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Draft guidance for the risk assessment of the low level presence of genetically modified plant material in imported food and feed under Regulation (EC) No 1829/2003

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Abstract

This document provides draft guidance for the *a priori* risk assessment of the unintended, adventitious or technically unavoidable low level presence in food and feed of genetically modified (GM) plant material and derived products developed for third countries and not intended to be exported to Europe. The low level presence is defined to be maximum 0.9% of a GMO per ingredient. A first draft document underwent a first consultation dedicated to EU (European Union) Member States and was revised by the GMO Panel taking into account received comments. This second draft document is now open for a public consultation where stakeholders, including EU Member States can contribute further to the guidance development.

Keywords: guidance document, GMO, low level presence, risk assessment, 1829/2003, food, feed

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47 **Summary**

48 A summary will be provided after the public consultation.

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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 European Union (EU). In this process, the role of the European Food Safety Authority (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 in 2006 (EFSA, 2006) and updated for the last time in 2011 (EFSA GMO Panel, 2011a) to assist applicants in the preparation and the presentation of GMO applications submitted under Regulation (EC) No 1829/2003[1] on GM food and feed (hereafter referred as to "GMO standard applications"). The European Commission subsequently adopted in April 2013 Regulation (EU) No 503/2013[2] on applications for authorisation of GM food and feed. Annex II of this Regulation lists the scientific requirements to be provided in accordance with Articles 5(3) and 17(3) of Regulation (EC) No 1829/2003. Article 5(2) of Regulation (EU) No 503/2013 states that by way of derogation, a GMO application not satisfying all the requirements of Annex II may be submitted, provided that it is not scientifically necessary to supply such information.

Genetically modified (GM) plants and derived 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 GM products at low levels cannot completely be excluded in exports to the EU.

In 2009, *Codex Alimentarius* issued guidelines for the food safety assessment of low level presence (LLP) situations of recombinant DNA plant material in food (Codex Alimentarius, 2009, Annex 3).[3]

In 2014[4] the European Commission mandated EFSA, in accordance with Article 29 of Regulation (EC) No 178/2002[5], to advise whether or not all requirements of Annex II to Regulation (EU) No 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 presence of 0.9% or below. If not, EFSA is required to indicate which requirements are unnecessary and to give the underlying rationale. Following a request for clarification by EFSA[6] the European Commission further clarified[7] that:

- the EFSA LLP guidelines should be applicable to the low level presence of GM products, independently of the existence or not of a third country risk assessment;
- LLP applications should only concern GM products developed for specific health or market needs in third countries not intended for the EU market. Therefore they should not be submitted for GM products for which a full scope application was previously submitted;

[1] Regulation (EC) No 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, L268, 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 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L157, 8.6.2013, p. 1–48.
[3] Guideline for the conduct of Food Safety Assessment of foods derived from recombinant-DNA Plants. CAC/GL 45-2003. Adopted 2003, Annex 3 adopted 2008.
[4] Ref. Ares(2014)3096951 – 22/09/2014
[5] 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, 01.02.2002, p. 1-24.
[6] Ref. BU/PB/EW/AL/shv(2014) - out - 11201195
[7] Ref. Ares(2015)1362776 – 27/03/2015

- exposure scenarios through commodities such as grains, beans, etc. or through foods consumed whole and undiluted should be considered under the EFSA LLP guidance (further clarification on this point is provided in the following Section 1.2 of this document);
- a cumulative risk assessment should be performed in case of similar traits present in different LLP applications;
- for stacks, the same principles as those referred to in Regulation (EU) No 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[8] EFSA accepted the mandate from the European Commission and committed to issue an EFSA Scientific Opinion providing guidance on possible derogations of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) No 1829/2003.

1.2. Interpretation of the Terms of Reference

Following an exchange with the European Commission, it was further clarified that an application of GM food and feed at low levels submitted under Regulation (EC) No 1829/2003 (hereafter referred to as "LLP application") covers a request for the authorisation of a GMO[9] 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 "LLP ingredient") is the mixture of the GMO subject of the LLP application (hereafter referred to as "LLP GMO") and the same plant species and/or derived product, at the predefined proportion of a maximum of 0.9% and 99.1% respectively.

It is presupposed that in a LLP application the LLP GMO is present at a level of maximum 0.9% per LLP 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 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 higher than 0.9% of consumers (or animals) to that GMO. Therefore, even if included in the EC mandate, these situations are not within the remit of this guidance.

The decision on whether a given GMO can constitute a LLP application is a risk management issue, and 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 LLP situations of recombinant DNA plant material in food (Codex Alimentarius, 2009, Annex 3) as a document to consider during the development of this guidance. The GMO Panel took into consideration principles and requirements outlined in the abovementioned document and identified some differences between the *Codex Alimentarius* approach on LLP and the terms of reference of this mandate. These differences are listed in Appendix A.

[8] Ref. BU/JK/EW/CP/AL/lg (2015) - out - 14440308

[9] A GM plant and/or derived food and feed products, in alignment with the scope of Regulation [EC] No 1829/2013: Chapter II Genetically modified food, Article 3. Scope. a) GMOs for food use; (b) food containing or consisting of GMOs; (c) food produced from or containing ingredients produced from GMOs; Chapter III Genetically modified feed: Article 15. Scope. (a) GMOs for feed use; (b) feed containing or consisting of GMOs; (c) feed produced from GMOs.

2. Data and Methodologies

2.1. Data

In delivering this guidance, the GMO Panel took into account the data requirements outlined in Regulation (EC) No 1829/2003, Regulation (EU) No 503/2013, *Codex Alimentarius* (Codex Alimentarius, 2009) and EFSA guidance documents (EFSA GMO Panel, 2010, 2011a).

2.2. Methodologies

EFSA established an *ad hoc* Working Group (LLP WG) to address the mandate on the risk assessment of the low level presence of GM plant material in imported food and feed under Regulation (EC) No 1829/2003. In accordance with the Terms of Reference of the mandate, the LLP WG scrutinised which data requirements of Annex II of Regulation (EU) No 503/2013 are necessary to conclude on the safety of GMOs present in food and feed and derived products 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 is now open for a second public consultation where all stakeholders, including EU Member States, can contribute further to the development of the guidance document. As an outcome, a technical report will be published on the EFSA website together with the adopted guidance document.

3. Assessment

3.1. Introduction

3.1.1. Scope of the guidance

This document is intended to assist applicants in the preparation of LLP applications by indicating which technical requirements of Annex II of Regulation (EU) No 503/2013 are necessary and which are not, in this case providing justification, in order to conclude on the safety of a GMO in a LLP application. This document supports Regulation (EU) No 503/2013 and it is not intended to serve as a stand-alone guidance.

Definitions and requirements of Regulation (EC) No 503/2013 other than those indicated in its Annex II apply to LLP applications.

This guidance does not cover GMOs for cultivation purposes; GM microorganisms; GM animals; GMOs for non-food/feed uses, novel foods as these are not in the scope of Regulation (EU) No 1829/2003.

This guidance does not consider issues related to risk management (e.g. traceability, labelling, and coexistence). Socio-economic and ethical issues are also outside the scope of this guidance.

3.1.2. General risk assessment considerations for LLP situations

The risk assessment strategy for GMO standard applications is driven by the comparative assessment principle, which aims to demonstrate that 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 GMO standard application is assessed assuming the possibility of a 100% replacement of the corresponding conventional crop and derived products. To achieve this objective, the GMO Panel identified scientific requirements and deployed a wide range of tools and methods (EFSA GMO Panel, 2011a), which have been incorporated into Annex II of Regulation (EU) No 503/2013 by the European Commission and EU Member States. These requirements are followed in GMO applications submitted under Regulation

(EC) No 1829/2003. In a LLP situation as defined in this guidance, exposure to the LLP GMO will be at maximum 0.9% per LLP ingredient. This pre-defined threshold implies a lower exposure to the LLP GMO than that foreseen in standard GMO applications. The adventitious or technically unavoidable reasons leading to a LLP situation do not exclude the possibility of repeated exposure of consumers/animals to the LLP GMO. Therefore, both single and repeated exposure scenarios are considered.

Based on the above considerations and in line with the *Codex Alimentarius* guideline on LLP situations (Codex Alimentarius, 2009, Annex 3), the GMO Panel considers that certain requirements for the risk assessment of GMO standard applications are necessary in LLP situations, others are not or should be adapted. Detailed description of which technical requirements of Annex II of Regulation (EU) No 503/2013 are necessary and which are not to conclude on the safety of a GMO in a LLP application are given in Section 3.2 of this guidance.

For the risk assessment of LLP situations of stacked events applicants will provide a risk assessment of each single transformation event or, in accordance with Article 3(6) of Regulation (EU) No 1829/2003, refer to already submitted application(s).

3.2. Scientific requirements for the risk assessment of LLP applications submitted under Regulation (EC) No 1829/2003

3.2.1. Introduction: Definitions (Regulation [EU] No 503/2013; Annex II.I,1)

Paragraph 1 of Annex II.I of Regulation (EU) No 503/2013 applies.

3.2.2. Introduction: Specific considerations (Regulation [EU] No 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 tract (Regulation [EU] No 503/2013; Annex II. I, 2.1)

All requirements in Paragraph 2.1 of Annex II.I of Regulation (EU) No 503/2013 are considered necessary for LLP applications.

3.2.2.2 Risk assessment of genetically modified food and feed containing stacked transformation events (Regulation [EU] No 503/2013; Annex II. I, 2.2)

In accordance with the terms of reference of this mandate, the same aspects for the risk assessment of GMOs containing stacked transformation events (stacks) described in paragraph 2.2 of Annex II. I of Regulation (EU) No 503/2013 are considered relevant for stacks under LLP situations:

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 of Regulation (EU) No 503/2013 relative to toxicology (section 1.4), allergenicity (section 1.5) and nutritional assessment (section 1.6).

In Regulation (EU) No 503/2013, data requirements to address the above points are provided in specific molecular characterisation and food and feed sections. Their relevance for LLP applications is discussed in the specific sections of this document.

Requirements laid down in paragraph 2.2 of Annex II. I of Regulation (EU) No 503/2013 as regards the assessment of sub-combinations in stacked events are considered necessary in LLP applications.

3.2.3. Scientific requirements: Hazard identification and characterisation (Regulation [EU] No 503/2013; Annex II. II, 1)

3.2.3.1 Information relating to the recipient or (where appropriate) to parental plants (Regulation EU No 503/2013; Annex II. II, 1.1)

All requirements described in paragraph 1.1 of the Annex II.II of Regulation (EU) No 503/2013 are considered necessary in LLP applications.

3.2.3.2 Molecular characterisation (Regulation [EU] No 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 LLP situations, the exposure to the LLP 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 of Regulation (EU) No 503/2013 are not considered necessary, or necessary only on a case-by-case basis. In the following sections, the rationale for considering necessary or not specific requirements is described.

Information relating to the genetic modification (Regulation [EU] No 503/2013; Annex II. II, 1.2.1, subsections 1.2.1.1-1.2.1.3)

Data 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 the Regulation (EU) No 503/2013 are considered necessary in LLP applications.

Information relating to the genetically modified plant (Regulation [EU] No 503/2013; Annex II. II, 1.2.2, subsections 1.2.2.1-1.2.2.5)

Data 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" serve to characterise the genetic modification(s) and therefore are considered necessary in LLP applications.

Subsection 1.2.2.3 "Information on the expression of the insert(s)" describes the 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. They also serve to characterise the potential unintended expression of new Open Reading Frames (ORFs) identified as raising a safety concern. Protein expression data related to 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 LLP applications on single transformation events. However, only the expression levels from those plant 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 the Regulation (EU) No 503/2013 are not considered necessary in LLP applications. The likelihood of off-target effects resulting from silencing approaches by RNAi expression large enough to raise safety concerns in a LLP situation is considered negligible. Therefore the potential 'off-target gene(s)' *in silico* search described in point 1.2.2.3(e) is not considered necessary.

Point 1.2.2.3 (d) requiring the analysis of potential unintended expression of new ORFs identified under point 1.2.2.2(f), which could raise a safety concern in an LLP situation, is considered necessary.

In the case of LLP stacks the GMO Panel considers that the likelihood for changes in the expression levels of the newly inserted sequences in comparison to the assessed single transformation events as a consequence of interactions between the transformation events that would be large enough to raise safety concerns is negligible in LLP situations. Hence it is not considered necessary to provide data

comparing the expression levels of the newly inserted sequences in LLP stacked transformation events to those in the single transformation events. Therefore, point 1.2.2.3(f) of the Annex II of Regulation (EU) No 503/2013 is not routinely required. On a case-by-case basis, and when the nature or the characterisation of the transformation events combined in a stack GMO suggests an interaction that may result in changes of the expression levels of the newly inserted sequences large enough to raise safety concerns in a LLP situation, this data should be provided.

Data requirements in subsection 1.2.2.4 "Genetic stability of the insert and phenotypic stability of the genetically modified plant" serve to characterise the genetic modification(s) of the plant and are considered necessary in LLP applications.

Data requirements in subsection 1.2.2.5 "Potential risk associated with horizontal gene transfer" (Regulation [EU] No 503/2013; Annex II. II, 1.2.2.5) are considered necessary in LLP applications.

Conclusions of the molecular characterisation (Regulation [EU] No 503/2013; Annex II. II, 1.2.3)

Based on considerations from the above paragraphs, 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 a LLP application.

3.2.3.3 Comparative analysis (Regulation [EU] No 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 GMOs under Regulation (EC) No 1829/2003 (EFSA GMO Panel, 2011a). It aims at identifying similarities and differences in composition (intended and unintended alterations) 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 similarities and differences in agronomic performance and phenotypic characteristics (intended and unintended alterations) 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 Regulation (EU) No 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 requirements on comparative analysis of Regulation (EU) No 503/2013 can be adapted in LLP applications. Since in LLP situations the level of exposure of consumers and animals to the LLP GMO is defined to be at a maximum 0.9% per ingredient, not all differences in comparative analysis endpoints between the LLP GMO and the plant (and/or derived product) constituting the remaining part of the ingredient may be relevant.

As regards compositional analysis, the level of an endogenous compound in a LLP ingredient is determined by the respective levels of such endogenous compound in the LLP GMO and in the plant (and/or derived product) constituting the remaining part of the ingredient. The ratio between these two levels determines the extent to which the level of the compound of the LLP GMO impacts the overall level of that compound in the LLP ingredient. For example, if the level of an endogenous compound in the LLP GMO is 100X larger than that of the ingredient without the LLP GMO, the increase of the compound in the LLP ingredient is approximately 2-fold (~1.891).[10] Similarly, a decrease in the level of an endogenous compound in the LLP GMO results into a level in the LLP ingredient never lower than 0.991 folds with respect to the ingredient without the LLP GMO. In Table 1, other examples of how the 0.9% LLP GMO can affect the overall level of an endogenous compound in an LLP ingredient are shown.

[10] If the level of an endogenous compound (A) in the LLP GMO is 100X compared to the level of A in the ingredient without the LLP GMO, then the level of A in the LLP ingredient= 100 x 0.9% + 99.1%=189.1%=1.891 folds with respect to level of A in the ingredient without the LLP GMO.

Table 1: Impact of variations in the levels of an endogenous compound in a LLP GMO on the level of the same compound in a LLP ingredient.

Level of a compound in LLP GMO/ level of the compound in the ingredient without the LLP GMO	Level of the compound in LLP ingredient/ level of the compound in the ingredient without the LLP 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 the current knowledge, the GMO Panel is of the opinion that variations in the level of compound(s) in LLP GMOs are generally not large enough to impact on the nutritional or safety characteristics of the LLP ingredient, with the possible exception of GMOs with output traits developed to improve nutrition (e.g. nutritionally enhanced crops, Perez-Massot et al., 2013; EFSA GMO Panel, 2014); or in the cases of GMOs expected to show compositional changes on the basis of precedent investigations (e.g. EFSA GMO Panel, 2011b).

Therefore the GMO Panel is of the opinion that comparative compositional analysis in LLP situations is only necessary in any of the following cases:

- the intended trait targets the composition of the LLP GMO (output trait);
- 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;
- or if compounds are *de novo* produced in the LLP GMO.

In these cases, the GMO Panel considers that a targeted comparative compositional analysis is needed to quantify differences of the LLP 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.

When there is the expectation of interactions between the transformation events stacked by conventional crossing leading to differences in the composition of stack LLP GMO possibly impacting the composition of the LLP ingredient, experimental data is needed.

The inclusion of agronomic and phenotypic endpoints in the comparative assessment studies in Regulation (EU) No 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 LLP situations is to quantify target compositional differences in the LLP GMO with respect to its conventional counterpart, confirming the hypothesis that triggered the analysis, a comparative analysis of agronomic and phenotypic characteristics is not considered necessary in the context of LLP situations, representing a possible derogation to paragraph 1.3.5 of

Regulation (EU) No 503/2013. On a case-by-case basis a comparative analysis of agronomic and phenotypic characteristics may be needed to support the environmental risk assessment (ERA) (Section 3.3).

Choice of conventional counterpart and additional comparators (Regulation [EU] No 503/2013; Annex II. II, 1.3.1)

When targeted comparative compositional analysis is needed, requirements laid down in this paragraph are considered necessary in LLP applications, including requirements regarding stacks.

Experimental design and statistical analysis of data from field trials for comparative analysis (Regulation [EU] No 503/2013; Annex II. II, 1.3.2, subsections 1.3.2.1a,b, 1.3.2.2)

The GMO Panel considers that, when compositional comparative assessment is needed, the targeted comparative compositional analysis should include a difference test in accordance with the "Principles of experimental design" described in subsection 1.3.2.1a of "Description of the protocols for the experimental design". However the GMO Panel considers that the test of equivalence in not necessary in LLP situations requiring targeted comparative compositional analysis. The test of equivalence is aimed to verify whether the GM plant is equivalent or not to reference varieties, apart from the introduced trait(s). Estimation of natural ranges of compositional endpoints variability is of limited relevance in a LLP situation since the focus is on the quantification the level(s) of a compound expected to be changed in the LLP GMO with respect to its conventional counterpart.

Regarding the "Specific protocols for experimental design" detailed in subsection 1.3.2.1,b the GMO Panel considers that when needed, studies for the targeted comparative compositional analysis in a LLP application should be conducted under conditions maximising expected change(s) in the composition of the LLP GMO, based on available knowledge. Both field trials and greenhouse studies could be fit for such purpose. This deviates from Regulation (EU) No 503/2013, which always requires the performance of trials under representative field conditions. Furthermore, since in LLP situations the estimation of equivalence limits is not considered necessary, reference varieties are not required to be included in the experimental design.

In case of field trial studies, the number of sites to support the targeted comparative compositional analysis in LLP applications can be less than the eight prescribed by Regulation (EU) No 503/2013. One site could be sufficient, provided this is adequate to quantify the expected differences in the composition of the LLP GMO compared to the conventional counterpart and to perform 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 adequacy to quantify differences in the composition of the LLP GMO and 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 subsection 1.3.2.1b are considered necessary for both field trials and greenhouse studies.

The "Statistical analysis" requirements laid down in paragraph 1.3.2.2 are needed apply for LLP applications, with the possible exception of the equivalence test (as explained above).

Selection of material and compounds for analysis (Regulation [EU] No 503/2013; Annex II. II, 1.3.3)

The requirements laid down in this paragraph are necessary in LLP applications. In particular the 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 (Regulation [EU] No 503/2013; Annex II. II, 1.3.4)

In LLP applications the analysis of the composition will be targeted to compounds selected to address the specific hypothesis triggering the requirement for compositional data; justification on the choice of

the compounds should be provided. This represents a derogation to Regulation (EU) No 503/2013 requirements, where the minimum range of compounds to be analysed are those 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 (Regulation [EU] No 503/2013; Annex II. II, 1.3.5).

The GMO Panel considers that a comparative analysis of agronomic and phenotypic characteristics is not necessary in the context of LLP situations, representing a possible derogation to paragraph 1.3.5 of Regulation (EU) No 503/2013 (see considerations on Comparative analysis, section 3.2.3.3). On a case-by-case basis it may be needed to support the ERA (see Section 3.3).

Effects of processing (Regulation [EU] No 503/2013; Annex II. II, 1.3.6)

The requirement laid down in this paragraph of Regulation (EU) No 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 LLP applications.

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

In derogation to Regulation (EU) No 503/2013, the GMO Panel considers that comparative assessment studies that have been conducted in accordance with *Codex Alimentarius* (Codex Alimentarius, 2009) could support the targeted comparative compositional analysis in LLP situations, provided that the relevant compositional endpoints, i.e. those of interest on the basis of the hypothesis triggering the analysis, or addressing the output trait, have been reliably measured; and that all *Codex Alimentarius* (Codex Alimentarius, 2009) principles and requirements have been duly fulfilled.

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

Conclusions of the comparative assessment (Regulation [EU] No 503/2013; Annex II. II, 1.3.7)

In LLP applications comparative compositional analysis is considered necessary when the composition of the LLP GMO is expected to impact on the nutritional or safety characteristics of the LLP ingredient. In these situations, a targeted comparative compositional analysis is requested. The applicant should state the rationale for conducting the targeted comparative compositional analysis, or the justification why this was not conducted. In the case a targeted comparative compositional analysis has been conducted, the applicant is requested to provide justification of the conditions used; to indicate whether the outcome of the targeted comparative compositional analysis confirms the expectations; if it allows to properly quantify differences versus its conventional counterpart in order to perform an exposure assessment; to provide information relevant for cumulative risk assessment; and to indicate if further investigation is needed.

3.2.3.4 Toxicology (Regulation [EU] No 503/2013; Annex II. II, 1.4)

This section of Regulation (EU) No 503/2013 requires to assess 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 over-expression of an endogenous genes.

More specifically, Annex II of the Regulation (EU) No 503/2013 requires assessing:

- the toxicity of individual compounds, represented by newly expressed proteins (paragraphs 1.4.1 and 1.4.5) and/or new constituents (paragraphs 1.4.2 and 1.4.5); and by 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 (Annex II.II, paragraphs 1.4.4 and 1.4.5).

Testing of newly expressed proteins (Regulation [EU] No 503/2013; Annex II. II, 1.4.1)

Requirements laid down in this paragraph are considered necessary in LLP applications.

Testing of new constituents other than proteins (Regulation [EU] No 503/2013; Annex II. II, 1.4.2)

Requirements laid down in this paragraph are considered necessary in LLP applications.

Information on altered levels of food and feed constituents (Regulation [EU] No 503/2013; Annex II. II, 1.4.3)

Where, following the principles of comparative analysis described in Section 3.2.3.3 of this document, relevant compositional changes in the levels of target food and feed constituents from the LLP GMO are expected, these should be analysed. In this case, the toxicological assessment of altered levels of natural constituent(s) [i.e. compound(s) constitutively expressed or endogenous compound(s)] in the LLP GMO should be conducted according to the requirements laid down in paragraph 1.4.3 of Regulation [EU] No 503/2013; Annex II. II.

Testing of whole genetically modified food and feed (Regulation [EU] No 503/2013; Annex II. II, 1.4.4 subsections 1.4.4.1-1.4.4.3)

In line with this paragraph of Regulation (EU) No 503/2013 in LLP situations the applicant should primarily base its risk assessment of the food and feed derived from LLP GMO on molecular characterisation and on the toxicological evaluation of the LLP GMO, as above described. In derogation to subsection 1.4.4.1 of Regulation (EU) No 503/2013 "Testing of whole GM food and feed" the GMO Panel considers that in LLP situations a 90-day feeding study is not needed to corroborate information on the toxicological characteristics of the whole LLP GM food and feed in rodents and/or to reduce the remaining uncertainties,, considering the limited exposure to the LLP GMO. On a case-by-case basis, depending on the LLP GMO characteristics and on the results from preceding analysis, a 90-day study might be necessary if appropriate to test specific toxicological hypothesis. In line with subsections 1.4.4.2 and 1.4.4.3, animal studies with respect to reproductive and developmental toxicity testing or to examine the safety and the characteristics of food and feed from the LLP GMO in target species might be considered on a case-by-case basis, if appropriate to test specific toxicological hypothesis.

Conclusions of the toxicological assessment (Regulation [EU] No 503/2013; Annex II. II, 1.4.5)

In LLP situations the conclusion of the toxicological assessment should indicate whether:

(a) potential adverse effects identified in other parts of the safety assessment have been confirmed or discarded;

(b) the available information on the newly expressed protein(s) and other new constituents resulting from the genetic modification gives indications of potential adverse effects in particular whether and at which dose levels adverse effects were identified in specific studies;

(c) in case of a LLP GMO with altered levels of food and feed constituents, indication of potential adverse effects of such constituents, in particular, whether and at which dose levels adverse effects were identified in specific studies;

(d) in the case animal feeding studies on the whole food/feed are conducted, adverse effects have been identified from the studies and at which dose levels.

3.2.3.5 Allergenicity (Regulation EU No 503/2013; Annex II. II, 1.5)

Considerations and requirements relative to the allergenicity assessment of the GMO of Annex II.II of Regulation (EU) No 503/2013 refer to:

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

Assessment of allergenicity of newly expressed proteins (Regulation [EU] No 503/2013; Annex II. II, 1.5.1)

Requirements laid down in paragraph 1.5.1 of Annex II of Regulation (EU) No 503/2013 are considered necessary in LLP applications.

Assessment of allergenicity of the genetically modified food or feed (Regulation [EU] No 503/2013; Annex II. II, 1.5.2)

The GMO Panel considers that due to the maximum 0.9% contribution of the LLP GMO to the ingredient, requirements laid down in paragraph 1.5.2 of Annex II of Regulation (EU) No 503/2013 are not necessary on a routine basis.

However in the case where there is the expectation of changes in the level of known endogenous allergens in the LLP GMO impacting the allergenicity of the LLP ingredient, these endogenous allergens should be analysed (section 3.3.3 - Comparative assessment). In this case, the assessment of allergenicity of the food or feed from the LLP GMO should be conducted according to requirements of paragraph 1.5.2 of Regulation [EU] No 503/2013.

Assessment of adjuvanticity (Regulation [EU] No 503/2013; Annex II. II, 1.5.3)

Requirements laid down in paragraph 1.5.3 of Annex II of Regulation (EU) No 503/2013 are considered necessary in LLP applications.

Conclusions of the allergenicity assessment (Regulation [EU] No 503/2013; Annex II. II, 1.5.4)

Requirements laid down in this paragraph to conclude on the allergenicity assessment are considered necessary as regards the newly expressed proteins. The assessment of the allergenicity of food or feed from the LLP GMO should be conducted in the case changes in the levels of endogenous allergens are expected in the LLP GMO, possibly impacting the allergenicity of the LLP ingredient. In such situations, relevant identified endogenous allergens should be analysed and the assessment should indicate whether the GMO could impact the allergenicity of the LLP ingredient.

3.2.3.6 Nutritional assessment (Regulation [EU] No 503/2013; Annex II. II, 1.6)

Considering that the scope of LLP applications is limited to a level of maximum 0.9% of a LLP GMO per ingredient a nutritional assessment is not considered as necessary on a routine basis, unless, following the principles of comparative analysis described in Section 3.2.3.3, relevant changes in the levels of food and feed constituents from the LLP GMO are expected. In this case, these constituents (i.e. compositional endpoints) should be analysed and nutritionally assessed. The GMO Panel considers that in such situations the paragraph 1.6.2 of Annex II. II of Regulation EU] No 503/2013 "Points to consider for the nutritional assessment of genetically modified food and feed" points a,b,c can be adapted as follows: a) the nutritional assessment should be focused on hypothesis-driven target compounds, taking into account their levels (see considerations in Section 3.2.3.3 - Comparative analysis); b) should consider their bioavailability and biological efficacy (c) the anticipated dietary intake of the ingredient without the LLP GMO and the resulting nutritional impact of the LLP GMO in the LLP ingredient (at a maximum 0.9% incorporation). The assessment should include both acute and repeated dietary intake scenarios.

For LLP GMOs stacks (LLP GMO single transformation events combined by conventional crossing), the applicant should provide an assessment of the potential changes in nutritional value that may arise from synergistic or antagonistic effects of the gene products including compositional changes, if these impact the ingredient containing the LLP GMO stack.

Nutritional studies of genetically modified food (Regulation [EU] No 503/2013; Annex II. II, 1.6.3) and feed (Regulation [EU] No 503/2013; Annex II. II, 1.6.4)

In line with Regulation (EU) No 503/2013, on a case by case basis, depending on the LLP GMO characteristics and results from preceding analysis, nutritional studies on food and feed from the LLP GMO might be considered if appropriate to test specific hypothesis.

In the case a nutritional assessment is needed in a LLP application, requirements laid down in paragraph 1.6.3 and 1.6.4 of Annex II.II of Regulation (EC) No 503/2013 are considered necessary.

Conclusion of the nutritional assessment (Regulation [EU] No 503/2013; Annex II. II, 1.6.5)

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

3.2.3.7 Standardised guidelines for toxicity tests (Regulation [EU] No 503/2013; Annex II. II, 1.7)

Paragraph 1.7 of Annex II. II of Regulation (EU) No 503/2013 applies.

3.2.4. Scientific requirements: Exposure assessment (Regulation [EU No 503/2013]; Annex II.II,2)

In a LLP application the exposure to the LLP 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, 2 of Regulation (EU) No 503/2013 should be based on this predetermined exposure level and adapted accordingly.

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

3.2.5. Scientific requirements: Risk Characterisation (Regulation [EU] No 503/2013; Annex II.II,3)

3.2.5.1 Issues to be considered for risk characterisation (Regulation [EU] No 503/2013; Annex II. II, 3.2)

Molecular characterisation (Regulation [EU] No 503/2013; Annex II. II, 3.2.1)

Requirements in paragraph 3.2.1 are considered necessary in LLP applications.

Comparative analysis (Regulation [EU] No 503/2013; Annex II. II, 3.2.2)

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

Food and feed safety in relation to intake (Regulation [EU] No 503/2013; Annex II. II, 3.2.3)

In a LLP 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 LLP ingredient. Requirements described in paragraph 3.2.3 of Regulation (EU) No 503/2013 are considered necessary, providing these are adapted to the specific context of the LLP situation under assessment.

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

3.2.5.2 The result of risk characterisation (Regulation [EU] No 503/2013; Annex II. II, 3.3)

In accordance with these requirements of Annex II of Regulation (EU) No 503/2013, the applicant should ensure that the final risk characterisation clearly demonstrates that the LLP GMO does not

impact the safety and nutritional characteristics of the LLP ingredient (where it is unavoidably, adventitiously present at maximum 0.9%) to such an extent that the normal consumption of the LLP ingredient would be nutritionally disadvantageous for the consumer or for 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 boundaries of the scope of LLP applications.

3.2.5.3 Cumulative risk assessment

The risk assessment of LLP applications described in this guidance is based on a pre-defined maximum 0.9% exposure level to the LLP GMO per ingredient. In this context, the expected effects of the genetic modification(s) are characterised as regards its/their safety. These include the assessment of novel compound(s) (e.g. new protein) and of endogenous compound(s) showing large variations in level(s) with respect to the ingredient without the LLP GMO.

In the case of multiple LLP applications for LLP GMOs showing similar traits, the possible cumulative contribution from the various LLP GMOs to the ingredient should be taken into consideration in the risk assessment. For example, if a similar output trait is expressed in different LLP GMOs subject of multiple LLP applications, the relative contribution to the ingredient of each of these GMOs should be taken into account to allow an estimation of the total contribution of all these LLP GMOs, via the addition of the respective trait-related constituent(s). Information from the outcome of the targeted comparative compositional analysis (see considerations in Section 3.2.3.3 - Comparative analysis) of each of these LLP GMOs is relevant to establish the strategy to perform the cumulative assessment, on a case-by-case basis.

3.3. Environmental risk assessment

As mentioned in the Implementing Regulation (EU) No 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 ERA of GM plants (EFSA GMO Panel, 2010) to determine the data requirements for ERA of GM plants under LLP situations.

ERAs conducted under LLP situations should be case-specific, and will vary depending on the biology of the plant species, the intended trait(s), the potential receiving environments, and interactions among all three.

ERAs should begin with an explicit problem formulation where the LLP 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.

As for GMO standard applications for food/feed uses for import/processing, the ERA of GM plants under LLP conditions can 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. These two exposure pathways need to be taken into account in the problem formulation.

In general, a comparative analysis of agronomic and phenotypic characteristics of the LLP GM plant to identify potential hazards is not considered mandatory under LLP situations, representing a derogation to Annex II requirements of Regulation (EU) No 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 LLP GM plant.

4. Conclusions

Conclusions will be provided after the public consultation.

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Glossary

LLP 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 LLP 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.

LLP application: an application for a GMO (and derived food/feed) at low levels (i.e. under a LLP situation), submitted under Regulation (EC) No 1829/2003.

LLP GMO: the GMO subject of a LLP application.

LLP ingredient: the mixture of the LLP GMO and the same plant species and/or derived product, at the predefined proportion of a maximum of 0.9% and 99.1% respectively.

GMO standard application: an application submitted under Regulation (EC) No 1829/2003, for food/feed, import and processing and assessed according to Regulation (EU) No 503/2013 and relevant EFSA guidance documents (EFSA GMO Panel, 2010, 2011).

703 # Abbreviations

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DNA	Deoxyribonucleic acid
EC	European Commission
ERA	Environmental Risk Assessment
EFSA	European Food Safety Authority
EU	European Union
GM	Genetically Modified
GMO	Genetically Modified Organism
LLP	Low Level Presence
OECD	Organisation for Economic Co-operation and Development
ORF	Open Reading Frame
RNAi	Ribonucleic acid interference
WG	Working Group

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Appendix A – Differences in principles and requirements of *Codex Alimentarius* on LLP (Codex Alimentarius, 2009, Annex 3) and the terms of reference of the LLP mandate of the European Commission

Scope

- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) provides an approach for the risk assessment of food. Instead the GMO Panel guidance on LLP is intended to cover the risk assessment of food and feed, in accordance with Regulation (EC) No 1829/2003.
- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) considers only the dietary exposure. In contrast, the GMO Panel guidance on LLP is requested to cover all possible routes of exposure of consumers/animals to the LLP GMO in addition to the diet, in accordance with Regulation (EC) No 1829/2003.
- *Codex Alimentarius* (Codex Alimentarius, 2009, Annex 3) is applicable to LLP situations either before or after these have occurred (*a priori* and *a posteriori* assessment). Instead, the GMO Panel guidance on LLP is intended to support only the risk assessment of LLP situations before these occur (*a priori* assessment).
- In contrast to *Codex Alimentarius* (Codex Alimentarius,2009, Annex 3), the GMO Panel guidance on LLP includes ERA considerations, as Regulation (EU) No 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) .

Pre-requisites to identify an LLP 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, LLP 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 LLP (Codex Alimentarius, 2009, Annex 3) stipulates that a GMO can only be considered for LLP risk assessment 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 LLP applications for any GMO, independently of the existence of a third country risk assessment.

Threshold definition

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

Possible dietary exposure scenarios in case of LLP situations and risk assessment strategies

Codex Alimentarius (Codex Alimentarius, 2009, Annex 3) distinguishes two categories of food possibly subject of LLP situations; 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 LLP 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 LLP situation. In this case each particle of such food might constitute an entire consumed portion of the LLP 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 on LLP is requested to cover an exposure scenario for which a LLP GMO is present at a level of maximum 0.9% per ingredient in the final food or feed.