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Principles for the risk assessment of genetically modified microorganisms and their food products in the European Union ☆

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ABSTRACT

Genetically modified microorganisms (GMMs) are involved in the production of a variety of food and feed. The release and consumption of these products can raise questions about health and environmental safety. Therefore, the European Union has different legislative instruments in place in order to ensure the safety of such products. A key requirement is to conduct a scientific risk assessment as a prerequisite for the product to be placed on the market. This risk assessment is performed by the European Food Safety Authority (EFSA), through its Scientific Panels. The EFSA Panel on Genetically Modified Organisms has published complete and comprehensive guidance for the risk assessment of GMMs and their products for food and/or feed use, in which the strategy and the criteria to conduct the assessment are explained, as well as the scientific data to be provided in applications for regulated products. This Guidance follows the main risk assessment principles developed by various international organisations (Codex Alimentarius, 2003; OECD, 2010). The assessment considers two aspects: the characterisation of the GMM and the possible effects of its modification with respect to safety, and the safety of the product itself. Due to the existing diversity of GMMs and their products, a categorisation is recommended to optimise the assessment and to determine the extent of the required data. The assessment starts with a comprehensive characterisation of the GMM, covering the recipient/parental organism, the donor(s) of the genetic material, the genetic modification, and the final GMM and its phenotype. Evaluation of the composition, potential toxicity and/or allergenicity, nutritional value and environmental impact of the product constitute further cornerstones of the process. The outcome of the assessment is reflected in a scientific opinion which indicates whether the product raises any safety issues. This opinion is taken into account by the different European regulatory authorities prior to a decision regarding authorisation to commercialise the product.

1. Introduction

Microorganisms have been the source of food and food products from the dawn of civilisation. With the advent of the recombinant DNA technology, the use of microorganisms as biofactories for the synthesis of new products had a boost. Currently, the use of genetically modified microorganisms (GMMs) in the food industry is well established. Estimations from 2009 indicate that around 40% of the food enzymes marketed in Europe are produced by recombinant strains, both bacterial and fungal (AMFEP, 2009). Food applications of GMMs go far beyond enzymes. Additives such as vitamins, amino acids, and polysaccharides can also be obtained from recombinant strains. The future commercial landscape of GMMs in food will also likely include biomass-derived products, and even whole GMMs. There are developments on food supplements made from GM microalgae with an enriched oil content (Franklin et al., 2011). Recombinant baker's yeasts with enhanced fitness for industrial baking are not a novelty (Prieto et al., 2006), and there are already GM yeast for wine-making purposes commercially available in the USA and Canada (FDA, 2003). Possible future uses of GMMs in foods extend to dairy products such as yogurt or cheese.

2. Regulatory framework

Food and feed consisting of, containing, or derived from genetically modified organisms (GMOs, mainly GM grain crops) are circulating on the world markets for more than a decade and, as for other fields of the food and feed industry, the need for a safety evaluation of such products (to be introduced or already existing on the market) is largely agreed. In fact, international standards on the safety of GMOs, including GMMs, have been developed (Codex Alimentarius, 2003; OECD, 2010), and the safety of GMM-produced food enzymes has been reviewed elsewhere (Pariza and Johnson, 2001; Olempska-Beer et al., 2006). Regulation of GMOs exists in many countries. In the European Union, there are several legislations in place to ensure that GM food products are safe for humans, animals and the environment. Attending to the nature

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of the product, food and food products obtained with the use of GMMs would fall under different legislative pieces:

- Food enzymes, food additives and food flavourings. These products, whatever their origin, fall under either Regulation (EC) No 1332/2008 (EC, 2008a) on food enzymes, Regulation (EC) No 1333/2008 (EC, 2008b) on food additives, or Regulation (EC) No 1334/2008 (EC, 2008c) on food flavourings, respectively. Regulation (EC) No 1331/2008 (EC, 2008d) on the common authorisation procedure applies to the three types of substances. When the product is obtained by fermentation of a GMM, these regulations apply if the GMM has been totally removed.[1] No particular authorisation or labelling is foreseen other than those already foreseen for any product under these regulations. However, the safety aspects of the genetic modification of the production strain are taken into account in the risk assessment (see below).
- Products derived from biomass of a GMM (i.e. containing rests of cells of the GMM, such as biomass-based food supplements or bread) fall under Regulation (EC) No 1829/2003 on genetically modified food and feed (EC, 2003). This regulation applies to food and feed consisting of, containing or derived from GMOs, and covers food and feed safety issues, as well as environmental risks potentially posed by such food and feed. Food enzymes, food additives and food flavourings produced by GMMs also fall under this Regulation if the GMM has not been totally removed from the product.
- Products consisting of or containing GMMs (i.e. the GMM is not destroyed or inactivated, such as yeast for baking, yogurt, and starter cultures for cheese) also fall under Regulation (EC) No 1829/2003. In addition, as the GMM is still viable, they fall under Directive 2001/18/EC on the deliberate release into the environment of GMOs (EC, 2001). This Directive covers environmental safety issues resulting from the release of GMOs, and establishes the principles and structure to articulate an environmental risk assessment (ERA). By virtue of a mechanism known as "one door-one key", a single application under the Regulation, containing all the data covering food and environmental safety of the product, can be submitted to request authorisation under both the Regulation and the Directive.

Although each of the above-mentioned legislations is independent and covers the particularities of the different products under their scope, they share some essential principles relative to safety and marketing. Products must be safe for humans, animals and/or the environment. For the product to be put into the EU market, an authorisation is required and, as a prerequisite to gain the authorisation, a risk assessment of the product must be done, which enables to conclude on its safety. Those who intend to commercialise a product must prepare an application, which contains all the necessary scientific information to conduct the risk assessment. This application is forwarded to the European Food Safety Authority (EFSA), which performs an independent evaluation of the application. EFSA can request from applicants additional information, including experimental data, if deemed necessary for the risk assessment. In addition, EFSA takes into account other relevant data, such as peer-reviewed scientific publications. After its evaluation, EFSA issues a scientific opinion on the safety of the product in question. This opinion is considered by the European Commission which, assisted by the Member States, decides on whether to authorise or not authorise the product.

In order to provide guidance on how the risk assessment should be conducted, and to help applicants to prepare applications, EFSA has released a series of Guidance Documents, which set out the methodology for the safety evaluation, and indicate the data requirements for applications for different products. Documents exist covering food enzymes, flavourings, additives, and GMMs. For the latter, the relevant document is the *Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use* (EFSA, 2011a, hereafter the "GMM Guidance"). This document fully covers the risk assessment of GMMs and food and feed products consisting of, containing, or derived from GMMs (and therefore falling under Regulation (EC) No 1829/2003). In case of enzymes and other fermentation products made with GMMs, the guidance covers the safety aspects related to the genetic modification of the GMM production strain. For the evaluation of the product itself, it provides cross-references to other applicable guidance from EFSA or other sources. Out of the scope of the GMM Guidance are tissue cultures of plant or animal cells, viruses or viroids, GMMs used as plant protection products or biocides, or GMMs released for experimental purposes and for research.

3. Principles of GMM risk assessment and categorisation of products

The general principles of the risk assessment of GMOs are outlined in Directive 2001/18/EC, and reflected in the GMM Guidance. The objective of the risk assessment is to determine the potential adverse effects of the GMM on human and/or animal health and the environment, compared to the non-modified microorganism from which it is derived. Comparison with the non-modified organism is an internationally accepted principle for the assessment of risks derived from GMOs (known as the comparative approach) (Codex Alimentarius, 2003; OECD, 2010). The assessment should also be conducted on a case-by-case basis (each GMM is assessed independently and taking into account its particularities), and should address direct and indirect effects, immediate or delayed.

According to the comparative approach, the characteristics of the GMM with potential to cause harm should be identified and compared to those presented by the non-modified microorganism (called conventional counterpart) in the context of the intended uses. The conventional counterpart should also have a history of safe use in order to obtain adequate baseline data. The same principle applies for food derived from GMMs: it should be compared with food produced using the traditional microorganisms. Given the wide range of microorganisms used in industrial applications, some of them with a long history of modifications from a wild ancestor (which might not even exist anymore), the ideal situation for a comparative assessment may not always occur. If the conventional counterpart has not a history of safe use, well-known close relatives (e.g. another strain, an ancestor) can be used as additional comparators to obtain reference data, taking into account their relationship and differences. It is also common that the strain which receives the genetic modification has been subject to other genetic modifications in the past, in the context of previous uses. In this case, the recipient strain might be used as comparator if its safety has been established in previous assessments towards a safe non-modified strain. Otherwise, it will be necessary to identify the first wild ancestor and assess all the genetic modifications introduced so far, in addition to the one which is subject to the application. Even so, there might be cases when no adequate comparator can be identified, and therefore the comparative approach is not possible. In those cases, the GMM guidance provides indications on how to conduct a comprehensive risk assessment, which would include a full toxicological and nutritional assessment of the GMM-derived food (see Sections 4.3.1. and 4.3.3.).

The strategy to be followed for the safety evaluation of the different products covered in the GMM Guidance (including the suitability of the comparative approach) will depend on the nature of each product, which will also determine the extent of the scientific data required. For this reason, products are classified into four categories:

- Category 1. The first category corresponds to chemically defined compounds and their mixtures in which both GMMs and newly

[1] Such products are, from a legal point of view, considered as made *with* GMMs, in contrast to products in which material derived from the GMMs is still present, that are considered made *from* GMMs (EC, 2003).