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Advancements in Genetic Engineering

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The European Union's Regulatory Framework on Genetically Modified Organisms and Derived Foods and Feeds

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Abstract

Many countries have established policies and laws with regard to the introduction of genetically modified organisms into the environment already in the early 1990s. Although these jurisdictions differ, approaches to risk assessment are similar since they are following general principles and guidelines elaborated by international organizations. The European Union's regulatory framework and the approach to risk assessment of genetically modified organisms and derived food and feed are reviewed in this paper.

Keywords: GMO; GM plants; genetic modification; safety assessment

Introduction

he first Genetically Modified (GM) food crop to be commercialized was a tomato with extended shelve life. It was introduced to the US market after completion of its evaluation performed by the US FDA [1] in accordance with their Statement of Policy related to foods derived from new plant varieties [2]. This policy clarified that no new laws are necessary but that foods derived from GM plants are regulated within the existing framework of the Federal Food, Drug, and Cosmetic Act, i.e. that an approach identical in principle to that applied to foods developed by traditional plant breeding will be utilized.

Different from this 'product based' approach, where the product of genetic modification, its characteristics and use constitute the primary basis for decisions, irrespective of its method of production, the European Union (EU) had introduced a 'process-oriented' approach where the process of production triggers the regulatory process. Accordingly, Genetically Modified Organisms (GMO) and derived products are regulated as such because they are produced through genetic engineering which is considered a specific production process.

Whilst jurisdictions differ, the approaches to safety assessment are similar in most countries [3] as they are based on general principles developed and agreed upon by supra-national organizations such as the OECD [4], FAO and WHO [5,6]. Here the EU approach to regulation and safety assessment of GMO and derived food and feed is outlined, resulting challenges are discussed.

Development of the EU legislative framework

In the EU, the governing of activities involving genetic engineering began in 1990 with the adoption of Directive 90/219/EEC on the contained use of genetically modified microorganisms [7] and Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms [8]. Directive 90/220/EEC covered experimental releases of GMO (part B) and the placing on the market of GMO and GMO containing products for cultivation, import and/or processing (part C).

The procedure to be followed for the placing on the market of a GMO requires that an application is send to the Competent Authority (CA) of the Member State where the product is to be placed on the market for the first time. The application needs to be accompanied by data and results obtained from laboratory and greenhouse research as well as from experimental releases, and by an assessment of any risks to human health and the environment related to the GMO.

The opinion of the CA on the risk assessment together with the dossier is forwarded to the European Commission and to the other Member States. If the case of a favorable opinion, and if no objections are raised by other Member States, consent can be given to the placing on the market. If any of the Member states raises an objection and if no agreement can be reached, the commission would table a draft decision to a committee composed of representatives of the Member states. If this committee fails to achieve a qualified majority for the adoption of an opinion, the Council of Ministers of the Members States will be asked to take a decision. In case the majority of the committee or the council has voted positively, followed by a favorable decision taken by the commission, the CA that received the notification shall give consent to the placing on the market of the product.

Under this legislation, authorizations were granted between 1992 and 1996 for the commercialization of two live vaccines for animals, for the production of seeds from herbicide tolerant tobacco, chicory and oilseed rape, and for the import of the first GM plant for food and feed use: Monsanto's herbicide tolerant soybean [9]. In January 1997, an insect tolerant Bt-maize was the second GM plant authorized for food and feed use and the first crop to be cultivated in the European Union.

Since Directive 90/220/EEC focused mainly on environmental aspects, a new Regulation [1] providing specific criteria for food safety assessment of GMO was established. The scope of Regulation (EC) No. 258/97 [10], the so-called Novel Foods Regulation, covered not only GMO derived foods but also other foods considered novel because they had not been used for human consumption to a significant degree within the EU before May 1997, when this Regulation entered into force. Therefore, between June 1997 and April 1998 authorizations under Directive 90/220/EEC were granted only for feed use of cultivated and/or imported GM crops [11].

In all cases, the Member States' CAs in charge of risk assessment concluded in their reports that the assessed GMOs are as safe as their

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conventional counterparts. However, objections were raised by some member states during the committee procedure or in the council. In addition, several Member States invoked a safeguard clause provided in Directive 90/220/EEC enabling them to provisionally restrict or prohibit the use and/or sale of a product they consider a risk to human health or the environment on its territory. As a consequence, the commission had ceased authorizing the commercialization of further GM crops under Directive 90/220/EEC after October 1998 [2], leading to a moratorium described as de facto because it had no legal basis.

This de facto moratorium had negatively influenced also the placing on the market of GMO and GMO containing foods under the Novel Foods Regulation. This regulation provides for an authorization procedure comparable to that introduced with directive 90/220/EEC for foods consisting of or containing GMO, and a simplified notification procedure for foods produced from but not containing GMO. While the notification procedure was used for placing on the market of products such as refined oils derived from GM rape seeds and of processed food products from GM maize varieties during 1997 and 1998 and of refined GM cotton seed oil in 2002 [12], applications for GM crops for food use were not successful before May 2004 when the import of insect tolerant sweet maize was approved [13]. At this time the Commission had already taken measures in order to respond to the criticism concerning the existing legislation on GMO.

Current Laws on GMO and derived foods and feeds

Cultivation of GM plants

With Directive 2001/18/EC [14] replacing Directive 90/220/EEC a first step was taken to overcome the de facto moratorium by introducing a more efficient and more transparent procedure for granting consent for the deliberate release of GMO into the environment. Public consultation, GMO labeling, traceability and post-market monitoring had been made compulsory. The first authorization under Directive 2001/18/EC was granted for the import for feed use of a herbicide tolerant maize variety in July 2004, followed by authorizations in 2005 and 2006 for further GM rape seed and GM maize varieties [15].

Placing on the market of GM food and feed

A second step followed with Regulation (EC) No 1829/2003 on genetically modified food and feed [16] and with Regulation (EC) No 1830/2003 concerning the traceability and labeling [17], both becoming effective in April 2004. Regulation (EC) No 1829/2003 replaced the GM food related part of the Novel Food Regulation but dismissed the simplified notification procedure. It covers also GMO derived feed which until then was regulated by Directive 2001/18/EC. Cultivation of GMO, however, still needs an additional authorization in accordance with Directive 2001/18/EC.

The old system has been replaced by a one door–one key procedure for the scientific assessment and authorization of GMOs and derived foods and feeds. A single risk assessment is conducted, and a single authorization is granted for a GMO and its derived products. GMO likely to be used as food and feed can only be authorized for both uses, or not at all.

Authorizations are limited to a ten years period but are renewable. GM foods and feeds which have been lawfully placed on the EU market before Regulation (EC) No 1829/2003 (EC, 2003) entered into force can be further marketed provided that they had been notified to the commission by 17 April 2004. Applications for renewals of authorizations are required within nine years from the date of which the products were first placed on the market.

Labeling provisions

In order to enable consumers and users to make informed choices, the labeling requirements that had already been introduced with the Novel Foods Regulation were extended and are now applicable to all GM foods and feeds, including those produced from, but not containing GMO derived material, such as refined oils from GM oilseed plants. Applicants are requested to provide an event-specific detection method as well as reference material for its validation. A threshold of 0.9 percent has been established for the adventitious or technically unavoidable presence of GM modified material from authorized GMO in foods or feeds.

A zero tolerance applies to GMO that have not been authorized in the EU. However, a new Regulation for low level presence of material derived from GMO that have not yet been authorized in the EU but elsewhere entered into force in July 2011. It provides for a so-called technical threshold by identifying criteria for sample preparation and methods of analysis which ensure that analysis can be performed at the level of 0.1 percent GM material with an adequate precision. So far, this Regulation applies only to feeds containing traces of GMO that have already received a positive opinion by EFSA or of which the authorization has expired, given that certified reference material is available [18].

Authorization procedure

The safety assessment of GM food and feed as well as the assessment of environmental risks is no longer the responsibility of Member States but of the newly established European Food Safety Authority (EFSA) [19]. The EFSA opinions are made available to the public with the opportunity to make comments. Member States' CAs are also invited to provide EFSA with comments.

Based on the EFSA opinion, the European Commission drafts a proposal for granting or refusing authorization. A standing committee on the Food Chain and Animal Health (SCFCAH) consisting of Representatives of Member States then decides whether to accept the commission's proposal through a weighted voting system. If the committee's proposal is neither accepted nor rejected by a qualified majority of Member States, it is referred to an Appeal Committee that also consists of Member States' Representatives. If this committee takes no decision within three months, or does not reach a qualified majority indicating that it opposes the proposal, the European Commission can adopt its decision (Figure 1).

By June 2013, of the 116 applications submitted to EFSA in accordance with Regulation (EC) No 1829/2003 ten have been withdrawn, 35 were approved. The approvals grant the import for food and feed use of GM maize, soybean, cotton, rape seed, sugarbeet and potato varieties. Except for GM potatoes (whose starch composition has been modified) all other authorized GM crops are either herbicide or insect tolerant, or both [20].

Risk assessment of GMO derived foods and feeds

Regulation (EC) No 1829/2003 tasked EFSA to provide guidance in order to assist applicants in the preparation and presentation of the application. The first edition of the Guidance for risk assessment of food and feed from GM plants was elaborated by EFSA's GMO Panel and published in April 2004. It was updated several times, most recently in 2011 [21]. In June 2013, a modified version of this EFSA Guidance was annexed to Regulation (EU) No 503/2013 [22] und thus became legally binding.

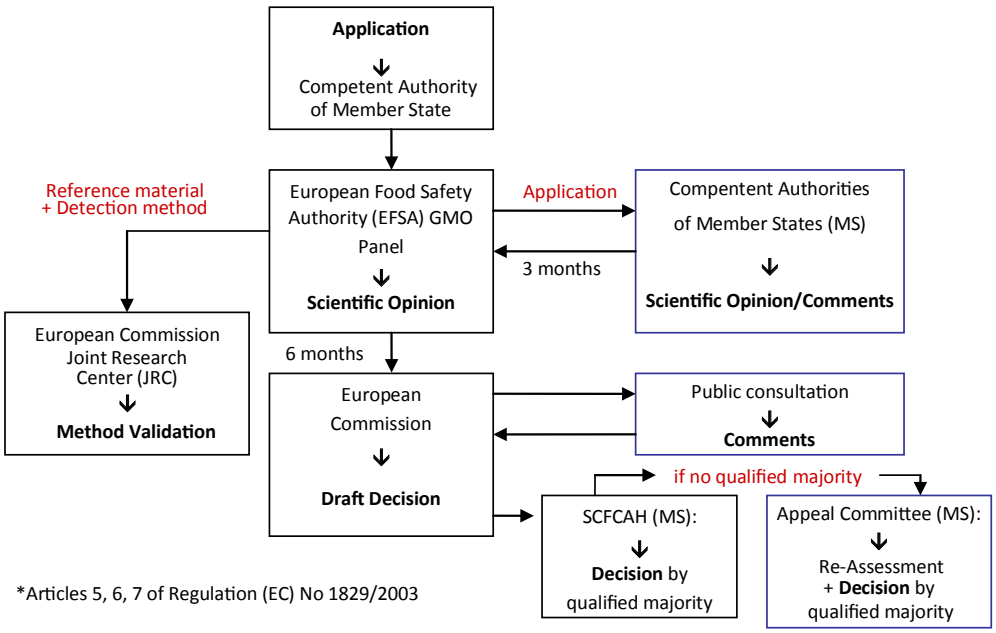

Figure 1: Authorization procedure for food and feed derived from GMO according to Regulation (EC) No 1829/2003.

Strategy of risk assessment

The objective of the assessment is to determine whether the applicant has adequately and sufficiently demonstrated that the GMO and its derived foods and feeds are as safe and as nutritious as comparable conventional products. The EFSA Guidance for risk assessment is based on the internationally accepted recommendations agreed upon by the Codex Alimentarius Member States [23]. Common to both approaches is the underlying concept of substantial equivalence [24] that requires a comparative analysis of the GMO and a non-GM counterpart.

In contrast to conventional breeding techniques genetic engineering allows the transfer into the plant genome of single genes coding for new traits. In addition to the introduction of the intended new characteristics, unintended effects may also occur. The random insertion of the transgene may disrupt or activate endogenous genes causing unintended effects. There is no indication that such unintended effects are more likely to occur in GM crops than in conventionally bred crops where changes in the genome sequence can be caused by genetic rearrangements or metabolic perturbations [25]. Whereas the safety of conventionally bred crops is taken for granted based on a history of safe use, for GM crops a pre-market safety assessment is mandatory.

This assessment includes the characterization of the new genes and expressed products and an array of analyses in order to detect any unintended effects which may be evident in the phenotype or the chemical composition of the GM plant when grown under the same conditions as its comparator and non-modified controls. Identified differences are then subject to further analyses with regards to any potential impact on human and animal health.

The comparative assessment of a GM plant intended for foods and feed use is conducted on a case-by-case basis taking into account the following elements.

Molecular characterization

The molecular characterization aims at the identification of any potential hazards related to the genetic modifications. A first step is the characterization of both, the parental plant used as host for the new gene(s) and the donor(s) of these gene(s).

In order to determine whether rearrangements within the inserted transgene construct had occurred and whether endogenous genes might have been disrupted or new open reading frames have been created through the insertion, the DNA sequences of the inserted DNA and of the genomic flanking regions need to be determined. The amino acid sequences deduced from identified open reading frames are to be compared to known sequences of allergens and toxicants using bioinformatic tools and up-to-date databases. Further, information on the expression of the newly introduced genes as well as on the genetic and phenotypic stability of the new traits is required.

Phenotype and compositional analyses

Unintended alterations in the phenotype are identified through a comparative analysis of the GM plant with a closely related, near-isogenic plant with a history of safe food use and with non-GM reference varieties with regard to agronomic characteristics such as growth performance, yield and disease resistance. These characteristics are studied in field trials that are also used for the generation of material for the comparative compositional analysis.

The interpretation of the results of these targeted analyses depends on the knowledge of the biology and of the chemical compounds that are typical to the respective plant species. For this purpose the OECD's Working Group on Harmonization of Regulatory Oversight in Biology and the Task Force for the Safety of Novel Foods and Feeds are continuingly elaborating series of Consensus Documents to be used for environmental risk assessment and for the food safety assessment of GM plants [26], respectively. The Working Group's Consensus Documents on the biology of plants address a core set of information on the characteristics of certain plants, on selected traits and the environment in which the plant is normally cultivated. The Task Force's Consensus Documents on compositional considerations identify key

components of specific crops, such as nutrients, endogenous toxins and anti-nutrients, and their natural ranges of variation.

Endogenous allergens are not included in the OECD Consensus Documents' lists of constituents suggested to be analyzed. However, in the case of plants, e. g. soybean, known to contain allergens the EFSA Guidance requires a comparative analysis of these allergens. Detailed guidance for the statistical analysis of the data generated in the comparative analyses was published by EFSA in 2010 [27]. Those characteristics that either show differences between the GM plant and the comparator or lacking equivalence with non-GM varieties outside the range of natural variation need further consideration. Additional testing of the GM plant needs to be considered on a case-by-case basis, taking into account whether statistically significant differences are consistent, biologically relevant and whether they might adversely affect human or animal health.

Critics point to the restriction of the comparative analyses that can only detect differences of known characteristics or parameters but not any unpredictable modifications. Since non-targeted profiling technologies being developed in order to analyze and compare whole genomes, transcripts, proteins and metabolites may in the future also contribute to the safety assessment of GMOs, EFSA recommends in its recent guideline that these technologies should be further explored.

Newly expressed proteins

In case of a new protein with no history of safe consumption, its characteristics should be compared to those of known toxicants and allergens, using in silico, *in vitro* and *in vivo* analyses. As a first step, databases should be screened for amino acid sequence similarities with known toxins and allergens as well as with proteins known to be safe.

Since there is no single test for the sensitizing activity of a novel protein, further specific characteristics that are shared by many food allergens such as resistance to proteolytic digestion in simulated gastric fluid, to high temperature, low pH and rigid processing methods as well as post-translational modifications such as glycosylation should be analyzed.

Further toxicological test requirements, such as animal feeding trials, should be considered on a case-by-case basis, taking into account the source, familiarity and characteristics of the protein. In the case of newly expressed proteins with an insufficient database and, in particular, if the available data suggest the existence of any cause of concern a repeated dose 28-days oral toxicity study in rodents should be carried out in accordance with the OECD test guideline for chemicals [28].

If microbial produced protein is used in *in vitro* or *in vivo* studies, evidence of its structural, biochemical and functional equivalence to the GM plant derived protein needs to be provided. This includes comparisons of the molecular weight, immunoreactivity, N-terminal sequences, glycosylation, *in vitro* degradation and functionality tests.

Antibiotic resistance genes

Antibiotic resistance genes have been used in many GM plants for selection of transformants. The safety assessment of these marker genes needs to consider the potential for horizontal gene transfer to microorganisms in the gastrointestinal tract of humans and animals or in the soil and its consequences. Therefore, information on the levels of natural bacterial resistance as well as on clinical and veterinary relevance of the antibiotic is of importance. Marker genes conferring resistance to clinically important antibiotics must not be present in GMO intended for cultivation and for food or feed use [29].

Whole food testing

According to the recent EFSA guidance GM foods and feeds need to be tested for potential toxicity only if the composition of the GM plant is substantially modified or if there are indications for the potential occurrence of unintended effects based on the preceding molecular, compositional or phenotypic analyses. However, in the new Annex of Regulation (EU) No 503/2013 a 90-day feeding study with whole food in rodents is mandatory.

The design of the toxicity study should be performed in accordance with the principles of the OECD test guideline for repeated dose 90-day oral toxicity studies in rodents [30]. Since this guideline was elaborated for testing of chemicals, the application of whole foods requires special attention to be paid to the selection of doses. The lowest dose should approximate the anticipated human intake while the highest dose should reach the maximum achievable level without causing nutritional imbalances. Statistically significant differences observed between test and control groups should be compared to historical data on existing natural ranges of variation and analyzed for consistent patterns and toxicological relevance [31].

Supplemental information on the occurrence of unintended effects such as modified digestibility of nutrients can be obtained from comparative growth studies conducted with rapidly growing animal species such as broiler chickens. Long-term livestock feeding studies with target species are not generally viewed as an essential, sensitive, and specific element of the safety assessment of food. They are limited to the assessment of the dietary feeding value and generally add little to a nutritional assessment once compositional equivalence has been established [32]. They may, however, provide further evidence of tolerance that can be taken into account in the overall assessment of safety.

GM Stacked events

Crop varieties with multiple GM events combined by conventional crossing of GM plants with single GM events have become more important. Different from other parts in the world, these so-called GM stacked events are considered as new GMO in the EU. According to current regulatory practice within the EU, these new GMO require an authorization even where the single events have already been authorized. This includes a safety assessment similar to that required for single events, focusing particularly on potential synergistic or antagonistic effects of the combined transformation events [33].

Critics point out that this approach is not consistent with the objectives of Directive 2001/18/EC where a GMO is defined as "an organism … in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination", and it is not covered as such by Regulation (EC) No 1829/2003 which refers to the placing on the market of "a GMO" as defined in Directive 2001/18/EC.

It is also not obvious why GM stacked events that are as such not products of genetic engineering but results from classical breeding are treated differently than hybrids obtained from crosses between GM and non-GM plants which are not subject of the EU legislation. Meanwhile, however, with Regulation (EU) No 503/2013 risk assessment of stacked transformation events has become mandatory.

Conclusion

The EU legislation on GMO and derived foods and feeds provides that only GM products that have been demonstrated to be as safe as

their conventional counterparts are commercialized. It also provides for transparent procedures for safety assessment and labeling requirements, thus enabling consumers and users to make informed choices.

However, the poor acceptance of GM food by the public in many of the EU Member States has caused internal disagreement. Given the procedure of decision-making as laid down in the EU's regulatory framework, the European Commission is facing difficulties in fulfilling its function to balance diverging national interests with the aim of reaching a common European position.

This might explain that, while the acreage of genetically modified crops and also the number of countries where these crops are cultivated have consistently grown since 1996, the development in the EU rather tends to head into the opposite direction [34]. At present, only two GM crops are authorized for cultivation: the insect tolerant MON810 maize and the amylopectin-rich potato cultivar Amflora. Only few EU member states have made use of these authorizations.

France, Germany and Spain started growing MON810 maize in 1998, followed by Romania (EU member state since 2007) in 2004, Portugal and the Czech Republic in 2005, Slovakia in 2006 and Poland in 2007. France, Germany and Poland, however, prohibited MON810 maize cultivation in 2008, 2009 and 2012, respectively. The Amflora potato was grown in 2010 at very small scale in the Czech Republic, in Germany and Sweden and in 2011 at even smaller scale in Germany and Sweden. In 2012, Amflora potato cultivation was discontinued.

Several GM soybean varieties have been authorized and are imported for feed purposes. However, the lack of consumer acceptance in several EU Member States obviously has caused hesitation among manufacturers to use GM crops for food production. While the current EU regulatory framework has been introduced in order to improve consumer confidence, it has also created new challenges.

The existing zero tolerance requires testing of imported crops and derived foods and feeds because in practice, it is not always possible to avoid the unintended presence of traces of unauthorized GMO in commodities such as soybean or maize imported from countries with large scale cultivation of different GM varieties. Although efforts have been made towards a more realistic tolerance limit at least for feeds with the introduction of a technical threshold, plans for the extension of this threshold to foods and seeds have not yet been realized.

In a study, commissioned by the European Commission's Directorate General for Health and Consumers (DG SANCO), the authors concluded that the current EU approach on GM stacked events has increased the workload for both EFSA and the commission as well as for the national CAs. It also contributes to the increasing gap between authorizations in third countries and those in the EU and to consequential impact in terms of low level presence incidents [35].

The authors of this study also stated that public trust in science-based risk assessment in the context of GMO is currently low and better communication may be needed. As main factors to be taken into account in general communication strategies on GM they have identified: increased engagement of the industry and government organizations; better definition of the target audience; and, a need to contextualize potential risks against potential benefits.

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