potential for negative effects;
- the potential for gene transfer;
- the potential for negative effects or consequences based on interactions with indigenous microorganisms;
- possible effects on humans, animals and plants;
- possible effects or (non-reversible) perturbations on biogeochemical processes.

These points may be assessed by a combination of laboratory studies, micro- and mesocosm experiments and small-scale field releases to identify hazards and to quantify actual levels of exposure. However, based on the nature of the microorganisms in

question, a case-by-case approach should be followed. For example, for many starter and intestinal and/or probiotic organisms it could be envisaged that an exhaustive environmental risk assessment may not be relevant, given that these microorganisms may not be expected to survive or persist in external environments and in many cases would have limited direct contact with the environment. If, however, the genetic modification makes survival and persistence more likely, then a more extensive environmental risk assessment must be undertaken.

It is recognised that an environmental risk assessment is only as good as the state of scientific knowledge at the time it is conducted. Under current EU legislation, environmental risk assessment is required to identify uncertainties or risks beyond current knowledge and the limited scope of the environmental risk assessment. These include specific factors such as the impact of large-scale exposure of different environments, of exposure over long periods and cumulative long-term effects. Legislation requires that plans for monitoring for such effects are presented in the application.

The scientific knowledge and experiences gained from monitoring will in turn inform the risk assessment process. Thus, the results of monitoring provide opportunities to update the risk assessment continually in the light of any new knowledge.

5. The framework for risk assessment of genetically modified microorganisms and derived food and feed

The risk assessment of a GMM or a food or feed derived from a GMM consists of a step-by-step process that addresses different requirements described in Chapter III and summarized in Table 1 of this guidance document.

6. General recommendations

Whenever possible, applicants are encouraged to develop those GMMs in which only DNA essential to the modification of the trait in question is transferred to the microorganism for commercial release (ACRE, 2002; SSC, 2003b).

The choice of a particular marker gene should be given careful consideration. Particular attention should be given to the use of marker genes (EFSA, 2004a) that confer resistance to therapeutically relevant groups of antibiotics and, whenever possible, such markers should be avoided altogether.

At an early stage in the development of a GMM, some strain improvement considerations and strategies analogous to those suggested for genetically modified crops (ACRE, 2001) are relevant. Adoption of these strategies could help reduce potential risks and may avoid some unidentified risks in the environment. The overall aim is to reduce environmental exposure and the potential risks associated with transgenes and their products. Three principle approaches can be considered useful to achieve this:

- avoid or minimise the inclusion of superfluous transgenes or sequences;
- avoid or minimise superfluous expression of the transgene;
- avoid or minimise the unnecessary dispersal of transgenes into the environment.

7 - http://www.entransfood.com/RTDprojects/GMOCARE.
8 - http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/novelfoodsresearch/g02programme/

7. Forthcoming developments

To increase the chances of detecting the potential for unintended effects due to the genetic modification of organisms, profiling technologies such as transcriptomics, proteomics and metabolomics, extend the breadth of comparative analyses (Kuiper *et al.*, 2003; ILSI, 2004). The utility and applicability of these technologies in the detection of altered gene and protein expression and metabolite composition in GM crops and their derived foods has been under scrutiny in specific research projects funded, for example, by EU FP5 (GMOCARE project[7]) and the UK Food Standards Agency (G02 research programme[8]). These technologies may also be helpful in the detection of intended and unintended effects in GMMs. Since many complete genome sequences are already available in databases, these tools may be more easily applied to microorganisms than they are currently to crop plants. The applicability of metabolomic techniques, such as gas chromatography coupled to mass spectrometry (GC-MS) and off-line liquid chromatography (HPLC) coupled to nuclear magnetic resonance (NMR), for the simultaneous analysis of a wide variety of metabolites in GMOs and their conventional counterparts has been demonstrated. These non-targeted approaches may be of particular relevance for GMMs with specific metabolic pathways modified, *e.g.* those leading to enhanced nutritional profiles, obtained through the insertion of single or multiple genes.

Further exploration of profiling approaches is needed with respect to the evaluation of specificity, sensitivity and reproducibility. Profiling methods are not aimed at replacing conventional analyses but may be useful to confirm and complete other data. It must be appreciated however that many "omic" profiling technologies are not yet fully developed; since they are interfaced with the physiological status of cells, this may limit their applicability to certain GMMs. Thus, application of these tools is not a pre-requisite for the risk assessment of GMMs.
Nevertheless, the development of appropriate robust profiling technologies with particular emphasis on achieving harmonised and validated conditions for application together with the availability of appropriate functional databases for comparative analysis is strongly recommended.

8. Regulatory background for the risk assessment of GMOs, GM food and GM feed at Community level

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

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

General food law (Regulation (EC) 178/2002)

Regulation (EC) 178/2002 (EC, 2002c) lays down the general principles and requirements of food law, procedures in food safety and establishes the European Food Safety Authority (EFSA) and its tasks.

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

According to Regulation (EC) 1829/2003 (EC, 2003a), GM food and feed may only be authorised for placing on the market after a scientific assessment of any risks that they might present for human and animal health and, as the case may be, for the environment.

An application should be accompanied by the particulars specified by Articles 5(3) and (5) and/or Article 17(3) and (5) of the Regulation for GM food and feed, respectively. The European Commission has established implementing rules for the application of these Articles, including rules concerning the preparation and the presentation of the application (Regulation (EC) 641/2004; EC, 2004b).
EFSA uses the GMO EFSA-net to make the application available to the Member States and the Commission and makes the summary of the application available to the public.

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

The principles regulating the deliberate release of GMOs into the environment are laid down in Directive 2001/18/EC (EC, 2001a). Part C of the Directive deals with placing on the market of GMOs as, or in, products.

Annex IIIA of the Directive details the required information on which to base the risk assessment for organisms other than higher plants, *e.g.* GMMs. The principles for the environmental risk assessment, including aspects of human and animal health, are laid down in Annex II of the Directive. Several supporting documents have been prepared to assist the applicant. Commission Decision 2002/623/EC (EC, 2002a) establishes guidance notes on the objective, elements, general principles and methodology of the environmental risk assessment referred to in Annex II to Directive 2001/18/EC. Council Decision 2002/811/EC (EC, 2002b) establishes guidance notes supplementing Annex VII to the Directive, describing the objectives and general principles to be followed to design the environmental monitoring plan. The Directive also introduces an obligation to propose a monitoring plan in order to identify and trace any direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of GMOs as, or in, products after they have been placed on the market.
Council Decision 2002/812/EC (EC, 2002e) establishes the summary notification information format (SNIF).

Contained use of genetically modified microorganisms (Directive 98/81/EC)

The contained use of genetically modified microorganisms is regulated by Directive 90/219/EEC (EC, 1990), as amended by Directive 98/81/EC (EC, 1998).

Additives for use in animal nutrition (Regulation (EC) No 1831/2003)

Placing on the market of feed additives is authorised under Regulation (EC) 1831/2003 on additives for use in animal nutrition (EC, 2003b). In addition, feed additives containing, consisting of, or produced from GMOs fall within the scope of Regulation (EC) 1829/2003.

E. SUMMARY OF THE RISK ASSESSMENT REQUIREMENTS

A summary of the information required of applications for the placing of GMMs and their derived products intended for food and feed use on the market is provided in Table 1.

This table, based on the approach described in Chapter II, 2 and in Figure 1, contains the main items required to the risk assessment of GMMs and derived food and feed with cross-references to the text. It provides a simple and immediate list of the requirements for an application. However, the applicant should always refer to the main text of this guidance to address the requirements for the submission of an application in sufficient detail.

Table 1.

	Group 1	Group 2	Group 3	Chapter, paragraph
Characteristics of the recipient or parental microorganism				III, B, 1
1. Identity	X[a]	X[a]	X[a]	III, B, 1.1
2. Taxonomy	X[a]	X[a]	X[a]	III, B, 1.2
3. Other names	X[a]	X[a]	X[a]	III, B, 1.3
4. Phenotypic and genetic markers		X[a]	X[a]	III, B, 1.4
5. Degree of relatedness between recipient and donor(s)		X[b]	X[b]	III, B, 1.5
6. Description of identification and detection techniques		X[a]	X[a]	III, B, 1.6
7. Sensitivity, reliability and specificity of the detection techniques		X[a]	X[a]	III, B, 1.7
8. Source and natural habitat			X[a]	III, B, 1.8
9. Organisms with which transfer of genetic material is known to occur		X	X	III, B, 1.9
10. Information on the genetic stability		X	X	III, B, 1.10
11. Pathogenicity, ecological and physiological traits		X[a]	X[a]	III, B, 1.11

(a) Information not required if proposed QPS status is authorised
(b) Information not required in case of self-cloning within the same strain

	Group 1	Group 2	Group 3	Chapter, paragraph
12. Information on indigenous mobile genetic elements	X[a]	X[a]	X[a]	III, B, 1.12
13. Description of its history of use		X	X	III, B, 1.13
14. History of previous genetic modifications	X	X	X	III, B, 1.14

	Group 1	Group 2	Group 3	Chapter, paragraph
Characteristics of the donor organism(s) [a, b]				III, B, 2
1. Identity	X	X	X	III, B, 2.1
2. Taxonomy	X	X	X	III, B, 2.2
3. Other names	X	X	X	III, B, 2.3
4. Phenotypic and genetic markers		X	X	III, B, 2.4
5. Description of identification and detection techniques		X	X	III, B, 2.5
6. Sensitivity, reliability and specificity of the detection techniques		X	X	III, B, 2.6
7. Source and habitat of the organism			X	III, B, 2.7
8. Pathogenicity traits		X	X	III, B, 2.8
9. History of use	X	X	X	III, B, 2.9

(a) Information not required if proposed QPS status is authorised
(b) Information not required in case of self-cloning within the same strain

	Group 1	Group 2	Group 3	Chapter, paragraph
Description of the genetic modification process				III, B, 3
1. Characteristics of the vector		X	X	III, B, 3.1
2. Information relating to the genetic modification	X	X	X	III, B, 3.2

	Group 1	Group 2	Group 3	Chapter, paragraph
Identification of the conventional counterpart microorganism and its characteristics			X	III, B, 4

	Group 1	Group 2	Group 3	Chapter, paragraph
Information relating to the GMM and comparison of the GMM with its conventional counterpart				III, B, 5
1. Description of the genetic trait(s) or phenotypic characteristics and any new trait which can be expressed or no longer expressed	X	X	X	III, B, 5.1
2. Structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified microorganism	X	X	X	III, B, 5.2
3. Stability of the microorganism in terms of genetic traits		X	X	III, B, 5.3
4. Rate and level of expression of the new genetic material			X	III, B, 5.4

	Group 1	Group 2	Group 3	Chapter, paragraph
5. Description of identification and detection techniques	X	X	X	III, B, 5.5
6. Information on the ability to transfer genetic material to other organisms		X	X	III, B, 5.6
7. Information on the interaction of the GMM with other organisms			X	III, B, 5.7
8. History of previous releases or uses of the GMM	X	X	X	III, B, 5.8
9. Safety for humans and animals	X	X	X	III, B, 5.9
10. Information on monitoring, control, waste treatment and emergency response plans			X	III, B, 1.10

	Group 1	Group 2	Group 3	Chapter, paragraph
Information relating to the production process	X	X	X	III, C, 1

	Group 1	Group 2	Group 3	Chapter, paragraph
Information relating to the product purification process				III, C, 2
1. Technique used to remove microbial cells from the product	X	X		III, C, 2.1
2. Information on the technique used to kill the microbial cells	X	X		III, C, 2.2
3. Process used to purify the product from the microbial growth medium	X	X		III, C, 2.3

	Group 1	Group 2	Group 3	Chapter, paragraph
Description of the product				III, C, 1
1. Designation of the product	X	X	X	III, C, 3.1
2. Intended use and mode of action	X	X	X	III, C, 3.2
3. Composition	X	X	X	III, C, 3.3
4. Physical properties	X	X	X	III, C, 3.4
5. Technological properties	X	X	X	III, C, 3.5

	Group 1	Group 2	Group 3	Chapter, paragraph
Assessment of the presence of recombinant DNA and of the potential risk of gene transfer	X	X	X	III, C, 4

	Group 1	Group 2	Group 3	Chapter, paragraph
Comparison of the GM product with its conventional counterpart	X	X	X	III, C, 5

	Group 1	Group 2	Group 3	Chapter, paragraph
Considerations for human health and animal health of the GM product				III, C, 6
1. Toxicology	X	X	X	III, C, 6.1
2. Risk assessment of newly expressed proteins	X	X	X	III, C, 6.2
3. Testing of new constituents other than proteins	X	X	X	III, C, 6.3
4. Information on natural food and feed constituents	X	X	X	III, C, 6.4
5. Testing of the whole GM product	X	X	X	III, C, 6.5
6. Allergenicity	X	X	X	III, C, 6.6
7. Assessment of allergenicity of newly expressed proteins	X	X	X	III, C, 6.7
8. Assessment of allergenicity of the whole GM product	X	X	X	III, C, 6.8
9. Nutritional assessment	X	X	X	III, C, 6.9
10. Post-market monitoring of GM products		X	X	III, C, 6.10

	Group 1	Group 2	Group 3	Chapter, paragraph
Potential environmental impact of GMMs and derived products				III, D

	Group 1	Group 2	Group 3	Chapter, paragraph
Environmental assessment for level 1 cases				III, D, 1
1. Spread of the GMM from the product to external environments			X	III, D, 1.1
2. General ability of the GMM to survive and persist in external environments			X	III, D, 1.2
3. Transfer of recombinant DNA		X	X	III, D, 1.3

	Group 1	Group 2	Group 3	Chapter, paragraph
Environmental assessment for level 2 cases				III, D, 2
1. The potential for survival in receiving environments and selective advantage			X	III, D, 2.1
2. The potential for transfer of recombinant genes			X	III, D, 2.2
3. Effects on indigenous microorganisms			X	III, D, 2.3
4. Effects on humans			X	III, D, 2.4
5. Effects on animals			X	III, D, 2.5
6. Effects on plants			X	III, D, 2.6
7. Effects on biogeochemical processes			X	III, D, 2.7

	Group 1	Group 2	Group 3	Chapter, paragraph
Environmental monitoring plan			X[c]	III, D, 3

(c) Required only for those GMMs which persist in the environment

IV. RISK CHARACTERISATION OF GM MICROORGANISMS REGARDING FOOD OR FEED SAFETY AND ENVIRONMENTAL IMPACT

1. Introduction

The risk assessment process consists of a number of steps *i.e.* hazard identification, hazard characterisation and exposure assessment, which culminates in a final integrative risk characterisation.

Risk characterisation is defined as: "The quantitative or semi-quantitative estimate including attendant uncertainties, of the probability of occurrence and severity of adverse effect(s) or event(s) in a given population under defined conditions based on hazard identification, hazard characterisation and exposure assessment" (SSC, 2000). This chapter describes how the risk characterisation step should be carried out and gives examples of issues to be addressed.

An extensive overview of risk assessment procedures is provided by the Scientific Steering Committee of the European Commission (SSC, 2000; 2003b) and by ILSI (ILSI, 2003). A detailed strategy for risk assessment and risk characterisation of foods derived from GMMs has recently been described by FAO/WHO (WHO/FAO, 2001b), for chemicals in food and diet by Food Safety in Europe (FOSIE, 2002; 2003), and for environmental risk assessment by the EU (EC, 2002a). Guidelines for the risk assessment of foods derived from GMMs were published by Codex Alimentarius (*Codex Alimentarius,* 2003).

Risk assessment involves generating, collecting and assessing information on a GMO and its derived food or feed in order to determine its impact on human or animal health and the environment relative to current equivalents, and thus its relative safety. In order to carry out the risk assessment sufficient available scientific data must be available in order to arrive at qualitative and/or quantitative risk estimates. The final risk characterisation should result in informed qualitative, and if possible quantitative, guidance to risk managers. It should explain clearly what assumptions have been made during the risk assessment, and what is the nature and magnitude of uncertainties associated with establishing these risks.

When scientific information is insufficient, inconclusive, or uncertain, or when there are indications that the possible effects on the environment, or human, animal, or plant health may be potentially dangerous and inconsistent with the chosen level of protection, the precautionary approach may be invoked (EC, 2000b). Application of the precautionary approach is distinct from the normal conservative approach scientists take in the assessment of data when applying safety or extrapolation factors. Application of the precautionary approach is the responsibility of the risk manager and not of the risk assessor and will therefore not be dealt with in this Chapter.

2. How to carry out the risk characterisation

Risk analysis starts with defining the proper questions that should be addressed during the risk assessment, *i.e.* identification of potential risks of preparation of pure cultures of the GMM and human or animal consumption of derived foods or feed, and how these questions should be addressed. Problem formulation should involve risk managers, risk assessors and stakeholders *e.g.* producers, environmental and consumer groups. For instance, production processes, intake and exposure routes, population targets (humans, animals or the environment) and health end-points should be identified for the GMM and its derived food or feed and existing knowledge on the use of the non-modified counterpart and derived food or feed should be collected.

The final risk characterisation of GMMs and derived foods or feed is focused on data from hazard identification and hazard characterisation, using laboratory and, when appropriate, target animal studies, environmental studies and (large-scale) trials on exposure and intake data. A comprehensive risk characterisation should be carried out, *i.e.* considering all the available evidence from several approaches including molecular analysis, microbiological and biochemical analysis, compositional analysis, toxicity and allergenicity testing, and environmental impact analysis. The risk characterisation may give indications for specific activities for post-market monitoring of GM food or feed and for environmental monitoring of GMMs.

The risk characterisation should provide evidence whether the hazard identification and subsequent characterisation is complete. It is essentially an iterative process. Integration and evaluation of data from hazard characterisation and exposure assessment may indicate that an appropriate risk estimation can be made, or that further data should be generated in order to complete the risk characterisation. For instance, if an increased intake of a food or feed derived from a GMM by humans or animals may be expected, further data on toxicity at extended dose ranges may have to be generated.

Any uncertainties inherent in the different risk assessment steps should be highlighted and quantified as much as possible. Distinction should be made between uncertainties that reflect natural variations in ecological and biological parameters (including variations in susceptibility in populations), and possible differences in responses between species.

Estimation of uncertainties in experimental data should be handled by proper statistical analysis, while quantification of uncertainties in assumptions (*e.g.* extrapolation of data from animals to humans, extrapolation from environmental laboratory studies to complex ecosystems) may be more difficult, but should be highlighted.

The absence of data essential for the risk assessment should be indicated and the quality of existing data should be discussed. It should be clear from the discussion how this body of information has been taken into account when the final risk estimation is determined.

Risk estimation may be qualitative and, if possible, quantitative depending on the issue to be addressed and the available data. The terms for the expression of risks and associated uncertainties should be as precise as possible. For instance, expressions like ‘negligible/acceptable/significant risk’ need, if possible, further numerical quantification in terms of probability of exposure and/or occurrence of adverse effects.

3. Issues to be considered for risk characterisation

Risk characterisation of GMMs should be carried out in a holistic manner as stated above and on a case-by-case basis depending on the type of product derived from the GMM, on the genetic modification, on the production process and on the expected use of the derived food or feed for human or animal consumption. Below a number of issues are described for consideration in the risk characterisation step. The list of issues is by no means exhaustive.

Molecular characterisation

Evaluation of the characteristics and previous use of the recipient and, when appropriate, of the donor organism is a key element to identify the need for specific analyses *e.g.* occurrence of specific metabolites in the recipient microorganism which may be unintentionally increased as result of the genetic modification.

Transformation protocols, molecular characterisation strategies and the specificity and sensitivity of molecular detection methods should be discussed in relation to the intentional and possibly unintentional insertion and expression of gene sequences.

When flanking sequence analysis has identified chimeric ORFs, it should be demonstrated how approaches like bioinformatic analysis, biochemical and physiological analysis and possibly animal feeding trials with the whole GM food or feed contribute to the safety impact. The value of the results obtained should be evaluated in the light of the available knowledge on the structure and function of genomic databases of the microorganism in question.

Comparative analysis

An important issue to be evaluated is whether the comparative analysis between the GMM and its non-GM counterpart with respect to phenotypic and genotypic characteristics has been carried out appropriately according to current guidelines. It is also important to consider what body of knowledge is available regarding the conventional counterpart product so that it may be taken as a reference for safe human or animal use. Protocols for and performance of analysis should be evaluated, and the data generated assessed to confirm they are representative for the proposed use of the GMM and its derived product.

The goal of the comparative risk assessment is to identify possible differences between the GMM and its conventional counterpart. The choice of the comparator is a key consideration; both for the GMM and for derived products, and its use should be justified. The risk characterisation should concentrate on statistically significant differences in the physiology, biology, metabolic activity and genetic characteristics of the GMM compared to its non-GM counterpart and whether these differences are likely to have an environmental, and/or food or feed safety or nutritional impact. The same approach should be followed for the comparison of the GM product with its conventional counterpart. Moreover, an analysis should be made of the uncertainties associated with the comparative analysis.

Another important issue to be addressed is whether, besides intended effects, unintended effects may occur as result of the genetic modification. The strategy for detection of unintended effects should be discussed, particularly with respect to the probability that significant unintended effects have been missed. When the occurrence of unintended effects cannot be excluded, strategies to assess the potential human or animal health and environmental implications should be explained.

Food and feed safety in relation to intake

The data generated to estimate possible risks to human or animal health associated with the consumption of foods or feed derived from a GMM should be evaluated with respect to the expression of new proteins or metabolites as well as significantly altered expression of original microbial proteins or metabolites in GMM and of whole GM food or feed. Dose response relationships, threshold levels, delayed onset of adverse effects, risks for certain groups in the population, use of uncertainty factors in extrapolation of animal data to humans should be presented.

The relevance of short-term toxicity data in order to predict possible long-term adverse effects of newly expressed proteins or metabolites in the GM food or feed and of whole GM food or feed should be discussed as well as the absence of specific data (*e.g.* on reproductive and developmental toxicity) if applicable. Moreover, the relevance of the outcome of whole GM food or feed feeding trials should be evaluated with respect to experimental limitations (dose range, dietary composition, confounding factors).

In cases in which more complex genetic modifications are produced, *e.g.* transfer of multiple genes in a single construct, re-transformation of pre-existing GM strains, strategies for the assessment of any risk(s) associated with possible interactions between the newly expressed proteins, new metabolites and original microbial constituents should be discussed. A holistic approach for the assessment should be demonstrated, considering all available information on *e.g.* the mode of action of the newly expressed proteins, the molecular and compositional characteristics of the GM food or feed, and when applicable on the outcome of animal toxicity studies and feeding trials. When animal feeding trials are not performed, an explanation should be provided as to why these were not considered necessary.

Data provided to assess the allergenic potential of newly expressed proteins in GMMs should be evaluated with respect to a possible provocation of allergic reactions of susceptible individuals. Information is also required to demonstrate that the genetic modification process does not cause unwanted changes in the characteristics and/or levels of expression of endogenous allergenic proteins in the food derived from a GMM. In particular, the test models used should be discussed with respect to specificity, predictability and validation status.

With respect to intake estimations of foods for humans derived from GMMs, the methodologies applied should be evaluated with respect to uncertainties associated with the prediction of long-term intake. Specific attention should be paid to those GM foods that are aimed at modifying nutritional quality. For the GM products in questions the requirement for post-market monitoring should be discussed as a mechanism necessary for determining changes to overall dietary intake patterns of the GM food, to what extent this has occurred and whether or not the product induces known (side) effects or unexpected side-effects. If the performance of post-market monitoring is deemed necessary, the reliability, sensitivity and specificity of the proposed methods should be discussed.

Environmental impact

Predicting impacts of GMMs and derived food or feed on complex ecosystems that are continually in flux is difficult and largely based on experiences with other introductions and an understanding of the robustness of ecosystems. It is recognised that an environmental risk assessment is limited by the nature, scale and location of experimental releases, which environments have been studied and the length of time the studies were conducted. The likelihood of transmission of the GMM from the product to the environment and the likelihood of the GMM for survival and persistence in the external environment, as well as the possibility of transfer of recombinant DNA from the GMM and/or its derived product to other organisms are the key points to be considered in the environmental impact evaluation. Evaluations should be conducted against the background of hazards likely to be encountered. Probabilistic methods could be used to determine ranges of plausible values rather than single values or point estimates, which are subsequently combined in order to quantify the uncertainty in the end result. These methods could provide a powerful tool to quantify uncertainties associated with any steps in the risk assessment.

Among other issues to be addressed are whether or not sound predictions can be made regarding the stability of introduced and expressed traits in the GMMs under representative environmental conditions, whether the potential manifestation of adverse environmental effects can be predicted in the long term, and whether extrapolation of data from small- to large-scale use is possible.

Scientific knowledge and experience gained from placing on the market of food or feed derived from a GMM during the monitoring and provisional approval periods for GMM products will also inform the risk assessment process and are opportunities to update environmental risk assessments continually in the light of any new knowledge.

4. The result of risk characterisation

The final risk characterisation should result in informed qualitative and, where possible, quantitative guidance to risk managers. It should explain clearly what assumptions have been made during the risk assessment in order to predict the probability of occurrence and severity of adverse effect(s) or event(s) in a given population and/or on the environment, and the nature and magnitude of uncertainties associated with establishing these risks.

When a scientific risk assessment cannot be completed because of the lack of essential data or the availability of poor quality data, this should be indicated.

The risk characterisation should include:

- whether placing on the market of a GMM and its derived products is as safe for the environment as the placing on the market of the equivalent non-GMM;
- whether consumption of food or feed derived from GM microorganisms is as safe for humans or animals as the conventional counterparts;
- specific conditions for production process of food and feed derived from a GMM, if required;
- the scientific basis for different options to be considered for risk management.