Guidance for the risk assessment of the presence at low level of genetically modified plant material in imported food and feed under Regulation (EC) No 1829/2003

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Guidance for the risk assessment of the presence at low level of genetically modified plant material in imported food and feed under Regulation (EC) No 1829/2003

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Abstract

This document provides guidance for the risk assessment under Regulation (EC) No 1829/2003 of the unintended, adventitious or technically unavoidable presence in food and feed of low level of genetically modified plant material intended for markets other than in the European Union. In this context, the presence at low level is defined to be maximum 0.9% of genetically modified plant material per ingredient. This guidance is intended to assist applicants by indicating which scientific requirements of Annex II of Regulation (EU) No 503/2013 are considered necessary for the risk assessment of the presence at low levels of genetically modified plant material in food and feed.

Keywords: guidance, GMO, presence at low level, risk assessment, Regulation (EC) No 1829/2003, Regulation (EU) No 503/2013, food/feed

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Summary

Following a request of the European Commission, the European Food Safety Authority (EFSA) provides guidance on the scientific requirements of Annex II of Regulation (EU) No 503/2013 considered necessary (and those not) to conclude on the safety of applications covering the adventitious or technically unavoidable presence at low level (0.9% or below per ingredient) of genetically modified plant material in food and feed intended for markets other than in the European Union (EU).

This guidance provides support to and should be read in conjunction with Regulation (EU) No 503/2013 and it is not intended to serve as a stand-alone guidance.

The characterisation of the transformation event and of its intended effects should be performed. Not all the scientific requirements of the Annex II of Regulation (EU) No 503/2013 aiming at identifying unintended effects are considered necessary on a routine basis, since the safety and nutritional impact of these effects on the ingredient are considered limited in the context of the presence of a genetically modified plant material at low level. These requirements include some data concerning the expression of the insert, *in silico* RNAi off–target searches, routine comparative analysis studies of the genetically modified plant; 90-day toxicity studies in rodents on the whole food and feed are not considered necessary.

On a case-by-case basis, when a hypothesis can be formulated for compositional changes that may impact the safety and nutritional characteristics of the ingredient, a targeted compositional analysis is requested. The experimental design, selection of endpoints and data analysis of such a targeted analysis would not need to follow all the scientific requirements of Annex II of Regulation (EU) No 503/2013. Comparative compositional studies performed according to *Codex Alimentarius* could support such assessment.

The applicant needs to justify the approach followed and to indicate what assumptions have been made during the risk assessment as well as the nature and magnitude of uncertainties.

Both acute and repeated exposure scenarios should be envisaged.

The possible cumulative contribution to an ingredient from various genetically modified plants and derived products present at low level and showing similar traits should be considered.

Environmental risk assessments conducted under situations of the presence at low levels should follow the principles and approach outlined in the Genetically Modified Organisms Panel Guidance Document on the environmental risk assessments of genetically modified plants and other applicable EFSA guidelines.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Genetically modified organisms (GMOs) and derived food and feed products are subject to a risk assessment and regulatory approval before they can enter the market in the EU. In this process, the role of the EFSA is to independently assess and scientifically advise risk managers on any possible risk that the use of GMOs may pose to human's and animal's health and the environment. EFSA's scientific advice is elaborated by its GMO Panel with the scientific support of specific working groups and EFSA scientists.

Detailed guidance was adopted by EFSA (2006) and updated in EFSA GMO Panel (2011a) to assist applicants in the preparation and the presentation of applications of food and feed from genetically modified (GM) plants submitted under Regulation (EC) No 1829/2003[1] (Reg. (EC) 1829/2003) and hereafter referred to as 'standard GMO applications'. The European Commission subsequently adopted in April 2013 Regulation (EU) No 503/2013[2] (Reg. (EU) 503/2013) on applications for authorisation of GM food and feed. Annex II of this Regulation lists the scientific requirements to be provided for GM plants for food and feed uses in accordance with Articles 5(3) and 17(3) of Reg. (EC) 1829/2003. Article 5(2) of Reg. (EU) 503/2013 states that by way of derogation, an application may be submitted that does not satisfy all the scientific requirements for the risk assessment of GM food and feed set out in Annex II, provided that 'particular information is not necessary owing to the nature of the genetic modification or of the product; or it is not scientifically necessary, or technically possible to supply such information'.

Genetically modified organisms and derived food and feed products not intended to be exported to the EU have been or are being developed for specific health or market needs in third countries. The accidental presence of some of these GMOs at low levels cannot completely be excluded in exports to the EU. In this context and in accordance with Article 29 of Regulation (EC) No 178/2002,[3] the European Commission in 2014 mandated EFSA to advise whether or not all requirements of Annex II to Reg. (EU) 503/2013 are necessary to conclude on the safety of applications covering the unintended presence of GMOs in food and feed at the adventitious or technically unavoidable level of 0.9% or below. If not, EFSA was required to indicate which requirements are unnecessary and to give the underlying rationale. Following a request for clarification by EFSA, the European Commission further explained that:

- the EFSA guidance should be applicable to the presence at low level of GMOs, independently of the existence or not of a third country risk assessment;
- applications submitted under this EFSA guidance should only concern GMOs developed for specific health or market needs in third countries and not intended for the EU market. Therefore, they should not cover GMOs for which a full scope application has been previously submitted;
- exposure scenarios through commodities, such as grains, beans, or through foods consumed whole and undiluted should be considered under this EFSA guidance (further clarification on this point is provided in Section 1.2 of this document);
- a cumulative risk assessment should be performed in case of similar traits present in the same crop in different applications submitted under this EFSA guidance;
- for stacks, the same principles as those referred to in Reg. (EU) 503/2013 will apply and the implementation of the 0.9% threshold should follow the same rules as for labelling purposes, i.e. the threshold applies to individual events.

In 2015, EFSA accepted the mandate from the European Commission and committed to issue an EFSA Scientific Opinion providing guidance on which scientific requirements of Annex II of Reg. (EU) 503/2013 are necessary to conclude on the safety of applications submitted under Reg. (EC) 1829/2003 covering the unintended presence of GMOs in food and feed at the adventitious or technically unavoidable presence of 0.9% or below, and which are not, providing the underlying rationale.

[1] Regulation (EC) No Reg. 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. Official Journal of the European Communities, L 268, 1–23.

[2] Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No Reg. 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L 157, 8.6.2013, p. 1–48.

[3] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 031, 1.2.2002, p. 1–24.

1.2. Interpretation of the Terms of Reference

Following an exchange with the European Commission, it was further clarified that an application of a GMO at low level submitted under Reg. (EC) 1829/2003 (hereafter referred to as 'LL application') covers a request for the authorisation of a GMO[4] present at a level of maximum 0.9% per ingredient in any food and/or feed, due to adventitious or technically unavoidable circumstances.

For the purpose of this document, an ingredient (hereafter referred to as 'LL ingredient') is the mixture of the GMO subject of the LL application and the same plant species and/or derived product at the predefined proportion of a maximum of 0.9% and minimum of 99.1%, respectively.

It is assumed that in a LL application the GMO is present at a level of maximum 0.9% per LL ingredient from point of entry into the EU through the food/feed production and processing chain, up to the food (or feed) portion consumed.

Situations where a GMO can achieve levels higher than 0.9% per LL ingredient are therefore not in the remit of this guidance. This could be the case of GM fruits and vegetables (e.g. papaya, potatoes) constituting either a full portion or part of a consumed portion resulting in an exposure of consumers (or animals) to that GMO higher than 0.9%. Therefore, even if included in the European Commission mandate, these situations are not within the remit of this guidance.

The decision on whether a given GMO can constitute a LL application is a risk management issue, and it is therefore not in the remit of this guidance.

In its mandate, the European Commission referred to *Codex Alimentarius* guideline for the food safety assessment of Low Level Presence (LLP) of recombinant DNA plant material in food[5] as a document to consider during the development of this guidance. The GMO Panel took into consideration principles and requirements outlined in the above-mentioned document to develop this guidance. Some adaptations were needed to address the Terms of Reference of this mandate; these are summarised in Appendix A of this guidance.

2. Data and methodologies

2.1. Data

In delivering this guidance, the GMO Panel took into account the requirements outlined in Reg. (EC) 1829/2003, Reg. (EU) 503/2013, *Codex Alimentarius* (2009),[6] EFSA guidance documents (EFSA GMO Panel, 2010, 2011a) and relevant scientific publications.

2.2. Methodologies

EFSA established an ad hoc Working Group of the GMO Panel to address the mandate on the risk assessment of the presence at low levels of GMOs not intended for the EU market in imported food and feed under the frame of Reg. (EC) 1829/2003. In accordance with the Terms of Reference of the mandate, the Working Group scrutinised which scientific requirements of Annex II of Reg. (EU) 503/2013 are necessary to conclude on the safety of GMOs present in food and feed at the adventitious or technically unavoidable level of maximum 0.9% per ingredient. Possible derogations from existing requirements were identified, and justified reasons provided.

In order to adequately take EU Member States and stakeholders comments into account, two consultations were organised in a stepwise manner. The first consultation (from 28 October to 9 December 2016) was dedicated to EU Member States. Following this consultation process, the document was revised by the GMO Panel and then opened for a second public consultation (from 2 May to 13 June 2017) where all stakeholders, including EU Member States, contributed further to the development of the guidance. As an outcome of these consultations, a technical report will be published on the EFSA website.

[4] Genetically modified plants for food or feed uses, food or feed containing or consisting of genetically modified plants and food or feed produced from such plants in accordance with Reg. (EU) 503/2013 (Preamble 5).

[5] Annex 3 (Food safety assessment in situations of low-level presence of recombinant-DNA plant material in food - adopted 2008) of the Guideline for the conduct of food safety assessment of foods derived from recombinant-DNA Plants, CAC/GL 45-2003, adopted 2003 (Codex Alimentarius, 2009).

[6] Codex Alimentarius, 2009 includes the *Guideline for the conduct of food safety assessment of foods derived from recombinant-DNA Plants*, CAC/GL 45-2003, adopted 2003; and its Annex 3 *Food safety assessment in situations of low-level presence of recombinant-DNA plant material in food* adopted in 2008.

3. Assessment

3.1. Introduction

3.1.1. Scope of the guidance

This document is intended to assist applicants in the preparation of LL applications by indicating which scientific requirements of Annex II of Reg. (EU) 503/2013 are necessary and which are not, in this case providing justification, in order to conclude on the safety of a GMO not intended for the EU market present at low level in any food/feed (maximum 0.9% per ingredient). This document supports Reg. (EU) 503/2013 and it is not intended to serve as a stand-alone guidance.

Definitions and requirements of Reg. (EU) 503/2013 other than those indicated in its Annex II apply to LL applications.

This guidance does not cover the risk assessment of GMOs for cultivation purposes, GM microorganisms, GM animals, GMOs for non-food/feed uses and novel foods as this is not in the scope of Reg. (EU) 503/2013. This guidance does not consider issues related to risk management (e.g. traceability, labelling and coexistence). Socioeconomic and ethical issues are also outside the scope of this guidance.

3.1.2. General considerations for the risk assessment of LL applications

The risk assessment strategy for standard GMO applications is driven by the comparative assessment principle, which aims to evaluate whether the GMO is as safe and as nutritious as traditionally cultivated crops (and derived products) with a history of safe use for consumers and/or animals (Codex Alimentarius, 2009; EFSA GMO Panel, 2011a). Within this comparative frame, a standard GMO application is assessed assuming the possibility of a 100% replacement of the corresponding conventional crop and derived products. To support the assessment, the GMO Panel identified the scientific requirements and deployed a wide range of tools and methods (EFSA GMO Panel, 2011a), which have been incorporated into Annex II of Reg. (EU) 503/2013 by the European Commission and EU Member States.

In a LL situation as defined in this guidance, exposure to the GMO will be at maximum 0.9% per LL ingredient. This predefined threshold implies a lower exposure to the GMO than that foreseen in standard GMO applications. The adventitious or technically unavoidable circumstances leading to a LL situation do not exclude the possibility of repeated exposure of consumers/animals to the GMO. Therefore, both single and repeated exposure scenarios are considered.

Based on the above considerations and taking into account the *Codex Alimentarius* guideline for the 'Food safety assessment in situations of low-level presence of recombinant-DNA plant material in food' (Annex 3, adopted 2008), the GMO Panel considers that certain scientific requirements for the risk assessment of standard GMO applications are necessary in LL situations, others are not or should be adapted. Section 3.2 of this guidance describes in detail which scientific requirements of Annex II of Reg. (EU) 503/2013 are necessary and which are not to conclude on the safety of a GMO in a LL application.

For the risk assessment of LL applications of stacked events, the applicant will provide a risk assessment of each single transformation event or, in accordance with Article 3(6) of Reg. (EU) 503/2013, refer to already submitted application(s).

3.2. Scientific requirements for the risk assessment of LL applications submitted under Reg. (EC) 1829/2003 (Reg. [EU] 503/2013; Annex II)

3.2.1. Introduction: Definitions (Reg. [EU] 503/2013; Annex II.I, 1)

Paragraph 1 of Annex II.I of Reg. (EU) 503/2013 applies.

3.2.2. Introduction: Specific considerations (Reg. [EU] 503/2013; Annex II.I, 2)

3.2.2.1. Insertion of marker genes and other nucleic acid(s) sequences not essential to achieve the desired trait (Reg. [EU] 503/2013; Annex II.I, 2.1)

All the scientific requirements described in paragraph 2.1 of Annex II.I of Reg. (EU) 503/2013 are considered necessary for LL applications.

3.2.2.2. Risk assessment of genetically modified food and feed containing stacked transformation events (Reg. [EU] 503/2013; Annex II.I, 2.2)

The risk assessment of GMOs containing stacked transformation events (i.e. single transformation events combined by conventional crossing, also referred hereafter as stacks) described in paragraph 2.2 of Annex II.I of Reg. (EU) 503/2013 focuses on:

a) stability of the transformation events;
b) expression of the transformation events;
c) potential synergistic or antagonistic effects resulting from the combinations of the transformation events in accordance with the respective sections of Annex II.II of Reg. (EU) 503/2013 relative to toxicology (Section 1.4), allergenicity (Section 1.5) and nutritional assessment (Section 1.6).

The scientific requirements to address the above points are provided in the specific Molecular characterisation and Food and feed sections of Annex II.II of Reg. (EU) 503/2013. The relevance of these requirements for LL applications is discussed in the respective specific sections of this document.

The scientific requirements laid down in paragraph 2.2 of Annex II.I of Reg. (EU) 503/2013 as regards the assessment of subcombinations in stacked events are considered necessary in LL applications.

3.2.3. Scientific requirements: Hazard identification and characterisation (Reg. [EU] 503/2013; Annex II.II, 1)

3.2.3.1. Information relating to the recipient or (where appropriate) to parental plants (Reg. [EU] 503/2013; Annex II.II, 1.1)

All the scientific requirements described in paragraph 1.1 of the Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

3.2.3.2. Molecular characterisation (Reg. [EU] 503/2013; Annex II.II, 1.2)

The molecular characterisation of the GM plant serves two purposes: first, it allows the characterisation of the transformation event, and second, it is the first step to detect potential unintended effects linked to the genetic modification.

In the case of LL situations, the exposure to the GMO is defined to be at a maximum 0.9% per ingredient, and therefore, some of the molecular characterisation data requirements specified in Annex II.II of Reg. (EU) 503/2013 are not considered necessary, or necessary only on a case-by-case basis. In the following sections, the rationale for considering whether specific requirements are necessary or not is described.

Information relating to the genetic modification (Reg. [EU] 503/2013; Annex II.II, 1.2.1, subsections 1.2.1.1–1.2.1.3)

The scientific requirements of this paragraph (including all subsections) serve to characterise the genetic modification(s) of the plant. Therefore, all requirements described in paragraph 1.2.1 of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

Information relating to the genetically modified plant (Reg. [EU] 503/2013; Annex II.II, 1.2.2, subsections 1.2.2.1–1.2.2.5)

The scientific requirements in subsection 1.2.2.1 ('General description of the trait[s] and characteristics which have been introduced or modified') and subsection 1.2.2.2 ('Information on the sequences actually inserted/deleted') of Annex II.II of Reg. (EU) 503/2013 serve to characterise the genetic modification(s) and therefore are considered necessary in LL applications.

Subsection 1.2.2.3 ('Information on the expression of the insert[s]') of Annex II.II of Reg. (EU) 503/2013 describes the scientific requirements as regards the information on the expression of the insert(s). These requirements serve to demonstrate whether the inserted/modified sequence results in the intended changes in the GM plant.

Protein expression data obtained under the conditions in which the crop is grown as well as the description of the methods used for expression analyses (point 1.2.2.3(a)] and (e)) are considered necessary for characterising the GM plants in LL applications on single transformation events. However, only the expression levels from those part(s) of the plant used for food and feed purposes are considered needed to complete the risk assessment. Therefore, points 1.2.2.3(b) ('information on

developmental expression of the insert during the life cycle of the plant') and 1.2.2.3(c) ('parts of the plant where the inserted/modified sequences are expressed') of Annex II of Reg. (EU) 503/2013 are not considered necessary in LL applications. The likelihood of off-target effects resulting from silencing approaches by RNAi expression large enough to raise safety concerns in a LL situation is considered negligible. Therefore, the *in silico* search for potential 'off-target gene(s)' described in point 1.2.2.3(e) is not considered necessary.

The requirements described in subsection 1.2.2.3 ('Information on the expression of the insert[s]') of Annex II.II of Reg. (EU) 503/2013 also serve to characterise the potential unintended expression of new open reading frames (ORFs) identified as raising a safety concern. Point 1.2.2.3 (d) requiring such an expression analysis is considered necessary in a LL situation.

In the case of stacks, the GMO Panel considers that the likelihood for changes in the expression levels of the newly inserted sequences as a consequence of interactions between the events impacting the safety of the LL ingredient is negligible, given the defined presence of 0.9% of the stack per LL ingredient. Therefore, point 1.2.2.3(f) of Annex II of Reg. (EU) 503/2013 is not routinely required. On a case-by-case basis, when the nature or the characterisation of the transformation events combined in a stack suggests an interaction that may result in changes of the expression levels of the newly inserted sequences raising safety concerns in a LL situation, these data should be provided.

The scientific requirements in subsection 1.2.2.4 ('Genetic stability of the insert and phenotypic stability of the genetically modified plant') of Annex II.II of Reg. (EU) 503/2013 serve to characterise the genetic modification(s) of the plant and are considered necessary in LL applications.

The scientific requirements in subsection 1.2.2.5 ('Potential risk associated with horizontal gene transfer') of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

Conclusions of the molecular characterisation (Reg. [EU] 503/2013; Annex II.II, 1.2.3)

Based on the above, this section should contain concluding information on the molecular characterisation of the transformation event(s) as well as indications on whether the genetic modification(s) raises safety concerns considering the scope of the LL application.

3.2.3.3. Comparative analysis (Reg. [EU] 503/2013, Annex II. II, 1.3)

The comparative analysis of composition and agronomic and phenotypic characteristics constitutes, together with the molecular characterisation, the starting point to structure and conduct the risk assessment of food and feed from GM plants under Reg. (EC) 1829/2003 (EFSA GMO Panel, 2011a). It aims at identifying the differences in composition (intended and unintended) between the GM plant and its conventional counterpart, and between the food and feed derived from the GM plant and those derived from the conventional counterpart. It also aims at identifying differences in agronomic performance and phenotypic characteristics (intended and unintended) between the GM plant and its conventional counterpart. The methodological approach to conduct the comparative assessment on GMOs is detailed in paragraph 1.3 of Annex II.II of Reg. (EU) 503/2013, including criteria for the selection of appropriate comparator, experimental design of field trials and statistical analysis of results, selection of endpoints to measure and effects of processing.

The GMO Panel considers that the scientific requirements on comparative analysis of Reg. (EU) 503/2013 can be adapted for LL applications. Since in LL situations the level of exposure of consumers and animals to the GMO is defined to be at a maximum 0.9% per LL ingredient, not all differences identified in the comparative analysis may be relevant.

As regards compositional analysis, the level of a compound in a LL ingredient is determined by the levels of such compound in the GMO and in the plant (and/or derived product) constituting the remaining part of the LL ingredient. The ratio between these two levels determines the extent to which the level of the compound of the GMO impacts the overall level of that compound in the LL ingredient. For example, if the level of a compound in the GMO is 100X larger than that of the ingredient without the GMO, the increase of the compound in the LL ingredient as compared to the ingredient without that GMO is approximately twofold ($\sim$ 1.891).[7] A decrease in the level of a compound in the GMO results into a level in the LL ingredient never lower than 0.991 folds with respect to the ingredient without the GMO. In Table 1, other examples of how the 0.9% GMO can affect the overall level of a compound in a LL ingredient are shown.

[7] If the level of a compound (A) in the GMO is 100X compared to the level of A in the ingredient without the GMO, then the level of A in the LL ingredient = 100 $\times$ 0.9% + 99.1% = 189.1% = 1.891 folds with respect to level of A in the ingredient without the GMO.

Table 1: Impact of variations in the levels of a compound in a GMO on the level of the same compound in a LL ingredient

Relative level of a compound in a GMO with respect to the level of that compound in the ingredient without that GMO	Relative level of the compound in the LL ingredient with respect to the level of that compound in the ingredient without that GMO
0	0.991
0.001	0.991009
0.01	0.99109
0.1	0.9919
1	1
10	1.081
20	1.171
50	1.441
90	1.801
100	1.891
200	2.791

On the basis of current knowledge, the GMO Panel is of the opinion that variations in the level of compound(s) in GMOs are generally not large enough to impact the nutritional or safety characteristics of an ingredient in LL situations, with the possible exception of GMOs with traits developed to improve nutrition (e.g. nutritionally enhanced crops, Pérez-Massot et al., 2013; EFSA GMO Panel, 2014) or in cases of expected unintended compositional changes (e.g. EFSA GMO Panel, 2011b).

Therefore, the GMO Panel considers that comparative compositional analysis in LL situations is only necessary in any of the following cases:

- the intended trait targets the composition of the GMO (e.g. nutritionally enhanced GMOs);
- a hypothesis for a relevant compositional change can be formulated based on available information from the hazard identification, such as in the case of unintended compositional changes anticipated by the precedent analyses;
- if new constituents, other than newly expressed protein(s), are produced in the GMO.

In these cases, a targeted comparative compositional analysis is needed to quantify differences of the GMO with respect to its conventional counterpart, confirming the hypothesis that triggered the analysis. The outcome of the analysis will be used to perform an exposure assessment and to provide information relevant for cumulative risk assessment (see Section 3.2.5.3 of this guidance).

When there is the expectation of interactions between the transformation events stacked by conventional crossing that could lead to compositional changes in the stack GMO possibly impacting the composition of the LL ingredient, experimental targeted compositional analysis is needed.

The inclusion of agronomic and phenotypic endpoints in the comparative assessment studies in Reg. (EU) 503/2013 is intended to identify unintended effects related to the genetic modification and to address plant biology and agronomic traits. Considering that the main objective of comparative analysis in the context of LL situations is to quantify target compositional differences in the GMO with respect to its conventional counterpart confirming the hypothesis that triggered the analysis, a comparative analysis of agronomic and phenotypic characteristics described in paragraph 1.3.5 of Annex II.II of Reg. (EU) 503/2013 is not considered necessary in the context of LL situations. On a case-by-case basis, a comparative analysis of agronomic and phenotypic characteristics may be needed to support the environmental risk assessment (ERA) (see Section 3.3 of this guidance).

Choice of conventional counterpart and additional comparators (Reg. [EU] 503/2013; Annex II.II, 1.3.1)

When a targeted comparative compositional analysis is needed, the scientific requirements laid down in this paragraph of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications, including requirements regarding stacks.

Experimental design and statistical analysis of data from field trials for comparative analysis (Reg. [EU] 503/2013; Annex II.II, 1.3.2, subsections 1.3.2.1, 1.3.2.2)

When a targeted comparative compositional analysis is needed, it should include a difference test in accordance with the 'Principles of experimental design' described in point 1.3.2.1(a) of the subsection

'Description of the protocols for the experimental design' of Annex II.II of Reg. (EU) 503/2013. However, the GMO Panel considers that the test of equivalence is not necessary in LL situations. The test of equivalence aims to verify whether the GM plant is equivalent or not to reference varieties, apart from the introduced trait(s); estimation of natural ranges of variability of compositional endpoints is of limited relevance in a LL situation since the focus is to quantify the level(s) of target compound(s) in the GMO with respect to its conventional counterpart.

Regarding the 'Specific protocols for experimental design' detailed in point 1.3.2.1(b) of the above-mentioned subsection of Annex II.II of Reg. (EU) 503/2013, the GMO Panel considers that when needed, studies to obtain material for the targeted comparative compositional analysis should be conducted under conditions maximising change(s) expected in the composition of the GMO, according to the hypothesis triggering the analysis. Field trials and greenhouse studies could be fit for such purpose. This deviates from Reg. (EU) 503/2013, which always requires the performance of trials under representative field conditions. Furthermore, since in LL situations the estimation of equivalence limits is not considered necessary, the inclusion of reference varieties in the experimental design is not required.

In case of field trial studies, the number of sites to support the targeted comparative compositional analysis in LL applications can be less than the eight prescribed by Reg. (EU) 503/2013 but should be adequate to perform the subsequent risk assessment steps (i.e. exposure assessment and cumulative risk assessment).

Similarly, in case the targeted comparative compositional analysis is performed under greenhouse conditions, justifications for the specific conditions selected should be provided to demonstrate their adequacy to perform subsequent risk assessment steps (i.e. exposure assessment and cumulative risk assessment). Criteria used for the selection of specific study conditions (e.g. field trials or greenhouse studies) should be described and the choice scientifically and explicitly justified by the applicant.

All the other requirements detailed in point 1.3.2.1 (b) are considered necessary for both field trials and greenhouse studies.

The 'Statistical analysis' requirements laid down in subsection 1.3.2.2 of Annex II.II of Reg. (EU) 503/2013 are needed for LL applications, with the exception of the equivalence test (as explained above).

Selection of material and compounds for analysis (Reg. [EU] 503/2013; Annex II.II, 1.3.3)

The requirements laid down in this paragraph of Annex II.II of Reg. (EU) 503/2013 are necessary in LL applications. In particular, the targeted comparative analysis should be conducted on raw agricultural commodities, with additional analysis of processed products conducted where appropriate, on a case-by-case basis.

Comparative analysis of composition (Reg. [EU] 503/2013; Annex II.II, 1.3.4)

When a hypothesis triggering the requirement for specific compositional data is identified (see above), the targeted analysis of these specific compounds should be performed. A justification on the choice of compound(s) should be provided. This differs from requirements of Reg. (EU) 503/2013, where the minimum range of compounds to be analysed is that listed in the Organisation for Economic Cooperation and Development (OECD) consensus documents on compositional considerations for new plant varieties.

Comparative analysis of agronomic and phenotypic characteristics (Reg. [EU] 503/2013; Annex II.II, 1.3.5)

The GMO Panel considers that a comparative analysis of agronomic and phenotypic characteristics in general is not necessary in the context of LL situations, this differing from requirements of paragraph 1.3.5 of Annex II.II of Reg. (EU) 503/2013 (see considerations above). On a case-by-case basis, it may be needed to support the ERA (see Section 3.3).

Effects of processing (Reg. [EU] 503/2013; Annex II.II, 1.3.6)

The scientific requirements laid down in this paragraph of Annex II.II of Reg. (EU) 503/2013 regarding the assessment of the possible impact of the processing and/or preserving technologies on the characteristics of the derived products of the GMO are considered necessary in LL applications.

Comparative assessment studies performed under non-EU regulatory frames: applicability in LL applications

The GMO Panel considers that comparative assessment studies in accordance with *Codex Alimentarius* (2009) could support the targeted comparative compositional analysis in LL situations, provided that the relevant compositional endpoints, i.e. those of interest on the basis of the hypothesis

triggering the analysis, have been reliably measured; and that all *Codex Alimentarius* (2009) principles and requirements have been duly fulfilled.

In contrast, compositional analysis studies not aligned to requirements of *Codex Alimentarius* (2009) are not considered appropriate by the GMO Panel.

Conclusions of the comparative analysis (Reg. [EU] 503/2013; Annex II.II, 1.3.7)

In LL applications, comparative compositional analysis is considered necessary when the composition of the GMO is expected to impact on the nutritional or safety characteristics of the LL ingredient. In these situations, a targeted compositional analysis is requested and adaptations of the scientific requirements of Annex II.II Reg. (EU) 503/2013 as regards the experimental design, selection of endpoints and data analysis are indicated. The applicant should state the rationale for conducting the targeted compositional analysis, or justify why this was not conducted. When a targeted comparative compositional analysis is conducted, the applicant is requested to provide justification for the conditions used; to indicate whether the outcome of the targeted compositional analysis confirms the expectations and allows to properly quantify differences between the GMO and its conventional counterpart to perform the subsequent exposure assessment; to provide information relevant for cumulative risk assessment; and to indicate if further investigations are needed.

3.2.3.4. Toxicology (Reg. [EU] 503/2013; Annex II.II, 1.4)

This section of Annex II.II Reg. (EU) 503/2013 requires assessing the toxicological impact of any change on the whole GM food/feed resulting from the genetic modification such as the introduction of new genes, gene silencing or overexpression of endogenous genes.

More specifically, Annex II.II of the Reg. (EU) 503/2013 requires assessing:

- the toxicity of individual compounds, i.e. newly expressed proteins (paragraphs 1.4.1 and 1.4.5) and new constituents other than newly expressed proteins (paragraphs 1.4.2 and 1.4.5); and possible altered levels of food and feed constituents (paragraphs 1.4.3 and 1.4.5);
- the toxicity of the whole genetically modified food and feed (paragraphs 1.4.4 and 1.4.5).

Testing of newly expressed proteins (Reg. [EU] 503/2013; Annex II.II, 1.4.1)

The scientific requirements laid down in this paragraph of Annex II.II of the Reg. (EU) 503/2013 are considered necessary in LL applications.

Testing of new constituents other than proteins (Reg. [EU] 503/2013; Annex II.II, 1.4.2)

The scientific requirements laid down in this paragraph of Annex II.II of the Reg. (EU) 503/2013 are considered necessary in LL applications.

Information on altered levels of food and feed constituents (Reg. [EU] 503/2013; Annex II.II, 1.4.3)

When changes in the levels of specific constituents of the GMO (i.e. compositional endpoints) possibly impacting the toxicological profile of the LL ingredient are expected (see Section 3.2.3.3 of this guidance), these should be analytically confirmed and toxicologically assessed according to the scientific requirements laid down in paragraph 1.4.3 of Annex II.II of Reg. (EU) 503/2013.

Testing of whole genetically modified food and feed (Reg. [EU] 503/2013; Annex II.II, 1.4.4 subsections 1.4.4.1–1.4.4.4)

In line with this paragraph of Reg. (EU) 503/2013 in LL situations the applicant should primarily base its risk assessment of the GM food and feed on the molecular characterisation and toxicological evaluation of the GMO, as above described. The GMO Panel considers that in LL situations a 90-day feeding study as requested in subsection 1.4.4.1 of Annex II.II of Reg. (EU) 503/2013 ('Testing of whole GM food and feed') is not needed to corroborate information on the toxicological characteristics of the whole GM food and feed in rodents and/or to reduce the remaining uncertainties, considering the limited exposure to the GMO. On a case-by-case basis, depending on the GMO characteristics and on the results from preceding analysis, a 90-day study might be necessary to test specific toxicological hypothesis. In line with subsections 1.4.4.2 and 1.4.4.3 of Annex II.II of Reg. (EU) 503/2013, animal studies for reproductive and developmental toxicity testing or to examine the safety and the characteristics of food and feed from the GMO in target species might be considered on a case-by-case basis to test specific toxicological hypothesis. If animal studies are performed, the interpretation of

their relevance should be conducted according to the scientific requirements laid down in subsection 1.4.4.4 of Annex II.II of Reg. (EU) 503/2013.

Conclusions of the toxicological assessment (Reg. [EU] 503/2013; Annex II.II, 1.4.5)

The requirements of Section 1.4 of Annex II.II of Reg. (EU) 503/2013 apply to the toxicological assessment of newly expressed proteins and, when expected and analysed also to new constituents (other than new proteins) and altered levels of constituents.

Requirements of Section 1.4 of Annex II.II of Reg. (EU) 503/2013 on animal feeding studies on the whole food/feed apply in the case these were conducted.

3.2.3.5. Allergenicity (Reg. [EU] 503/2013; Annex II.II, 1.5)

Considerations and requirements of Annex II.II of Reg. (EU) 503/2013 relative to the allergenicity assessment of the GMO refer to:

- assessment of allergenicity of newly expressed proteins and adjuvanticity (paragraphs 1.5.1, 1.5.3 and 1.5.4);
- assessment of allergenicity of the GM food or feed (paragraphs 1.5.2 and 1.5.4).

Assessment of allergenicity of newly expressed proteins (Reg. [EU] 503/2013; Annex II.II, 1.5.1)

Requirements laid down in paragraph 1.5.1 of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

Assessment of allergenicity of the genetically modified food or feed (Reg. [EU] 503/2013; Annex II.II, 1.5.2)

The GMO Panel considers that due to the maximum 0.9% contribution of the GMO to the ingredient, requirements laid down in paragraph 1.5.2 of Annex II.II of Reg. (EU) 503/2013 are considered not necessary on a routine basis (see considerations in Section 3.1.2 of this guidance).

However, in the case where there is the expectation of changes in the level of known endogenous allergens in the GMO impacting the allergenicity of the LL ingredient, these endogenous allergens should be analytically measured (see considerations in Section 3.2.3.3 of this guidance). In this case, the assessment of allergenicity of the food or feed from the GMO should be conducted according to requirements of paragraph 1.5.2 of Annex II.II of Reg. (EU) 503/2013.

Assessment of adjuvanticity (Reg. [EU] 503/2013; Annex II.II, 1.5.3)

Requirements laid down in paragraph 1.5.3 of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

Conclusions of the allergenicity assessment (Reg. [EU] 503/2013; Annex II.II, 1.5.4)

Paragraph 1.5.4 of Annex II.II of Reg. (EU) 503/2013 applies for the allergenicity assessment of newly expressed proteins. The assessment of the allergenicity of food or feed from the GMO should be conducted in the case changes in the levels of endogenous allergens possibly impacting the allergenicity of the LL ingredient are expected. In such situations, relevant identified endogenous allergens should be analysed and the assessment should indicate whether the GMO could impact the allergenicity of the LL ingredient.

3.2.3.6. Nutritional assessment (Reg. [EU] 503/2013; Annex II.II, 1.6)

Considering that the scope of LL applications is limited to a level of maximum 0.9% of a GMO per LL ingredient, a nutritional assessment is not considered necessary on a routine basis (see Section 3.1.2 of this guidance) unless changes in the levels of constituents (i.e. compositional endpoints) in the GMO possibly impacting the nutritional characteristics of the LL ingredient are expected (see Section 3.2.3.3 of this guidance). In this case, these constituents should be analysed and nutritionally assessed. The GMO Panel considers that in such situation requirements of paragraph 1.6.2 of Annex II.II of Reg. (EU) 503/2013 ('Points to consider for the nutritional assessment of genetically modified food and feed') can be adapted as follows: point (a) the nutritional assessment should be focused on hypothesis-driven target compounds, taking into account their levels (see Section 3.2.3.3 of this guidance); point (b) should consider their bioavailability and biological efficacy; point (c) should consider the anticipated dietary intake of the ingredient without the GMO and

the resulting nutritional impact of the GMO (at a maximum 0.9% incorporation) in the LL ingredient. The assessment should include both acute and repeated dietary intake scenarios.

For LL situations concerning stacks, the applicant should provide an assessment of the potential synergistic or antagonistic interactions between the events which may have a nutritional impact on the LL ingredient.

Nutritional studies of genetically modified food (Reg. [EU] 503/2013; Annex II.I, 1.6.3) and feed (Reg. [EU] 503/2013; Annex II.II, 1.6.4)

In line with Reg. (EU) 503/2013, on a case-by-case basis, depending on the GMO characteristics and on the results from preceding analysis, nutritional studies on food and feed from the GMO might be appropriate to test specific hypothesis.

In the case nutritional assessment studies are needed in a LL application, requirements laid down in paragraphs 1.6.3 and 1.6.4 of Annex II.II of Reg. (EU) 503/2013 are considered necessary.

Conclusion of the nutritional assessment (Reg. [EU] 503/2013; Annex II.II, 1.6.5)

The conclusion of the nutritional assessment in a LL application should indicate if the GMO at maximum 0.9% incorporation in a LL ingredient has a nutritional impact on the LL ingredient after acute and repeated exposure.

3.2.3.7. Standardised guidelines for toxicity tests (Reg. [EU] 503/2013; Annex II.II, 1.7)

Section 1.7 of Annex II.II of Reg. (EU) 503/2013 applies.

3.2.4. Scientific requirements: Exposure assessment (Reg. [EU] 503/2013]; Annex II. II, 2)

In a LL application, the exposure to the GMO is defined to be maximum 0.9% per ingredient, under acute or repeated intake scenarios. The GMO Panel considers that the exposure assessment requirements laid down in Annex II.II of Reg. (EU) 503/2013 should be based on this predetermined exposure level.

In particular, exposure considerations should focus on newly produced components (e.g. newly expressed proteins) and on constituent(s) showing levels altered enough to impact the nutritional or safety characteristics of the ingredient (see Section 3.2.3.3 of this guidance).

3.2.5. Scientific requirements: Risk Characterisation (Reg. [EU] 503/2013; Annex II.II, 3)

3.2.5.1. Issues to be considered for risk characterisation (Reg. [EU] 503/2013; Annex II.II, 3.2)

Molecular characterisation (Reg. [EU] 503/2013; Annex II.II, 3.2.1)

Requirements in paragraph 3.2.1 of Annex II.II of Reg. (EU) 503/2013 are considered necessary in LL applications.

Comparative analysis (Reg. [EU] 503/2013; Annex II.II, 3.2.2)

The goal of the targeted comparative compositional analysis in a LL application is to quantify changes expected in the composition of the GMO, confirming the hypothesis that triggered the analysis. The applicant shall demonstrate that the targeted compositional analysis of the GMO has been carried out in accordance with the considerations presented in this guidance (see Section 3.2.3.3 of this guidance).

Food and feed safety in relation to intake (Reg. [EU] 503/2013; Annex II.II, 3.2.3)

In a LL application, this aspect of the risk characterisation should consider the data generated to estimate possible short- and long-term risks to human or animal health associated with the consumption of food/feed containing the LL ingredient. Requirements described in paragraph 3.2.3 of Annex II.II of Reg. (EU) 503/2013 are considered necessary, providing these are adapted to the specific context of the LL situation under assessment.

Post-market monitoring will be considered on a case-by-case basis.

3.2.5.2. The result of risk characterisation (Reg. [EU] 503/2013; Annex II.II, 3.3)

In accordance with the requirements of Annex II.II of Reg. (EU) 503/2013, the applicant should ensure that the final risk characterisation clearly demonstrates that the GMO does not impact the safety and nutritional characteristics of the LL ingredient (where it is unavoidably, adventitiously present at maximum 0.9%) to such an extent that the normal consumption of the LL ingredient would be nutritionally disadvantageous for consumers or animals.

The applicant should clearly indicate what assumptions have been made during the risk assessment in order to predict the probability of occurrence and severity of adverse effect(s) in a given population, and the nature and magnitude of uncertainties associated with establishing these risks.

Information justifying the inclusion or not of a proposal for labelling in the application is not required considering the scope of LL applications.

3.2.5.3. Cumulative risk assessment

The risk assessment of LL applications described in this guidance is carried out for a GMO present at a predefined maximum 0.9% exposure level per ingredient. In case of multiple LL applications for GMOs showing similar traits, the possible cumulative contribution of the various GMOs to the ingredient should be taken into consideration in the risk assessment, as required by the mandate (see Section 1.1 of this guidance). For example, if a similar trait intended for improving nutrition is expressed in different GMOs subject of different LL applications, the relative contribution to the ingredient of each of these GMOs should be taken into account to allow an estimation of their total contribution, via the addition of the respective trait-related constituent(s). Information from the outcome of the targeted compositional analysis (see Section 3.2.3.3 of this guidance) of each of these GMOs is relevant to establish the strategy to perform the cumulative assessment.

3.3. Environmental risk assessment

As mentioned in Reg. (EU) 503/2013, the ERA of GMOs or food/feed containing or consisting of GMOs should be performed according to the principles outlined in Annex II to Directive 2001/18/EC on the deliberate release into the environment of GMOs, and applicable GMO Panel Guidance Documents. The GMO Panel therefore recommends applicants to follow the principles and approach outlined in the GMO Panel Guidance Document on the environmental risk assessments of GM plants (EFSA GMO Panel, 2010) and other applicable EFSA guidelines (i.e. EFSA, 2017) to determine the data requirements for ERA of GM plants under LL situations.

ERAs conducted under LL situations should be case-specific (taking into account the biology of the plant species, the intended trait(s), the potential receiving environments and interactions among all three), and should begin with an explicit problem formulation where the GM plant is described using existing knowledge, and potential hazards and exposure routes are identified (OECD, 2013; Roberts et al., 2014). Taking this information into account, applicants should identify which areas of risk need to be addressed and hence the data requirements to inform the risk assessment. Risk should then be characterised by testing specific hypotheses about the likelihood and severity of adverse environmental effects that may occur.

The problem formulation should focus on the following exposure pathways: (1) exposure of microbial communities to recombinant DNA in the gastrointestinal tract of animals fed GM plant material or recombinant DNA in faecal material (manure and faeces) of these animals; and (2) accidental release into the environment of imported viable material from the GM plant during transportation and processing.

In general, a comparative analysis of agronomic and phenotypic characteristics of the LL GM plant to identify potential hazards is not considered mandatory under LL situations, representing a derogation to Annex II requirements of Reg. (EU) 503/2013. However, such analysis may be needed to support the ERA on a case-by-case basis depending on the persistence, invasiveness and hybridisation potential of the LL GM plant.

4. Conclusions

This guidance indicates which scientific requirements of Annex II of Reg. (EU) 503/2013 are necessary to conclude on the safety of applications covering the unintended and technically unavoidable presence in food and feed of low level of GM plant material (0.9% or below per ingredient) intended for markets other than in the EU.

To this aim, a comprehensive characterisation of the transformation event and of its intended effects should be performed. Not all the scientific requirements of the Annex II of Reg. (EU) 503/2013 aiming at identifying unintended effects are considered necessary on a routine basis, since the safety and nutritional impact of these effects on the ingredient is considered limited in the context of presence of a GM plant material at low level.

On a case-by-case basis, when a hypothesis for relevant compositional changes can be formulated, a target compositional analysis is requested. The experimental design, selection of endpoints and data analysis of such a targeted analysis would not need to follow all the scientific requirements of Annex II of Reg. (EU) 503/2013. Comparative compositional studies performed according to *Codex Alimentarius* could support such assessment.

The applicant needs to justify the approach followed and to indicate what assumptions have been made during the risk assessment, as well as the nature and magnitude of uncertainties.

Both acute and repeated exposure scenarios should be envisaged. The possible cumulative contribution to an ingredient from various genetically modified plants and derived products present at low level and showing similar traits should be considered.

ERAs conducted under situations of presence at low levels should follow the principles and approach outlined in the EFSA Guidance Document on the environmental risk assessments of GM plants (EFSA GMO Panel, 2010) and other applicable EFSA guidelines.

Relevant Documentation

Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. September 2014 (Ref. Ares (2014)3096951 – 22/9/2014). Submitted by the Deputy Director General for the Food Chain, Health and Consumers Directorate-General, European Commission.

Request for clarification on the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed, received by Austrian Competent Authority. October 2014 (Ref. BMG-76050/0020-II/B/12/2014).

Request for clarification on the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. November 2014 (Ref. BU/PB/EW/AL/shv(2014) – out – 11201195). Submitted by the Executive Director of EFSA.

Clarification on the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. March 2015 (Ref. Ares (2015)1362776 – 27/3/2015). Submitted by the Deputy Director General for the Food Chain, Health and Consumers Directorate-General, European Commission.

Acceptance of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed and request for extension of the proposed deadline. July 2015 (Ref. BU/JK/EW/CP/AL/lg [2015] – out – 14440308). Submitted by the Executive Director of EFSA.

Acceptance of the EFSA GMO Panel to establish a new Working Group to develop a guidance addressing request of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. July 2015. Submitted by the Chair of the GMO Panel.

Acceptance of the request of deadline extension of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. September 2015 (Ref. Ares (2015)4008240 – 29/9/2015). Submitted by the Deputy Director-General for the Food Chain, Health and Consumers Directorate-General, European Commission.

Request of deadline extension of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. Acceptance of the request of deadline extension of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. May 2016 (Ref. BU/JK/EW/AL/shv(2016) – out – 15636714). Submitted by the Executive Director of EFSA.

Acceptance of the request of deadline extension of the Mandate on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) 1829/2003 on GM food and feed. June 2016 (Ref. Ares (2016)2515582 – 31/5/2016). Submitted by the Director-General, Health and Consumers Directorate-General, European Commission.

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EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2010. Guidance on the environmental risk assessment of genetically modified plants. EFSA Journal 2010;8(11):1879, 111 pp. https://doi.org/10.2903/j.efsa.2010.1879

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2011a. Scientific Opinion on Guidance for risk assessment of food and feed from genetically modified plants. EFSA Journal 2011;9(5):2150, 37 pp. https://doi.org/10.2903/j.efsa.2011.2150

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2011b. Scientific Opinion on application (EFSA-GMO-UK-2007-43) for the placing on the market of herbicide tolerant genetically modified soybean 356043 for food and feed uses, import and processing under Reg. (EC) 1829/2003 from Pioneer. EFSA Journal 2011;9(7):2310, 40 pp. https://doi.org/10.2903/j.efsa.2011.2310

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Glossary and Abbreviations

LL situation	A situation where a GMO (i.e. a GM plant and/or its derived products or food or feed use) not previously authorised in the EU is present at a level of maximum 0.9% per ingredient in any food and/or feed, due to adventitious or technically unavoidable circumstances. A LL situation can occur from point of entry into the EU, through the food/feed production processing chain, up to the food (or feed) portion consumed.
LL application	An application for a GMO (and derived food/feed) at low levels (i.e. under a LL situation), submitted under Reg. (EC) 1829/2003.
LL ingredient	The mixture of the GMO subject of a LL application and the same plant species and/or derived product, at the predefined proportion of a maximum of 0.9% and 99.1%, respectively.
Standard GMO application	An application submitted under Reg. (EC) 1829/2003 for food/feed, import and processing and assessed according to Reg. (EU) 503/2013 and relevant EFSA guidance documents (EFSA GMO Panel, 2010, 2011a).
ERA	environmental risk assessment
GM	genetically modified
GMO	genetically modified organism
LL	Low Level
LLP	Low Level Presence
OECD	Organisation for Economic Co-operation and Development
ORF	open reading frame
RNAi	ribonucleic acid interference
WG	Working Group

Appendix A – Principles of *Codex Alimentarius* on situations at low level presence as compared to the terms of reference of the GMO Panel guidance on the risk assessment of the presence at low level of genetically modified plant material in imported food and feed under Regulation (EC) No 1829/2003

Scope

- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) provides an approach for the risk assessment of food. Instead, the GMO Panel guidance on LL is intended to cover the risk assessment of food and feed under the frame of Reg. (EC) 1829/2003.
- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) considers only the dietary exposure. In contrast, the GMO Panel guidance requested to cover all possible routes of exposure of consumers/animals to the GMO in addition to the diet, in accordance with Reg. (EC) 1829/2003.
- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) is applicable to situations of GMO presence at low level either before or after these have occurred (*a priori* and *a posteriori* assessment). Instead, the GMO Panel guidance is intended to support only the risk assessment of situations of GMO presence at low level before these occur (*a priori* assessment).
- In contrast to *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3), the GMO Panel guidance includes ERA considerations, as Reg. (EU) 503/2013 requires the ERA of GMOs or food and feed containing, or consisting of, GMOs to be performed according to the principles outlined in Annex II to Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of GMOs and repealing Council Directive 90/220/EEC, and the applicable GMO Panel guidance (EFSA GMO Panel, 2010).

Prerequisites to identify a low level presence situation

- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) recognises that an increasing number of GMOs is undergoing authorisation and commercialisation at different rates in different countries (asymmetric authorisations). As a consequence, LL situations may occur in importing countries where the GMO has not yet been assessed according to *Codex Alimentarius* (Codex Alimentarius, 2009). The *Codex Alimentarius* on such situations LLP (Codex Alimentarius, 2009, Annex 3) stipulates that a GMO can only be considered for risk assessment when present at low level if it has undergone a risk assessment according its guidelines in a third country. In contrast, this mandate requires the GMO Panel to set guidance for any GMO present at low level, independently of the existence of a third country risk assessment.

Threshold definition

- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) proposes a risk assessment strategy based on the expectation of a low exposure to the GMO, but does not define which amount of the GMOs constitutes a LLP situation. Instead, in the GMO Panel guidance, the threshold for situations of the presence at low levels of GMOs has been defined by European Commission as a level of maximum 0.9% of the GMO per ingredient in any food or feed containing the same ingredient.

Possible dietary exposure scenarios in case of situations of GMO low level presence and risk assessment strategies

Codex Alimentarius (Codex Alimentarius, 2009, Annex 3) distinguishes two categories of food possibly subject of situations of low level presence; and associates these to two distinct dietary exposure scenarios:

- food commodities small in particle size (e.g. grains, beans); these would constitute the most frequent situation. In this case, any inadvertently commingled GM material is expected to be present at low level in any individual serving of food, based on various assumptions (e.g. commodities are derived from multiple plants, are sourced from multiple farms, and/or are commingled during the food chain processing);

- food commodities large in particle size (e.g. tomato, papaya), and commonly consumed whole; these are expected to constitute a less frequent situation. In this case, each particle of such food might constitute an entire consumed portion of the GMO.

The risk assessment strategy and methodology advocated by *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) differs for the two dietary exposure scenarios, with compositional data (limited to key toxicants and allergens) required only for the second scenario. Instead, this GMO Panel guidance is requested to cover an exposure scenario for which a GMO is present at a level of maximum 0.9% per ingredient in the final food or feed.