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Safety Assessment of Viable Genetically Modified Micro-Organisms Used in Food

Consenus Guidelines reached at a Workshop held in April 1999

Organised by the ILSI Europe Novel Food Task Force

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FOREWORD

ILSI Europe Workshop on the Safety Assessment of Viable Genetically Modified Micro-organisms Used in Food: 14-16 April 1999, Salzburg, Austria

Micro-organisms are widely used in food production, and a considerable amount of research is being done to improve strains by gene technology. The safety evaluation of viable genetically modified micro-organisms used in food raises a number of issues that are not relevant to the safety assessment of foods containing non-viable genetically modified micro-organisms or obtained from genetically modified plants, e.g., gene transfer, colonisation and pathogenicity. On 14-16 April 1999, ILSI Europe convened a workshop to define guidelines for the safety evaluation of viable genetically modified micro-organisms used in food. The workshop was attended by 60 scientists from government, industry and academia and was chaired by Prof. B. Moseley (UK). Draft guidelines elaborated by an expert group as well as scientific background documents underpinning these guidelines served as a basis for discussion. After introductory presentations on the main issues, members broke into three working groups (intestinal flora and human health, gene transfer, and pathogenicity) and discussed their respective topics in the context of the guidelines. Reports on recommendations for amendments of the guidelines were presented and discussed in a final session, and consensus on the guidelines was reached among the participants of the workshop. The guidelines, which form the basis of this report, will also be published together with the scientific aspects underpinning these guidelines in *Food Biotechnology*.

1. INTRODUCTION

The EU Regulation concerning novel foods and food ingredients came into force during 1997 (European Commission, 1997). The regulation, which includes within its scope foods and food ingredients containing or consisting of genetically modified organisms, requires that novel foods must not present a danger to the consumer. Foods containing viable genetically modified micro-organisms must undergo a safety assessment before approval can be given for marketing.

The safety assessment of foods containing viable genetically modified micro-organisms raises a number of unique issues that are not relevant to the safety assessment of foods containing non-viable products from genetically modified micro-organisms, or from genetically modified plants and animals (FAO, 1996; OECD, 1996; SCF, 1997). This document has been developed by ILSI Europe to assist those already familiar with the general procedures for the safety assessment of foods containing genetically modified organisms in addressing these unique issues which include: pathogenicity, toxigenicity, genetic stability, and gene transfer.

Compared with other novel foods, experience in food safety assessment of viable genetically modified micro-organisms is limited. In order to establish a level of consumer safety comparable to that of other novel foods, the information requirements for viable genetically modified micro-organisms are more extensive. However, as experience grows, it may be possible to modify some requirements without compromising safety.

The guidelines in this report were developed by ILSI Europe to give a structured approach to the safety evaluation of genetically modified micro-organisms used in food. These guidelines focus on viable genetically modified micro-organisms contained in food but do not include genetically modified micro-organisms that are used for medicinal purposes. Furthermore, these guidelines address the safety assessment of viable genetically modified micro-organisms but not possible health benefits from their use.

These guidelines should be read in conjunction with the recommendations given in other guidelines for the safety assessment of foods produced from genetically modified organisms (IFBC, 1990; WHO, 1991; OECD, 1993; Jonas *et al.*, 1996; FAO, 1996; SCF, 1997) as they are not intended in themselves to provide a complete safety assessment procedure for genetically modified micro-organisms.

These guidelines will be published in the scientific literature together with aspects of the underpinning science. The first section of this underpinning science discusses the characteristics of viable micro-organisms used in food and gives examples of organisms currently in use which may be the subject of genetic modification in the future or may serve as comparators against which to assess the safety of modified strains. The second section discusses the role of intestinal microflora and human health. The third section discusses the fundamental aspects of gene transfer which, together with the nature of any transferred gene and gene product, is essential to determining food safety risk. The final section discusses aspects of the interaction between viable micro-organisms in food and consumers: toxicological concerns, allergenicity and pathogenicity, and interactions with intestinal microbiota.

These guidelines address, in particular, scientific aspects pertinent to food safety arising from the use in food production of genetically modified bacteria, yeasts and moulds where it is intended that these genetically modified micro-organisms remain in the food in a viable state when consumed. Food ingredients obtained from the use of genetically modified micro-organisms (e.g., enzymes or single cell proteins) are not included, nor are genetically modified micro-organisms which occur in food as a result of environmental contamination.

Viable micro-organisms occur in food from a number of sources: they may be added intentionally or they may arise from natural contamination. They contribute to the unique characteristics of the food although, in some cases (e.g., in some oriental food fermentations), they may not have been fully characterised. Examples of the deliberate addition of micro-organisms to a food to improve its properties include the use of yeasts to produce alcohol in fermented beverages or carbon dioxide in bread and the use of bacteria to produce lactic acid in fermented milk and meat products. Bacteria may also be added to foods with the intention of achieving health benefits, i.e. as probiotics.

Within the European Union, the use of genetically modified micro-organisms in containment is regulated by EU Directive 90/219/EEC (European Commission, 1990a), and the release into the environment of genetically modified organisms is regulated by EU Directive 90/220/EEC (European Commission, 1990b). A key feature of these two directives is the requirement for a risk assessment and both include a list of the issues that should be addressed in the risk assessment. Where the genetically modified organisms are micro-organisms to be used in food, much of the information pertinent to the risk assessment under containment or when released to the environment is also relevant to the food safety assessment.

Food-associated micro-organisms may have a potential to influence the human intestinal microflora which is characterised by vast numbers and a diversity of micro-organisms. There is a lifelong mutual co-existence between these commensal microflora and the human host. However, very little is understood about host: microbe and microbe: microbe interactions.

Until the 1980s, micro-organisms were largely characterised through their morphology and their ability to metabolise certain substrates. Micro-organisms with similar characteristics were deemed to be more closely related than those with widely different properties. Recent developments in microbial genetics have made it possible to examine the relationship between micro-organisms at a genetic level – leading in some instances to their reclassification. It is also clear that, within what had hitherto been regarded as a single strain, there is a constant genetic flux due to the rearrangement of DNA within the cell and to the acquisition or loss of genetic material from and to other cells.

2. GUIDELINES FOR THE SAFETY ASSESSMENT OF VIABLE GENETICALLY MODIFIED MICRO-ORGANISMS USED IN FOOD

2.1 General considerations

The aim of this section is to identify the information necessary to allow a comparison to be made between the genetically modified micro-organism and its conventional, food grade, counterpart where such exists (the "comparator"). This comparison will allow the genetically modified micro-organism to be placed in one of three classes as defined previously (Jonas *et al*., 1996) thus permitting the **s**afety **a**ssessment of **f**ood by **e**quivalence and **s**imilarity **t**argeting (SAFEST).

The choice of comparator is critical and should be justified. The comparator, or comparators, should be as closely as possible related to the genetically modified micro-organism. It is necessary to select the comparator(s) on a case by case basis. For example, in dicaryotic micro-organisms, back-crossing may be necessary to obtain a clean line. In bacteria, and especially those of importance in food fermentations, plasmids, transposons, and prophages lead to a natural fluctuation in some strain properties upon continuous industrial application. It might be required that a member of the clone or even the species instead of the parent strain has to be chosen as the comparator. The choice of comparator(s) should also take into account the way in which the genetically modified micro-organism will be used in food including the substrate/food matrix, potential intakes (including new uses), and processing. If the parent strain is not the chosen comparator, this does not preclude the use of other strains of the same species with a history of safe food use from being used as comparators, provided that this can be scientifically justified. However, it should be remembered that within a single species there may be strains that are safe and those which are unsafe.

The decision trees later in this section provide a schematic overview of the questions that should be asked to identify the information needed to establish the safety of a genetically modified micro-organism for use in food production.

2.1.1 Human gastrointestinal microflora

The potential effects of the genetically modified micro-organism on the gastrointestinal microflora need to be addressed, taking into account consideration of the characteristics of the human population (e.g., age, diet, health status, race) and the microbial population (e.g., location in the gut, substrate availability). It should be emphasised that it is not only the genetically modified micro-organism in isolation, but also its presence in the food product/matrix that needs to be evaluated, both in terms of direct and indirect effects.

It is preferred that the term "persistence" is used rather than "colonisation" to describe the establishment of a micro-organism in the gut microflora. Persistence is defined as "detection from a specified area of the gastrointestinal tract of an ingested micro-organism after cessation of oral intake, for a period of time at least twice as long as the gut transit time." In risk assessment, the impact of the traits of a genetically modified micro-organism on the gut ecosystem should be assessed.

2.1.2 Host micro-organisms

The following information should be provided concerning the micro-organism used as the host (parent or recipient) for the genetic modification:

Taxonomy

A full taxonomic profile of the host should be provided. This should take account of changes in classification when it concerns species of mixed safe and unsafe strains and include, where appropriate, the use of molecular methods.

History of use

There are three possibilities regarding the previous food use of the host: (a) the host is traditionally found in a viable state in safe food products because it is deliberately added to perform a particular purpose; (b) the host is traditionally found in a viable state in safe food products although it is not intentionally added, or (c) the host is not traditionally found in a viable state in safe food products. If the host, or a genetically related strain, is not traditionally found in safe food products, genetically modified micro-organisms derived from it are unlikely to be acceptable for food use without a full safety evaluation (SAFEST Class 3), including consideration of the effects on the human immune system. For host strains found in food although not deliberately added (category (b) above), safe history of use must be established on a case-by-case basis.

Information on previous safe food use should, where possible, be supported by scientific evidence and provide evidence of safe food use under conditions as close as possible to those anticipated for the genetically modified strain, including: level of use, intended function, potential intake, effects of processing, and populations and their dietary habits.

Potentially harmful metabolites

Information should be provided to show the absence from the host of silent genes known to be present in genetically related strains or species, and which, if expressed, code for gene products that have the potential to cause harm when consumed such as proteins with the characteristics of known food allergens or pathogenicity factors, e.g., toxins.

If there is any reason to believe that host-related strains or species of micro-organisms are unsafe for food use because they are capable of producing adverse effects, the absence of the production of such effects by the host strain and the genetically modified micro-organism should be demonstrated under all anticipated conditions of production and use. Where possible, information should be provided to show the absence from the host strain of the gene(s) responsible for the adverse effect or, alternatively, the mechanism for their suppression in the genetically modified micro-organism.

2.1.3 Foreign genetic materials

Most, but not all, genetic modifications of micro-organisms will involve the insertion into the genome of foreign genetic material. Exceptions include the use of genetic modification to delete existing genes or to inactivate existing genes. Where it can be shown that no foreign genetic material is inserted into the genome of the genetically modified micro-organism, this section can be ignored.

The following information is required for all inserted genetic material, including marker genes, nonfunctional genes (e.g., truncated or antisense genes) and linker sequences:

Source

Information should be provided on the source (donor) of the inserted genetic material including its history of food use. Two situations regarding inserted genetic material can be foreseen: (a) the inserted material is obtained from an organism(s) with a history of safe food use; and (b) the inserted material is obtained from an organism(s) with no history of safe food use. In case (a), the food use history of the source organism(s) should be fully documented and the function of the genetic material in the source organism described.

Characterisation of the gene

The inserted genetic material, including trait and marker genes, should be fully characterised, including a molecular characterisation. Non-coding and linker sequences inserted with any genes should also be fully characterised. If the source of any of the genetic material is an organism with no history of safe food use, sequence comparisons should be made with genetic material from organisms with a history of safe food use and the degree of homology indicated.

2.1.4 Vectors

Information on the procedures involved in the genetic modification should be provided including the source and previous use of the vector and the method of selection used. If it can be shown that all extraneous DNA (i.e., all DNA other than trait DNA) has been jettisoned from the genetically modified strain, no further information concerning the vector is required. However, this is not often the case with genetically modified micro-organisms.

If it cannot be shown that all extraneous DNA has been jettisoned from the genetically modified strain of micro-organism, information is required on the sequence of transposons, vectors and other non-coding segments used to construct the vector and insert the desired functionality into the genetically modified micro-organism. The vector DNA should be fully sequenced and compared for sequence homology with DNA from organisms with a history of safe food use. All vector sequences introduced into the host should be fully characterised including selectable markers, replicons, polylinkers and any other foreign DNA. Apart from polylinkers, evidence should be provided to show that the sequences are already found in food organisms or alternatively, it should be demonstrated that the sequences pose no safety hazard. If a plasmid vector is used, the plasmid should be fully characterised and information provided to show whether it is present in micro-organisms traditionally found in a viable state in safe food products.

2.1.5 Genetically modified micro-organisms

Information on the genetically modified micro-organism is essential for the food safety evaluation, whether the genetic modification has been achieved by the insertion of foreign genes or by the deletion or inactivation of existing genes.

The genetic modification of the micro-organism should be fully characterised. This will involve sequence data on any introduced genetic material and flanking regions (several hundred base pairs) or around the site of any gene deletion or inactivation. The effects of any rearrangement of the DNA at the sequence level should be characterised. The consequences of the modification on the physiology of the cell should be assessed, including the effect of any metabolic end products. It should be demonstrated that any differences do not cause harm, including adverse nutritional effects or effects on the human immune system. It should also be demonstrated that any changes are stable and that potential gene transfer to other species is not enhanced or, if it is, that it poses no conceivable hazard.

In addition, information should be provided to show that any foreign gene product(s) is identical to that expected, including the effects of any post-translational modification compared to the gene product as expressed by the source organism. Information should also be provided to show that any foreign gene product(s) has the intended activity. If there is evidence of any unintended activity, this will need to be explained and shown to be of no food safety concern. It should also be shown that there is no reading across the insert and host DNA to produce hybrid gene products or, if there is, that their food safety implications are evaluated.

Substantial equivalence

The genetically modified micro-organism should be compared to the chosen comparator with respect to the parameters listed below. Substantial equivalence should always remain the principal characteristic when a genetically modified micro-organism is compared to its comparator and these guidelines are a focus for case-by-case safety assessment. The aim of the studies is to investigate the likelihood for potentially adverse unpredictable secondary or unintended effects arising from genetic modification. Such effects might arise for a number of reasons including: (a) effects of any foreign gene product on the metabolism of the host, leading to altered levels of existing gene products or metabolites; or (b) insertional effects of the modification activating (or inactivating) existing genes; or (c) transcription of vector sequences.

Information should be provided to allow a comparison to be made between the genetically modified micro-organism and the chosen comparator so as to eliminate the possibility of unintended effects of the modification. In looking for possible unintended effects, the nature of the host and the foreign gene product will help to focus the search. It should be demonstrated that the intended modification is sufficiently stable and that the genetic stability of the host, including potential for horizontal gene transfer, is unchanged. If there are changes, the food safety implications will need to be considered, taking into account the properties of the micro-organism concerned. The basic physiology of the genetically modified micro-organism should be characterised under food production conditions and under conditions of stress. Persistence in the gastrointestinal tract and impact on natural gut microflora should be assessed. Consideration should be given to other risk factors that might be associated with the parent strain or species, the introduced genetic material, and the genetically modified strain. Negative effects known to be associated with the parent strain should be eliminated, including virulence, toxicity, allergenicity and antinutritional impact.

If differences between the genetically modified micro-organism and the comparator are observed this does not mean that the modified micro-organism is unsafe. However, any differences must be explained and the consequences for safety defined using the SAFEST approach. Comparisons with other edible strains of the same species may facilitate the safety evaluation, although, within a single species, there may be some strains that produce toxins and others that do not.

Genetic stability

It is generally accepted that no micro-organism can be considered to be completely genetically stable. Taking into account the properties of the micro-organism, information should be provided on the consequences for safety of any significant differences in genetic stability between the genetically modified micro-organism and the chosen comparator, e.g., increased toxin production, loss of antinutrient suppression or increased probability of gene transfer. It should include: (a) information on relative genetic stability with respect to the intended modification; and (b) information on genetic flux to, from, and within the genetically modified micro-organism relative to that of the host. This may be determined at the DNA level. If differences between the genetically modified micro-organism and the comparator are observed, it will be necessary to demonstrate that they are of no concern with respect to food safety. It may be necessary to consider the implications of genetic drift in the human gut.

Gene transfer

It is reasonable to assume that gene transfer from viable genetically modified micro-organisms will occur to organisms in the gastrointestinal tract. Therefore, safety assessment requires consideration of the impact of introduced genes and associated regulatory sequences on the resident gut microflora. Specifically, genes that confer a selective advantage are of particular concern. These include antibiotic resistance marker genes which should be avoided in viable genetically modified micro-organisms in food.

Metabolic profiling

Taking into account the nature of the genetic modification, information should be provided on the end products of those metabolic processes likely to be affected. To the extent practical, this information should cover the entire course of growth and under a variety of conditions of stress and conditions likely to be encountered during processing, shelf life and following consumption. If differences between the genetically modified micro-organism and the comparator are observed, it will be necessary to explain the metabolic basis of these and to demonstrate that they are of no concern with respect to food safety.

Risk factors

Information on the genetically modified micro-organism should be provided regarding any risk factors known to be produced by the host species and related species or known to be coded for, but not produced by, the host or related species. These risk factors include antinutritional factors, pathogenicity factors, e.g., the ability to produce toxins, and proteins with the characteristics of known food allergens. While micro-organisms *per se* used in food are not in a high risk category for food allergy, introduced genes may pose a risk of potential allergenicity, particularly if they come from sources known to produce food allergens.

Although allergens are listed alongside toxins as risks, the nature of the risks is different. Furthermore, there is a possibility that a viable genetically modified micro-organism may produce and deliver into the gut a protein that is not normally found in the food chain, or protect a protein that is normally degraded in the stomach.

If the genetically modified micro-organism includes marker genes, information should be provided to show that these do not provide a selective advantage in the gut or influence the existing microflora under both typical conditions and under extreme conditions that might be encountered (e.g., in consumers undergoing medication). If the marker does provide a selective advantage in the gut, the consequences for the consumer must be defined.

Basic physiology

Bearing in mind the SAFEST approach, information should be provided on the basic physiology of the genetically modified micro-organism to facilitate comparison with the conventional counterpart. Unexpected changes in physiology are indicators of possible secondary effects of the modification. Any physiological change may compromise safety, e.g., through the accumulation of toxic metabolites, and the consequences for safety should be evaluated.

2.2 Decision trees

The following decision trees are intended to facilitate the safety assessment of viable genetically modified micro-organisms intended for use in food. There is a wide variety of potential genetic changes that might be applied to such micro-organisms and the precise nature of this change will influence the safety evaluation. The principle followed in the decision trees is that outlined in the ILSI guidelines on "The Safety Assessment of Novel Foods" (Jonas *et al*., 1996). The genetically modified micro-organisms to be evaluated will belong to category (a) as defined in Article 1 (2) of the EU Novel Foods Regulation (European Commission, 1997), namely "foods and food ingredients containing or consisting of genetically modified organisms within the meaning of Directive 90/220/EEC." The decision trees are intended to highlight the main information that will be required to complete a safety evaluation for an individual genetically modified micro-organism, and they categorise individual cases according to the SAFEST principles established by an earlier ILSI task force (Jonas et al., 1996). The SAFEST approach involves "safety assessment of food by equivalence and similarity targeting" and uses the principle of substantial equivalence to establish safety by comparison to traditional foods that are already accepted as safe in use. The concept of substantial equivalence as an approach to the safety evaluation of novel foods was developed following an initial FAO/WHO consultation (WHO, 1991) and further refined by OECD (1993; 1996; 1997) and WHO/FAO (FAO, 1996).

The earlier ILSI guidelines on the SAFEST approach established three distinct classes, and the decision trees should allow any specific example of a viable genetically modified micro-organism to be placed in one of these. This, in turn, indicates the nature of the information required for safety assessment.

> **SAFEST Class 1** includes examples where the novel food is established as substantially equivalent to a traditional counterpart (or comparator). For a viable genetically modified micro-organism, the emphasis of the evaluation would be to demonstrate substantial equivalence. This would be by comparison of the genetically modified micro-organism

with a comparator that was already established as safe. For genetically modified micro-organisms in this class, no foreign DNA is added and there are no changes to gene expression. In view of the fact that genetic modification is usually undertaken to achieve a specific change to phenotype, few examples, if any, are likely to fall into this category.

SAFEST Class 2 includes foods and food ingredients defined as sufficiently similar to a traditional reference food for the safety evaluation to focus on the intended differences. For viable genetically modified micro-organisms derived from a source organism already established as safe, the emphasis of the evaluation would be on the nature and consequences of the genetic change.

With the safety of the source organism established, it is necessary to ensure that the intended genetic change does not compromise this safety and that there are no unintended adverse secondary effects of the genetic modification. Many viable genetically modified micro-organisms used in food are likely to fall into this class and it provides for an approach to safety evaluation that starts with the assumption that the source organism is safe. This allows the evaluation to focus on details of the genetic change and their consequences for the properties of the genetically modified micro-organism.

In some instances a genetically modified micro-organism might belong to a species that is used in food but the source organism may not itself have a history of safe food use. Here it is essential to provide a complete taxonomic classification, to include molecular taxonomy. Under such circumstances, provided that the species does not include strains with the potential to be pathogenic, a representative food-use strain could be used as a comparator and the principles of SAFEST Class 2 would apply.

SAFEST Class 3 includes foods and food ingredients for which a safe traditional reference food is not available. Foods in this class are not necessarily unsafe, but an extensive safety evaluation will be required. This may involve evidence of safety from alternative uses or it may require extensive toxicological or nutritional studies. The problems of performing nutritional or toxicological studies on food and the selection of appropriate endpoints are discussed elsewhere (Jonas *et al*., 1996; OECD, 1996). In the case of genetically modified micro-organisms in this class, an extensive safety evaluation will be required. However, in part, the safety of genetically modified micro-organisms might be established in the same way as food additives by feeding them to test animals. Evidence of non-toxicity could thus be assessed directly and there is less need to rely on comparative approaches.

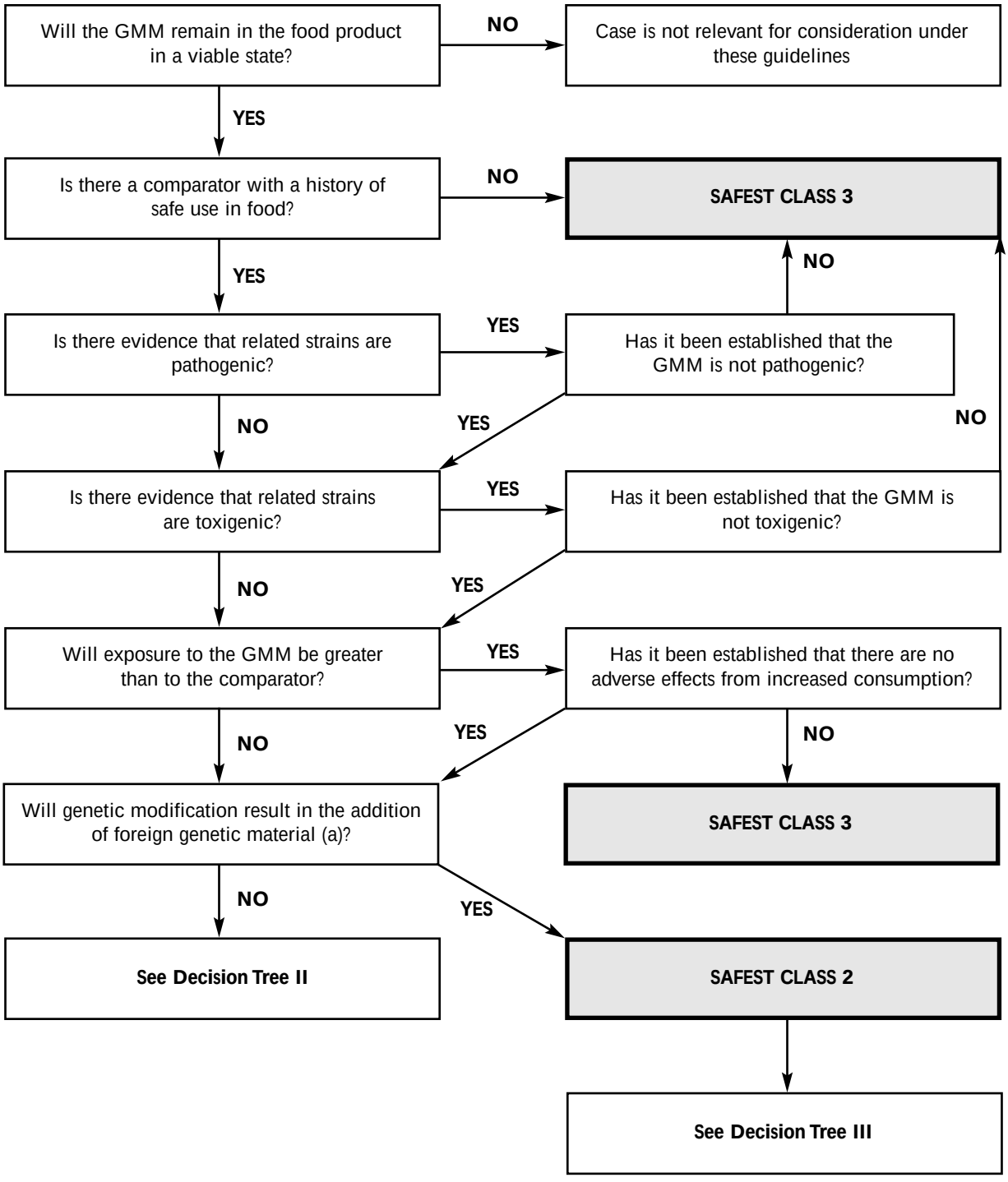
In establishing the appropriate SAFEST class for a genetically modified micro-organism, the comparator should be chosen to reflect not only its intrinsic characteristics but also its intake, role in the diet, and the effects of processing (Jonas *et al*., 1996). If it is proposed to use quantities in excess of those normally encountered in the diet for the comparator, this needs to be assessed as a separate risk issue. Unless it can be demonstrated that increased exposure will have no safety consequences, the genetically modified micro-organism should be evaluated under SAFEST Class 3.

Decision tree I is intended to separate those genetically modified micro-organisms falling within SAFEST Class 3 because: there is no comparator; it cannot be established that the comparator lacks the potential to produce adverse effects or that no such effects arise from increased consumption with respect to the comparator. Remaining genetically modified micro-organisms are then examined using decision tree II if they do not contain foreign genetic material, and decision tree III if they do contain foreign genetic material.

Decision tree II is applied to genetically modified micro-organisms that do not contain foreign genetic material apart from short, non coding, linker sequences, i.e. self cloning according to Directive 90/219/EEC (European Commission, 1990a). Examples include micro-organisms genetically modified to amplify existing gene expression (e.g., through the use of endogenous promoters) or to suppress it (e.g., using antisense or truncated sequences derived from the host strain); homologous rearrangement; and self cloning (European Commission, 1990a). If the modification is not intended to change gene expression, the genetically modified micro-organism is in SAFEST Class 1. If the modification is intended to change gene expression, the genetically modified micro-organism is in SAFEST Class 2.

Decision tree III is for application to those genetically modified micro-organisms that contain foreign DNA; either functional DNA or DNA included for marker purposes but non-functional in the genetically modified micro-organism.

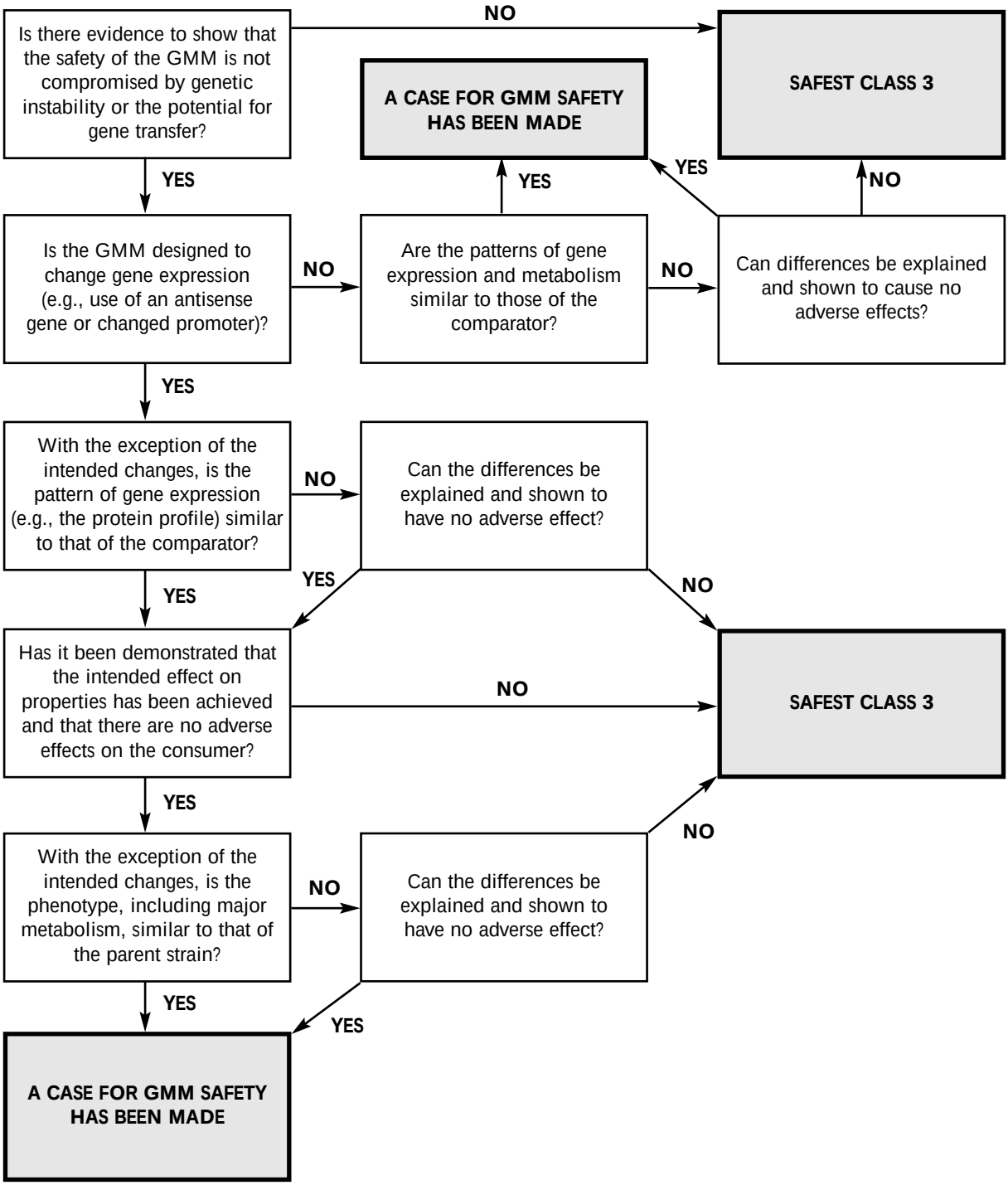
Decision Tree I



(a) In determining this, the definition of self cloning as defined by Directive 90/219/EEC (European Commission, 1990a) should be applied.

Decision Tree II

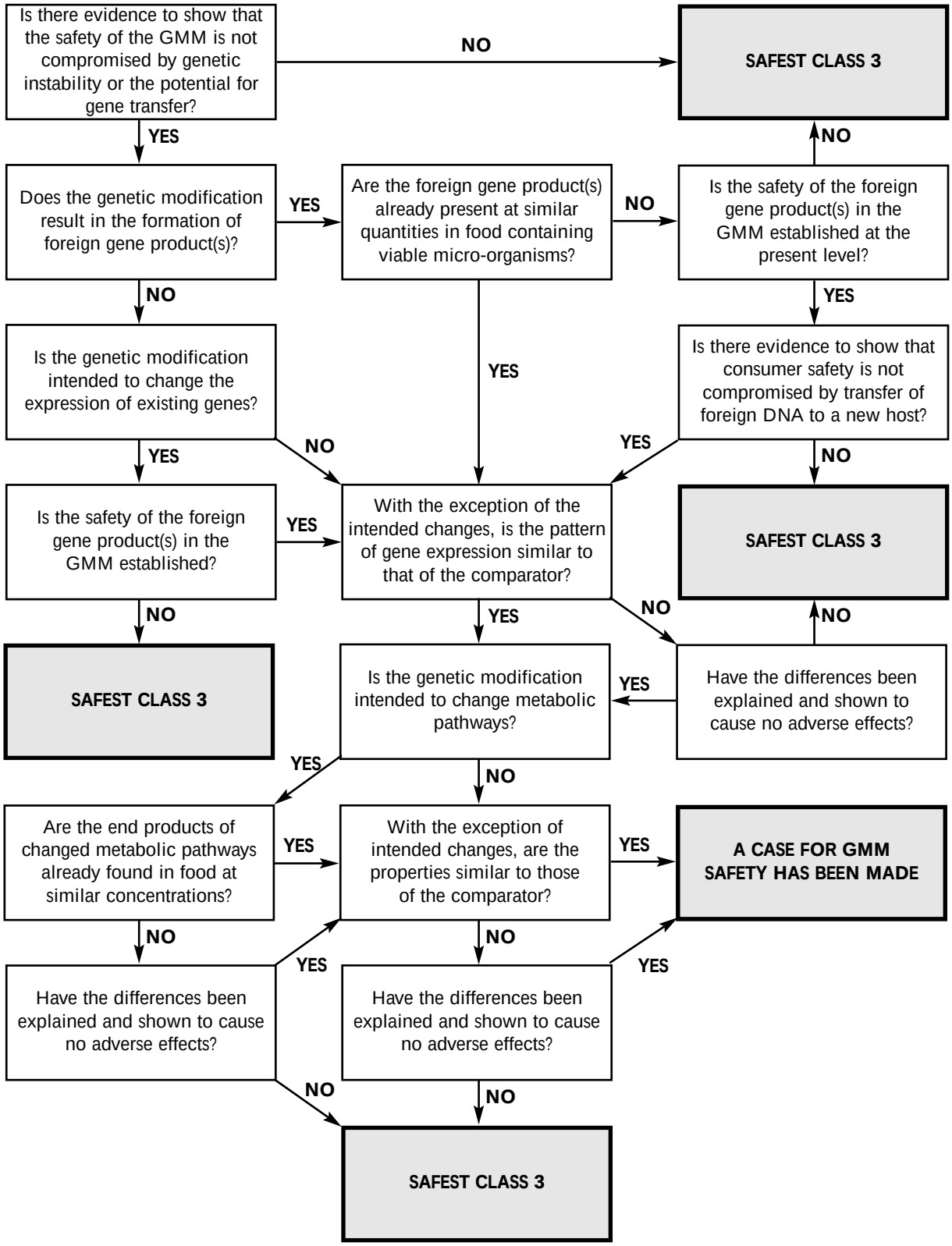
For use with GMMs with no foreign DNA: self cloning (a)



(a) Self cloning as defined by Directive 90/219/EEC (European Commission, 1990a)

Decision Tree III

For use with GMMs containing foreign DNA



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