Scientific and technical support by ANSES
Request No. 2014-SA-0243
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The Director General

Maisons-Alfort, 26 August 2015

SCIENTIFIC AND TECHNICAL SUPPORT NOTE by the French Agency for Food, Environmental and Occupational Health & Safety

concerning the studies necessary for the assessment of GMOs developed for non-EU countries and that could be unintendedly present at low levels on the European market

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 26 August 2015 shall prevail.

On 19 November 2014, ANSES received a request from the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) to produce a Scientific and Technical Support note on the studies necessary for the assessment of GMOs developed for non-EU countries and that could be unintendedly present at low levels on the European market.

1. BACKGROUND AND PURPOSE OF THE REQUEST

In September 2014, the European Commission mandated EFSA to identify the studies necessary for preparing applications for marketing authorisation of GMOs developed for non-EU countries and not intended for the European market, but that could be present at low levels on this market. This is because the marketing of certain GMOs developed in non-EU countries for local needs seems to have been frozen for fear about their unauthorised possible presence in export channels.

According to the European Commission, there are two possible options to prevent these GMOs from being regarded as unauthorised in Europe:

- submitting traditional applications, as if these GMOs were intended for the European market. However, it may be the case that these GMOs do not meet all the European evaluation criteria;
- exploring the possibility of submitting applications that take account of the fact that the GMOs in question should only be present in trace amounts, as they are not intended for the European market. Article 5(2) of Implementing Regulation (EU) No 503/2013 states that all scientific requirements provided for in Annex II of the said Regulation need not be met owing to the nature of the product, or because they are not justified from a scientific perspective.

If this second option should ultimately be chosen by the European Union, the product would be assessed according to criteria that would differ from those in a traditional authorisation application, before being permitted at a maximum level of 0.9%: the GMO would then be subject to a decision authorising traces of less than 0.9%.

As there is no overall consensus regarding the 0.9% threshold set by the European Commission, the purpose of the Request is to establish:

- which studies would be indispensable in the case of trace amounts lower than 0.9%;
- whether some of the studies thus identified would become irrelevant if the threshold were to be lowered (for example to 0.5 or 0.1%).

At present, it seems that the only GMOs that would be affected by these provisions are plants (rice enriched with vitamin A and iron (Golden Rice), virus-resistant cassava, etc.). As a result, only Genetically Modified Plants (GMPs) were studied (the cases of genetically modified microorganisms and animals were not considered). In addition, the Request concerns both raw products and processed products derived from GMPs.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)".

Four rapporteurs were appointed on 18 February 2015. Their expert appraisal reports were presented at the meeting of the "Biotechnology" Working Group (WG) on 19 March 2015. They then met on 8 April 2015 to compare their appraisals and form a consensual proposal. Lastly, the collective expert appraisal was conducted by the "Biotechnology" WG, meeting on 21 May and 20 August 2015.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The declarations of interest by experts are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE WORKING GROUP

3.1. Previous work

In 2007, AFSSA had participated in the discussions that led in 2008 to the adoption of Annexes 2 and 3 of the "Directive governing the conduct of the Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" of the Codex Alimentarius[1]. This Directive aims to define an approach for assessing foods that contain low concentrations of GMOs not yet authorised in Europe but that have undergone an assessment in a non-EU member country of the Codex.

In the absence of regulations relating to the presence of GMOs in trace amounts in foodstuffs and animal feed, and taking into account the policy of zero tolerance in force in European countries, the detection of GMOs unauthorised in Europe in products intended for food or feed has resulted in the destruction of the products concerned. In the face of this problem and its impact on trade flows (delays and additional costs), Europe has adopted Regulation (EU) No. 619/2011[2], which sets out

[1] Codex Alimentarius Commission (2008). Directive governing the conduct of the Food Safety Assessment of Foods Derived from Recombinant-DNA Plants, in "Foods Derived from Modern Biotechnology", Second Edition. Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO), Eds, Rome, pp. 7-37.

[2] European Commission Regulation (EU) No. 619/2011 of 24 June 2011 laying down the methods of sampling and analysis for the official control of feed as regards presence of genetically modified material for which an authorisation procedure is pending or the authorisation of which has expired. Official Journal of the European Union, L 166 of 25 June 2011, pp. 9-15.

methods for sampling and analysis for official controls on the presence of GMOs in animal feed by setting a tolerance threshold of 0.1%. This Regulation concerns only the GMOs that undergo an authorisation procedure or whose authorisation has expired in Europe and that may adventitiously be found in animal feed.

The objective of this Request is different, because the purpose is to define the information that an applicant should provide to obtain an authorisation for placing its GMP on the European market for use in animal feed and human food, provided that it is only present as traces in the products.

It appeared necessary to define separate approaches depending on whether the products can be consumed whole, or only in mixtures and/or after processing. For each of these two cases, the essential information needed for assessing the health risk related to the presence of these products in trace amounts has been defined, irrespective of which threshold (0.9%, 0.5% or 0.1%) is chosen.

3.2. Case of products consumed only in mixtures and/or after processing

In the case of grains (rice, rapeseed, soybeans, etc.) and derived products (flour, meal, oils, juices, purées, etc.), the health risk related to the consumption of the GMP in trace amounts (at a level below 0.9%) is greatly reduced by the dilution. To assess this type of product, the "Biotechnology" WG considers that the following information is necessary:

- a complete molecular characterisation (sequence of the insert(s) and of the flanking genomic sequences, site(s) of insertion, tissue-specificity), bioinformatic analyses to search for the possible presence of new open reading frames (ORFs) showing sequence homologies with known toxins or allergens and the possible interruption of endogenous genes, and measurement of the concentration of the newly-expressed protein(s) in the different tissues consumed.
- a 28-day toxicity study if the newly-expressed protein(s) have never undergone a toxicological assessment.

No allergenicity assessment seems necessary, except for plant species known to be highly allergenic. In effect, the reactogenic dose has been estimated in some studies at 1.3 µg (1/1,000,000 patients) of allergens for soy flour. This value appears particularly low. Other studies suggest allergen doses of 2.4 mg (1/1,000,000 patients) and 41 mg (1/100 patients), corresponding to quantities of flour ingested of 17.7 mg (1/1,000,000 patients) and 295 mg (1/100 patients). The results of another study show that the reactogenic dose for soy flour would be 1 mg of protein. The significant variations observed likely come from the estimation of the quantities of allergens, which is not always accurate. Be that as it may, for products consumed in mixtures and/or after processing, the traces of allergens supplied by the GMP are bound to be extremely diluted. This component of the risk assessment does not therefore appear necessary in this case.

3.3. Case of products that can be consumed whole

Especially in the case of fruit and vegetables (papaya, tomato, potato, eggplant, etc.), when a GMP is present at a level of 0.9% in a batch, the consumer may actually eat a product that is 100% genetically modified. This means that additional information seems necessary compared to the case of products consumed only in mixtures and/or after processing.

As noted earlier, the assessment of these products requires:

- a complete molecular characterisation (sequence of the insert(s) and of the flanking genomic sequences, site(s) of insertion, tissue-specificity), bioinformatic analyses to search for the possible presence of new ORFs showing sequence homologies with known toxins or allergens

and the possible interruption of endogenous genes, and measurement of the concentration of the newly-expressed protein(s) in the different tissues consumed.
- a 28-day toxicity study if the newly-expressed protein(s) have never undergone a toxicological assessment.

Then, if the trait(s) introduced in the GMP is (are) designed to change its composition (e.g. modification of the fatty acid profile) or certain metabolic pathways (e.g. delaying ripening of fruit by changes in the metabolic pathways for ethylene), an analysis of its composition based on the OECD consensus documents is necessary. The field trials shall be carried out and the data processed in accordance with the EFSA recommendations, in particular as regards the number of test sites, the choice and the number of comparators and the implementation of statistical tests of difference (comparison of the GMP with its non-genetically modified counterpart) and of equivalence (comparison of the GMP with commercial reference varieties).

In the other cases, and in particular for plant species especially rich in antinutritional compounds, whether mineral (phytates) or organic (trypsin inhibitors, lectins), and/or toxic compounds (alkaloids, glycosides, etc.), and/or allergens (fruit of the Rosaceae and Solanaceae families, banana, papaya, mango, kiwi, etc.), this analysis may be limited to the antinutritional, toxic and allergenic compounds. Many of these compounds are not listed in the OECD consensus documents. In addition, for certain species which are undergoing GMP development (e.g. eggplant, bean, melon, apple), the OECD has not yet published a consensus document. Additional information is therefore necessary.

Lastly, an allergenicity assessment shall be conducted according to the EFSA recommendations:
1) in the case where the concentration of the newly-expressed protein(s) in the edible organs (concentration likely to induce an allergic response) is of the order of magnitude of 1 mg/g of dry matter. This is because the doses of allergens capable of inducing a reaction vary considerably depending on:
- the allergen,
- the number of allergic patients considered (1/100 or 1/1,000,000),
- the route of exposure,
- other factors such as age or sex.

However, the reactogenic doses of several particularly allergenic foods (peanut, hazelnut, cashew nut, soy, milk, egg) have been estimated [1-6]. In desensitisation tests (specific immunotherapy) to peanut, treatment generally begins with a dose of 70 mg of peanut/week, which corresponds to 17 mg of protein (total proteins of the seed) and 2 mg of Ara h 1, 1 mg of Ara h 2 and 2.5 mg of Ara h 3 [5]. This dose is gradually increased to reach one or more grams of peanut/week. A threshold in the region of 1 mg/g of dry matter therefore seems reasonable for requesting an assessment of the allergenicity, as well as the evaluation of the adjuvant character in cases where the protein(s) expressed may be toxins.
2) when the plant is known for its natural allergenicity (soy, fruit with allergenic properties such as kiwi or papaya, etc.). In this case, a study of the possible modification of allergenicity linked to the genetic modification will be required, as is currently the case for applications for marketing authorisation under Regulation (EC) No 1829/2003[3]. Websites dedicated to the allergenicity of natural products (Allergome[4], for example) can be used to identify the plant species concerned.

3.4. Conclusion

In conclusion, the "Biotechnology" WG emphasises that if this approach is adopted, the dossiers submitted by applicants within this framework could not in any circumstances replace the

[3] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed; OJEU L 268 of 18 October 2003, pp. 1-23.
[4] http://www.allergome.org/

applications required to obtain traditional marketing authorisations under Regulation (EC) No 1829/2003. In other words, applicants ultimately wishing to obtain a marketing authorisation for a GMP in Europe and who have already obtained authorisation for traces lower than 0.9% will have to submit a complete application dossier, in order to obtain marketing authorisation under Regulation (EC) No 1829/2003.

Furthermore, if such provisions are implemented, applicants will need to provide the method for detecting and quantifying the GMP, as well as the reference material necessary for the validation of this method by the Joint Research Centre, as for usual applications for marketing authorisation under Regulation (EC) No 1829/2003.

In its analysis, the "Biotechnology" WG distinguished between products consumed only in mixtures and/or after processing and those that may be consumed whole. For the former, the information required will be a complete molecular characterisation and a 28-day toxicity study if the newly-expressed protein(s) have never undergone a toxicological assessment. For the latter, the same information would be required, as well as a composition analysis, complete if the purpose of the trait(s) introduced in the GMP is to change its composition or certain metabolic pathways, or limited to antinutritional and toxic compounds and allergens in the other cases. This analysis should be carried out according to the OECD consensus documents for the choice of the compounds (which will require supplementing the list of antinutritional and toxic compounds and allergens contained in the OECD consensus documents and creating such documents for species that are not yet covered) and according to the EFSA recommendations as regards the experimental protocol and data processing.

4. CONCLUSIONS AND RECOMMENDATIONS OF THE AGENCY

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions of the "Biotechnology" Working Group.

The Director General

Marc Mortureux

KEYWORDS

GMO, application for marketing authorisation, traces, Regulation (EC) No 1829/2003, Implementing Regulation (EU) No 503/2013

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