European Food Safety Authority

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TECHNICAL REPORT OF EFSA

Outcome of the Public Consultation on the Guidance of the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) on the Submission of a Dossier on Food Enzymes[1]

Prepared by the CEF Unit[2]

(Question No EFSA-Q-2007-080)

Issued on 11 August 2009

BACKGROUND

On 16 December 2008 the Regulation (EC) No 1332/2008 on food enzymes[3] was adopted and entered into force on 20 January 2009.

According to this Regulation food enzymes shall be subject to safety evaluation by the European Food Safety Authority (EFSA) and approval via a Community list. The inclusion of a food enzyme in the Community list will be considered by the Commission on the basis of the opinion from EFSA, taking into account also other general criteria such as technological need and consumer aspects.

This Regulation also provides that an implementing measure (Art. 9) shall be adopted by the Commission, which shall concern in particular the content, drafting and presentation of the application for the evaluation and authorisation of a food enzyme. With a view to the adoption of this implementing measure the Commission consulted the EFSA, which, within six months of the date of entry into force of the Regulation on food enzymes, i.e. by 20 July 2009 was asked to present a proposal concerning the data required for risk assessment of the food enzymes.

The Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) compiled and presented the data required for risk assessment in the format of a

[1]For citation purposes: Technical report of EFSA prepared by The Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) on the Submission of a Dossier on Food Enzymes. The EFSA Technical Report (2009) 341, 1-25.

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[3] OJ L 354, 31.12.2008, p.7

guidance document. A Working Group, composed of members of the Panel and external experts, was established and entrusted with the task to draft this document.

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders on its work, EFSA engages in public consultations on key issues. The work on guidance documents is considered to be such an issue. Accordingly, the guidance on submission of a dossier on food enzymes was placed for two month (from 8th April until 8th June 2009) on EFSA's homepage[4]. Stakeholders were informed and invited to submit comments. EFSA has committed to publish the comments received as well as a short report on the outcome of the consultation.

COMMENTS RECEIVED

At the end of the public consultation period EFSA had received 98 contributions from 15 interested parties (individuals, non-governmental organisations, industry organisations, academia and national assessment bodies). All comments received were scrutinised by the secretariat and subsequently compiled with reference to the contributor and the section of the draft opinion to which the comment referred (see appendix). Comments submitted formally on behalf of an organisation appear with the name of the organisation.

SCREENING AND EVALUATION OF COMMENTS RECEIVED

1. General

In general the comments were constructive and aimed to help improving the guidance document. It was noted that many of the contributions reiterated arguments brought forward already by other organisations. Thirty of the comments were endorsements of comments from a European industry association by a national industry association.

This report provides a summary of the main issues and their consideration.

1.1. Types of comments

The Scientific Committee on Food issued in 1991 `Guidelines for the presentation of data on food enzymes`. These guidelines formed the basis for the safety assessments of food enzymes performed by the Danish and French Authorities in the past. Many of the comments received were related to the differences in data requirements of the current guidance document and the former guidelines of the CEF.
Specifically the following issues were addressed:

- Suggestion to introduce the safe strain lineage as proposed by Pariza and Johnson in 2001

[4] http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902439387.htm

- Guidelines should provide decision criteria for the amount and quality of documentation needed. This holds especially true for toxicological testing.
- Concern that the specificity level of the identity requirements would make it necessary to submit one dossier per enzyme manufacturer and per food enzyme
- Suggestion to introduce the TOS to characterise the enzyme
- The budget method should be explicitly named as the default method to calculate consumer exposure.
- The requirement for strain deposition in a European database should be deleted.
- Clarification of the term fungi as source material

INCORPORATION OF THE COMMENTS IN THE GUIDANCE DOCUMENT

The EFSA CEF Working Group on enzymes was presented with the compilation of comments and discussed them at a dedicated meeting. Many of the comments received were appropriate and aimed to enhance the scientific quality and clarity of the guidance document. Most of the comments were taken into account and the guidance document was revised accordingly.

Examples of cases and situations when toxicological testing may not be needed were given in the draft guidance document and this section has now been extended. However, as not every possible situation can be anticipated, the guidance document provides for flexibility of interpretation as needed. Some borderline cases will need to be looked at on a case-by-case basis.

The potential for grouping the safety evaluation of several enzymes in one dossier is explicitly acknowledged in the guidance document. Examples when this might be possible are listed. However, the decision as to whether grouping is appropriate will be taken on a case-by-case basis.

The final guidance document was presented to the CEF Panel at its July meeting and adopted on the 23rd July 2009.

APPENDIX: COMMENTS RECEIVED ON THE ENZYME GUIDANCE DURING THE PUBLIC CONSULTATION PERIOD

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
Amfep	Background as provided by the European Commission	General comments on the whole document: Amfep welcomes the work done by the Panel on collating and updating safety requirements for food enzymes. We believe the document to be proportionate and a good starting point for further discussion. Apart from the specific comments outlined in the relevant sections, we have the following suggestions of a more general nature: - The draft sometimes contains duplicate requirements, which should be removed (cf. our comments to lines 241, 269-272, 277-278, 298-300, 391-394). - Some requirements are not described in the correct sections, there is in particular some confusion between Identity, Manufacturing process and Fate in food. - The Identity section should be clarified. Ideally, it should recognize that enzymes are not chemicals but substances of variable composition and hence cannot be chemically characterized except in a very generic way. - The guidelines should provide for decision criteria, so that the applicant is able to determine with a high probability level whether the amount and quality of documentation he intends to provide is adequate. Failure to do this would result in a waste of resources by both the applicant and EFSA. This applies in particular to the toxicological requirements sections. The draft guidelines do not make use of the TOS concept. This concept is in our opinion of primary importance when characterizing a food enzyme and assessing its safety, as exemplified in our comments below. We welcome the use of the EFSA GMM Guidance document and the simultaneous evaluation by the GMO Panel. This process is already successfully used for enzyme feed additives produced by genetically modified micro-organisms and will prevent unnecessary delays. The draft guidelines follow a path towards manufacturer-specific dossiers and evaluations: - This is far from being justified in all cases. A number of food enzymes are indeed produced by micro-organisms that can be considered as safe at a species or strain lineage level. - The proposed approach may create a huge burden for all parties: Industry, Risk Assessors and Risk Managers. Hundreds of dossiers may be necessary if one follows the draft guidelines strictly. In addition, it will unnecessarily increase the amount of animal testing. - We fear that this burden cannot be absorbed by the authorization system and might result in a positive list with a specificity level that may not be in line with the specificity of the dossiers and EFSA opinions.
Novozymes A/S	Background as provided by the European Commission	Novozymes totally supports the comments submitted by Amfep, the EU Association of Manufacturers and Formulators of Enzyme Products.
SYNPA	Background as provided by the European Commission	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	Background as provided by the European Commission	CIAA, the Confederation of the Food and Drink manufacturing industries of the EU, appreciates the opportunity to respond to "EFSA"s public consultation on Guidance of the Scientific Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF) on the Submission of a Dossier on Food Enzymes for Evaluation by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF)" and would like to offer the following comments.
SYNPA	Terms of Reference as provided by the European Commission	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Danish Veterinary and Food Administration	Introduction	The Danish Veterinary and Food Administration are pleased that the new guidelines on evaluation of food enzymes are based on the SCF guidelines from 1991. The SCF guidelines have been used for risk assessment of food enzymes in Denmark for many years and have shown to be efficient and user friendly for the risk managers, the risk assessors, and the enzyme industry.
Genencor, A Danisco Division	Introduction	This is to inform that Genencor, A Danisco Division, endorses all comments made by AMFEP to the public consultation. [AMFEP = Association of Manufacturers and Formulators of Enzyme Products]
SYNPA	Introduction	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
DSM Food Specialties	Introduction	Introduction : line 107 - 117 DSM fully underlines the comments on the EFSA Guidelines as given by AMFEP
AFSSA	Introduction	General principles of risk assessment of food enzymes Line 135 : The following sentence must be added “The new exposure to intended reaction products should also be considered”.
Amfep	Introduction	110 We suggest that this paragraph is also used as a reminder to all interested parties, to state that food imported into the EU shall be manufactured only with the help of food enzymes that can be legally used in the EU. 124 The list “animals, plants, fungi or micro-organisms” is confusing. Food enzymes can be made by extraction from plant or animal tissues, or by fermentation using micro-organisms such as: yeasts, bacteria or filamentous fungi. We suggest that the list reads “animals, plants, mushrooms or micro-organisms”. We consider “filamentous fungi” to be part of “micro-organisms” – in the same way as yeasts and bacteria. 130 This paragraph should be deleted. Industrial food enzymes have enzyme activities that can be found in Nature, in particular in food raw materials. Therefore the use of an industrial food enzyme should not lead to the creation of “unintended” or “unexpected” reaction products. The reaction products are already regular food components. 140 The most recent JECFA document on food enzyme safety and specifications is: “General specifications and considerations for enzymes used in food processing, in Compendium of food additive specifications, 67th meeting, 2006”.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	Scope	CIAA is concerned that the Guidelines does not provide for clear end-points for the enzyme producer or food manufacturer. This raises uncertainty as to the outcome of the evaluation, which is potentially prejudicial to the smooth operation of the EU market.
SYNPA	Scope	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	Scope	158 Even if not "exhaustive", the guidelines should provide for decision criteria, so that the applicant is able to determine with a high probability level whether the amount and quality of documentation he intends to provide is adequate. Failure to do this would result in a waste of resources by both the applicant and EFSA. This applies in particular to the toxicological requirements sections, cf. our comments to that part of the document.
Dyadic International, Inc.	Scope	Dear Madam or Sir, I have a brief background description and question. Enzymes are often produced and then concentrated into various concentrations and forms in order to accomodate various customer and end user requirments. For instance, the same cellulase might be produced as a low enzyme concentration liquid, a high enzyme concentration liquid, a powdered concentrate and a powdered granulated concentrate. Is it sufficient for enzyme testing to be performed on 1 of the concentrations and extrapolated to the other enzyme concentrations? Regards, Brian Murdoch
SYNPA	Submission of an application	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
AFSSA	Submission of an application	 Information to be supplied with an application for a food enzyme Lines 211-214 must be come down to line 222.
Amfep	Submission of an application	184 The double submission (electronic and paper) is an unnecessary administrative burden. An electronic submission should be sufficient and would waste fewer natural resources. 193 The requirement to submit all literature references as "full length paper" is in general an unnecessary administrative burden. This requirement can only be justified in the case of unpublished work, books, or papers that are not easily accessible. It should be limited to those papers that are essential to the safety evaluation.
SYNPA	Information to be supplied with an application for a food enzyme	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
SYNPA	1. Summary of Dossier Submission	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	1. Summary of Dossier Submission	216-221 These lines appear not to be numbered correctly.
SYNPA	2. Administrative Data	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	2. Administrative Data	241 We recommend that this requirement is deleted. It is already covered by section 3.6 of the guidelines and is not relevant in the "Administrative data" section. Assessing whether an existing evaluation for a related food enzyme is relevant for the present dossier is a scientific, not administrative task.
SYNPA	3. Technical Data	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	3.1. Identity of the Food Enzyme	The Regulation was not intended to operate by brand-specific authorisation. CIAA is concerned that the approach proposed by EFSA, will in effect require enzyme producers to provide data by individual company, not in the generic way we had understood it would be taken. The requirement for additional testing and hence use of more laboratory animals would be of concern to CIAA members and is contrary to general policy, e.g in REACH, to reduce the amount of testing on animals
ELC - Federation of European Food Additives, Food Enzymes and Food Cultures Industries	3.1. Identity of the Food Enzyme	ELC supports the comments made by its member association AMFEP. In particular, we consider that as regards the identity of the food enzyme, the characteristics of commercial food enzymes actually on the market have insufficiently been taken into account. Issue Section 3.1 of the draft guidelines describe the documentation elements that are needed to characterize the identity of a commercial food enzyme. Several aspects of this section are problematic: - The specificity of the requirements systematically goes down to the level of an individual product manufactured by one given food enzyme producer. - Food enzymes are treated the same way as pure chemicals – whereas commercial food enzymes are in fact biological isolates manufactured by fermentation of microorganisms or by extraction from plant or animal tissues. As a result they contain, apart from the enzyme in question, also other material derived from the production organism and/or fermentation raw materials, such as proteins, peptides and carbohydrates. This is the very reason why JECFA introduced the so-called Total Organic Solids (TOS) concept to accurately describe the characteristics of commercial food enzymes (see: http://www.fao.org/ag/agn/jecfa-additives/docs/enzymes_en.htm). From a safety point of view, the TOS values are of much higher importance than the molecular characteristics of the enzyme in question. - Enzymes are classified by their catalytic activity as defined by their IUB designation, not by their unique molecular structure. Moreover, the enzymatic activity of certain commercial products is not determined by one single protein molecule, but by a variety of different enzymes. An example is the hemicellulase complex. - A significant proportion of the documentation elements do not have any bearing on safety. Impact The exaggerated specificity level of the identity requirements would de facto render necessary the submission of one dossier per enzyme manufacturer and per food enzyme product – whereas this may not always be warranted for safety reasons. This will result in a waste of resources (applicant, risk assessor, risk manager), and in unjustified extra use of laboratory animals.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		Proposal In line with AMFEP, ELC suggest that the section is simplified, restructured and shortened, and that a number of requirements are deleted (cf. detailed Amfep's comments). We strongly recommend that the TOS (Total Organic Solids) concept should be used throughout the identity and safety sections of the guidelines – this concept is recognized world-wide (including in the SCF guidelines for food enzymes).
SYNPA	3.1. Identity of the Food Enzyme	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
SYNPA	3.1.1. Name(s), Synonyms, Abbreviations and Classification	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	3.1.1. Name(s), Synonyms, Abbreviations and Classification	257 We recommend that trade names are deleted. They are not relevant under Regulation 1332/2008, which does not foresee brand-specific or producer-specific approvals. 261-263 We propose to delete the CAS, EINECS or ELINCS numbers. Whereas the IUB name and number make sense for identification of enzymes, it is doubtful that CAS, EINECS or ELINCS references add any meaningful information: - CAS is neither an EU nor a global identification system. - EINECS and ELINCS are less relevant, now that REACH is in force. - There is no one-to-one correspondence between these systems – therefore the enzyme classification (IUBMB) should be the preferred one. A list of enzymes as substances will be published by ECHA in November 2010. This list will be based on the IUBMB classification.
Danish Veterinary and Food Administration	3.1.2. Chemical Composition and Properties of the Food Enzyme	The Danish Veterinary and Food Administration think that a chemical description of the food enzymes should include processing aids (anti-foam agents and filter aids). We would therefore like to have "processing aids" added to list in the parenthesis. Dossiers should include a clear definition and description of the used processing aids as these are not always compatible with food use.
SYNPA	3.1.2. Chemical Composition and Properties of the Food Enzyme	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
DSM Food Specialties	3.1.2. Chemical Composition and Properties of the Food Enzyme	3.1.2.3 Properties of the Food enzyme – 296 - 297 Enzyme activity cannot always be expressed in Katal per unit weight. In case of complex natural substrates f.e. hemicellulose or by a mixture of enzyme activities necessary to obtain the required effect this is impossible for pure theoretical reasons. Therefore DSM suggests to add "….. expressed in Katal per unit weight when possible, but also well defined company units or other well defined units may be used"
General Chemical State Laboratory	3.1.2. Chemical Composition and Properties of the Food Enzyme	3.1.2.1 line 268: Except from the primary structure (amino acid sequence), a description of the tertiary structure (if available) and/or the active center should be provided line 271-272: Among the other chemical impurities, residual proteins, which remain after the last purification step, should be mentioned, with reference to the potential toxic properties or enzymatic activities, different from the target activity.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
AFSSA	3.1.2. Chemical Composition and Properties of the Food Enzyme	3.1.2.1 Chemical composition ii. Lines 269-272: A chemical and microbiological contaminants' check list with their specifications should be drawn up.
DSM Nutritional Products Dept. Regulatory Affairs	3.1.2. Chemical Composition and Properties of the Food Enzyme	Lines 266-288 and lines 507-517 Microbial enzymes used in food processing, in contrast to chemicals, are typically sold as enzyme preparations that contain mostly a mixture of enzyme activities, including the desired enzyme activity. In addition it will contain also other metabolites of the production strain, as well as added materials such as preservatives and stabilizers. The added materials must be safe, food grade and meet regulatory standards. In order to assess the safety of the metabolites (proteins, peptides, carbohydrates, etc) that are produced by the production organism, in addition to the desired enzyme. Therefore, the concept of Total Organic Solids (TOS) was developed to express the concentration of all organic components produced by the production organism. The TOS concept is used worldwide by industry to characterize and standardize enzyme preparations, as recommended by JECFA. We highly recommend to incorporate the TOS concept in the EFSA guidance for Food Enzyme Evaluation.
University of Wisconsin	3.1.2. Chemical Composition and Properties of the Food Enzyme	Section 3.1.2; lines 266-288 and lines 507-517 Microbial enzymes used in food processing are typically sold as enzyme preparations that contain not only a desired enzyme activity but also other metabolites of the production strain, as well as added materials such as preservatives and stabilizers. The added materials must be food grade and meet applicable regulatory standards. The issue, then, is to establish the safety of the metabolites (proteins, peptides, carbohydrates, etc) that are produced by the production organism, including, but of course not limited to, the desired enzyme. Accordingly, the concept of Total Organic Solids (TOS) was developed to express the concentration of all organic components produced by the production organism. The TOS concept is used worldwide by industry to characterize and standardize enzyme preparations, as recommended by JECFA (http://www.fao.org/ag/agn/jecfa-additives/docs/enzymes_en.htm). TOS is defined as the sum of the organic compounds, excluding diluents, in the final enzyme preparation. It is derived experimentally as follows: % TOS = 100 - (A + W + D) where: A = % ash, W = % water and D = % diluents and/or other formulation ingredients. The TOS concept also allows determination of 'purity' when used as the basis of comparison of the active enzyme protein concentration vs. TOS between different enzyme preparations. Further, in a safety evaluation both dietary exposure and non-observed adverse effect levels (NOAEL) could be expressed on a standard TOS basis, allowing for more accurate risk assessment. It would be highly appropriate to incorporate the TOS concept in the EFSA guidance for Food Enzyme Evaluation.
University of Wisconsin	3.1.2. Chemical Composition and Properties of the Food Enzyme	I commend EFSA's efforts to provide guidelines to industry for food enzyme evaluation that will be used throughout the EU. It is important to establish scientifically sound standardized requirements and an evaluation process that are transparent to both manufacturers and consumers. Based on extensive experience in food enzyme safety evaluation and in setting and updating science based standards for food enzyme safety, I have three suggestions for EFSA consideration: Section 3.1.2; lines 266-288 and lines 507-517 Microbial enzymes used in food processing are typically sold as enzyme preparations that contain not only a desired enzyme activity but also other metabolites of the production strain, as well as added materials such as preservatives and stabilizers. The added materials must be food grade and meet applicable regulatory standards. The issue, then, is to establish the safety of the metabolites (proteins, peptides, carbohydrates, etc) that are produced by the production organism, including, but of course not limited to, the desired enzyme. Accordingly, the concept of Total Organic Solids (TOS) was developed to express the concentration of all organic components produced by the production organism. The TOS concept is used worldwide by industry to characterize and standardize enzyme preparations, as recommended by JECFA (http://www.fao.org/ag/agn/jecfa-additives/docs/enzymes_en.htm). TOS is defined as the sum of the organic compounds, excluding diluents, in the final enzyme preparation. It is derived experimentally as follows:

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		% TOS = 100 - (A + W + D) where: A = % ash, W = % water and D = % diluents and/or other formulation ingredients. The TOS concept also allows determination of 'purity' when used as the basis of comparison of the active enzyme protein concentration vs. TOS between different enzyme preparations. Further, in a safety evaluation both dietary exposure and non-observed adverse effect levels (NOAEL) could be expressed on a standard TOS basis, allowing for more accurate risk assessment. It would be highly appropriate to incorporate the TOS concept in the EFSA guidance for Food Enzyme Evaluation.
SYNPA	3.2. Source Materials and Manufacturing Process	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	3.2.1. Source Materials	Lines 397-420 - Monitoring of production strain. CIAA is concerned that this requirement would lead to additional costs, which will be passed on to the food industry and ultimately to the final consumer. This does not appear justified when there is no benefit in terms of additional consumer protection. Moreover, most food enzymes have a long history of safe use. Therefore, CIAA supports the deletion of this requirement.
ELC - Federation of European Food Additives, Food Enzymes and Food Cultures Industries	3.2.1. Source Materials	ELC supports the comments made by its member association AMFEP, in particular that strain deposition is unnecessary and points to strain- and thus manufacturer-specific approval and listing. Issue Section 3.2.1.3.iii of the draft guidelines requires that the production microorganisms for food enzymes manufactured by fermentation are deposited in a culture collection. This requirement does not provide any advantage in terms of safety evaluation: - Production microorganisms are not present in commercial enzyme products (this is part of the product specifications). - Production microorganisms are not a reference material in terms of quality or safety – the only valid reference material is the food enzyme. Getting access to the production microorganism would not allow the control authorities to check whether a particular food enzyme sample was indeed produced by this microorganism. - It is generally accepted that approvals and positive listing is generally based on species level (see a.o., the Codex Inventory of Processing Aids). If listing is to be more specific (on basis of strain or its lineage), then this should only apply in exceptional cases. Impact The requirement, which provides no advantage in terms of safety, quality or control, would potentially render all evaluations and authorizations manufacturer-specific. This will result in a waste of resources (applicant, risk assessor, risk manager), and in unjustified extra use of laboratory animals. Moreover, it would be against the principles of the EFSA QPS system. It would also create a competition distortion between EU-based enzyme manufacturers and manufacturers located in third countries – where controls in the production facilities would not be manageable. Proposal In line with AMFEP, ELC propose that this requirement is deleted.
SYNPA	3.2.1. Source Materials	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Enzyme Technical Association	3.2.1. Source Materials	LINE 418 STRAIN DEPOSITION REQUIREMENT Issue

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		Section 3.2.1.3.iii of the draft guidelines requires that the production microorganisms for food enzymes manufactured by fermentation are deposited in a culture collection. Although we agree that the safety of the enzyme preparation is largely determined by the absence of harmful substances produced by the production organism, this strain deposit requirement does not provide any advantage in terms of human or environmental safety evaluation: - Production microorganisms are not present in commercial enzyme products (this is part of the product specifications). - Production microorganisms are not a reference material in terms of quality or safety – the only valid reference material is the food enzyme. Getting access to the production microorganism would not allow the control authorities to check whether a particular food enzyme sample was indeed produced by this microorganism, or whether the food enzyme derived from it contains harmful substances. - Since the enzyme manufacture makes use only of non-pathogenic and non-toxigenic microorganisms and takes place in contained facilities, there is virtually no risk of environmental release. Impact The requirement, which provides no advantage in terms of safety, quality or control, would impose unnecessary burden on the industry and would potentially render all evaluations and authorizations manufacturer-specific. Proposal We strongly urge that this requirement is deleted. Instead, we propose that manufacturers provide information regarding the safety of the production organism used to manufacture the enzyme, which can include published literature on the species and unpublished safe strain lineage information. Our suggestion results in the following draft language for section 3.2.1.3.iii: iii. Production Organism Safety Provide information regarding the safety of the production organism used to manufacture the enzyme, which can include published literature on the species and unpublished safe strain lineage information.
AFSSA	3.2.1. Source Materials	Line 323: The internet reference for OECD could be added. 3.2.1.1 Production from animal sources iii. Line 340: The sentence should be specified with “Information shoud be provided on methods used to ensure the absence of any risk of infectivity (e.g. The agent of transmissible spongiform encephalopathies (TSEs), parasites or other zoonotic agents) in function of the present knowledge on animal diseases.” 3.2.1.2 Plant and fungal sources Lines 350-351 : The concept of history of safe use should be clearly defined and supported by both qualitative and quantitative data (Constable et al., 2007). 3.2.1.3 Microbial sources iv. Line 426 : “acquired” may be erased or supplemented with “natural and/or acquired”. Reference : Constable A., Jonas D., Cockburn A., Davi A., Edwards G., Hepburn P., Herouet-Guicheney C., Knowles M., Moseley B., Oberdörfer R., Samuels F. 2007. History

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms. Food. Chem. Toxicol. 45 2513-2525.
AFSSA	3.2.1. Source Materials	Line 323: The internet reference for OECD could be added. 3.2.1.1 Production from animal sources iii. Line 340: The sentence should be specified with "Information shoud be provided on methods used to ensure the absence of any risk of infectivity (e.g. The agent of transmissible spongiform encephalopathies (TSEs), parasites or other zoonotic agents) in function of the present knowledge on animal diseases." 3.2.1.2 Plant and fungal sources Lines 350-351 : The concept of history of safe use should be clearly defined and supported by both qualitative and quantitative data (Constable et al., 2007). 3.2.1.3 Microbial sources iv. Line 426 : "acquired" may be erased or supplemented with "natural and/or acquired".
DSM Nutritional Products Dept. Regulatory Affairs	3.2.1. Source Materials	Lines 366-694 and lines 586-603 The EFSA guidance document also does not refer to an overall decision tree approach such as the one developed by Pariza and Johnson (2001) for microbially derived enzymes, in which the concept of Safe Strain Lineage can be an integral component. Decision trees such as that in Pariza and Johnson (2001) are not limited to GMM-derived enzymes. For example, in the case of enzymes, derived from traditionally improved micro-organisms (non-GMM), this decision tree allows the safety assessment by merely by-passing a few GMM (or rDNA) specific steps in the decision tree (questions 2 - 5 or 3 - 4, respectively) followed by the several additional questions that are common for all enzymes regardless the source or method of strain development. In fact the decision tree published in 2001 was a logical expansion from a decision tree for traditional enzymes that has been in use since the early 1980s (Pariza and Foster, 1983) to evaluate enzymes derived from natural isolates and improved traditional strains. The use of a comprehensive decision tree would be an invaluable tool in the overall food enzyme safety evaluation by EFSA; its use could be incorporated in section 3.2 of the draft guidelines and also in section 4 to establish any need for new toxicology data.
DSM Nutritional Products Dept. Regulatory Affairs	3.2.1. Source Materials	lines 366-394 and lines 586-603 When asking for strain depositions and the default requirement of a full toxicology-package, it is evident that the draft EFSA guidelines appear to follow a road that leads to manufacturer-specific dossiers and evaluations. For food enzymes from traditional microbial sources (those with a history of safe use in food manufacture), manufacturer-specific dossier evaluation is not justified because the safety of traditional microbes can be established at the species level. For GMM-derived enzymes the safety of commonly used production organisms such as Aspergillus niger, A. oryzae, Bacillus amyloliquefaciens, B. subtilis, B. licheniformis, and Kluyveromyces lactis is well documented in the scientific literature and can be further confirmed at the strain lineage level (see e.g. van Dijck et al, 2003 for such an approach for Aspergillus neger). The use of the concept of Safe Strain Lineage as described in Pariza and Johnson (2001), is completely neglected in the draft guidelines, most probably as some people in the EFSA panel appear to think that the concept is restricted to enzymes from recombinant micro-organisms. This is not the case. The term safe strain lineage is defined and discussed in the Pariza-Johnson paper, as follows: "Thoroughly characterized nonpathogenic, nontoxigenic microbial strains, particularly those with a history of safe use in food enzyme manufacture, are logical candidates for generating a safe strain lineage, through which improved strains may be derived via genetic modification by using either traditional/classical or rDNA strain improvement strategies. The elements needed to establish a safe strain lineage include thoroughly characterizing the host organism, determining the safety of all new DNA that has been introduced into the host organism, and ensuring that the procedure(s) that have been used to modify the host organism are appropriate for food use."

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		The concept of safe strain lineage and the use of a decision tree approach builds on an earlier publication by Pariza and Foster, 1983. We strongly recommend to include this concept in sections 3.2.1.3. and/or 4.1.2. Use of this concept in safety evaluation of food enzymes will reduce unnecessary animal testing and is scientifically justified as it builds on the available body of scientific evidence of safety for commonly used production organisms supported by strain lineage specific data.
DSM Nutritional Products Dept. Regulatory Affairs	3.2.1. Source Materials	Lines 416-420 Only the company that has developed a production strain for a given product optimally knows how to maintain the strain. Companies have an elaborate strain management system to keep the genetic stability of the strain and to eliminate batch-to-batch variability in the production fermentations. Deposition of an industrial strain in a public strain collection does not warrant that the genomic make-up of the strain is maintained. And since the production strain is not released into the environment there is no need for controlling bodies to check its genetic composition. The need has been copied from the feed guidelines, which in turn have been copied from the requirements for GM crops (where it does make sense for governmental bodies controlling e.g. imports of seeds).
DSM Nutritional Products Dept. Regulatory Affairs	3.2.1. Source Materials	lines 366-394 and lines 586-603 When asking for strain depositions and the default requirement of a full toxicology-package, it is evident that the draft EFSA guidelines appear to follow a road that leads to manufacturer-specific dossiers and evaluations. For food enzymes from traditional microbial sources (those with a history of safe use in food manufacture), manufacturer-specific dossier evaluation is not justified because the safety of traditional microbes can be established at the species level. For GMM-derived enzymes the safety of commonly used production organisms such as Aspergillus niger, A. oryzae, Bacillus amyloliquefaciens, B. subtilis, B. licheniformis, and Kluyveromyces lactis is well documented in the scientific literature and can be further confirmed at the strain lineage level (see e.g. van Dijck et al, 2003 for such an approach for Aspergillus neger). The use of the concept of Safe Strain Lineage as described in Pariza and Johnson (2001), is completely neglected in the draft guidelines, most probably as some people in the EFSA panel appear to think that the concept is restricted to enzymes from recombinant micro-organisms. This is not the case. The term safe strain lineage is defined and discussed in the Pariza-Johnson paper, as follows: “Thoroughly characterized nonpathogenic, nontoxigenic microbial strains, particularly those with a history of safe use in food enzyme manufacture, are logical candidates for generating a safe strain lineage, through which improved strains may be derived via genetic modification by using either traditional/classical or rDNA strain improvement strategies. The elements needed to establish a safe strain lineage include thoroughly characterizing the host organism, determining the safety of all new DNA that has been introduced into the host organism, and ensuring that the procedure(s) that have been used to modify the host organism are appropriate for food use.”
University of Wisconsin	3.2.1. Source Materials	Sections 3.2 and 4; lines 366-694 and lines 586-603 In addition to not using the Safe Strain Lineage concept appropriate for the safety evaluation of food enzymes, the EFSA guidance document also does not refer to an overall decision tree mechanism such as the one in Pariza and Johnson (2001) for microbially derived enzymes, or anything similar, in which the concept of Safe Strain Lineage can be an integral component. Decision trees such as that in Pariza and Johnson (2001) are not limited to GMM-derived enzymes. For example, in the case of non-GMM (or non-rDNA) derived enzymes, this decision tree allows the safety assessment by merely by-passing a few GMM (or rDNA) specific steps in the decision tree (questions 2 to 5 or 3 and 4, respectively) followed by several additional steps that are common for all enzymes regardless of their source or development method. It is noteworthy that the decision tree published in 2001 was expanded from a basic decision tree for traditional enzymes that has been in use since the early 1980s (Pariza and Foster, 1983) to evaluate enzymes derived from natural isolates and improved traditional strains. Use of a comprehensive decision tree would be an invaluable tool in the overall food enzyme safety evaluation by EFSA; its use could be incorporated in section 3.2 and also in section 4 to establish the need for new toxicology data.
University of Wisconsin	3.2.1. Source Materials	Sections 3.2.1 and 4.1.2; lines 366-394 and lines 586-603 The draft EFSA guidelines appear to follow a path towards setting requirements for manufacturer-specific dossiers and evaluations. This is because the guidelines ask for strain depositions and the default requirement of a full toxicology-package. For food enzymes from traditional microbial sources (those with a history of safe use in food manufacture),

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		manufacturer-specific dossier evaluation is not justified because the safety of traditional microbes can be established at the species level. For GMM-derived enzymes the safety of commonly used production organisms such as Bacillus subtilis, B. licheniformis, Aspergillus niger, A. oryzae and Trichoderma reesei is well documented in the scientific literature and can be further confirmed at the strain lineage level. The draft guidelines do not make use of the concept of Safe Strain Lineage as described in Pariza and Johnson (2001), and inclusion of this concept in sections 3.2.1.3. and/or 4.1.2 of the guidelines would be very helpful. The term safe strain lineage is defined and discussed in the Pariza-Johnson paper, as follows: "Thoroughly characterized nonpathogenic, nontoxigenic microbial strains, particularly those with a history of safe use in food enzyme manufacture, are logical candidates for generating a safe strain lineage, through which improved strains may be derived via genetic modification by using either traditional/classical or rDNA strain improvement strategies. The elements needed to establish a safe strain lineage include thoroughly characterizing the host organism, determining the safety of all new DNA that has been introduced into the host organism, and ensuring that the procedure(s) that have been used to modify the host organism are appropriate for food use." Use of this concept in safety evaluation of food enzymes will reduce unnecessary animal testing and is scientifically justified as it builds on the available body of scientific evidence of safety for commonly used production organisms supported by strain lineage specific data.
Amfep	3.2.1. Source Materials	316 and 345 The list "animal, plant, fungal or microbial sources" is somehow confusing. Food enzymes can be made by extraction from plant or animal tissues, or by fermentation using micro-organisms such as: yeasts, bacteria or filamentous fungi. Therefore "fungi" should not be a separate item but instead be implicitly part of "micro-organisms" – as is the case for yeasts and bacteria. Moreover, the definition in Regulation 1332/2008 does not distinguish between fungi and micro-organisms. 368 We believe that "certain microbial fungi […] can produce […]" should read instead: "individual strains of certain microbial fungal species […] may produce […]". 378 We believe that this should read: "The taxonomic identity…". 386-389 We welcome the use of the EFSA GMM Guidance document and the simultaneous evaluation by the GMO Panel. This process is already successfully used for enzyme feed additives produced by genetically modified micro-organisms and will prevent unnecessary delays. 391-394 This section forms part of the EFSA GMM Guidance document and hence should be deleted here to prevent duplication. 397-420 We believe that this section should be included in the "Manufacturing process" part of the guidelines. 403 We propose to delete "and their effect on strain drift and reproducibility between the different batches of food enzymes"..."Strain drift" is not analyzed as such. Instead, enzyme manufacturers focus on ensuring that the production strain is genetically stable (the acquired features are not lost during successive generations) and that the fermentation is performed in pure culture conditions. This ensures that the yield and hygiene parameters are optimal. 416

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		The strain identification method should simply ensure that the manufacturer is able to control that the production strain is the one really used during production. As production microorganisms are kept in containment, there is no further safety or control issue which would warrant the need for such a method of identification. 418-420 For the reasons listed below we do not believe that strain deposition will add value to the safety evaluation process and hence would like to see this requirement deleted. The production micro-organism is absent from industrial enzyme products (incl. food enzymes). This is for the protection of industrial property as well as technological (stability and homogeneity) reasons. Therefore the production micro-organism is not in itself a reference material for the food enzyme. In terms of quality and safety, the reference material is the food enzyme preparation itself. Only the company that has developed a production strain for a given product optimally knows how to maintain the strain. Deposition of an industrial strain in a public strain collection does not warrant that the genomic make-up of the strain is maintained. And since the production strain is not released into the environment there is no need for controlling bodies to check its genetic composition. It is also difficult to imagine which benefit the deposition would provide, when the production site itself is outside of the European Union and therefore not easily accessible to official controls. The suggested requirement inspired from the genetically modified crops - where it does make sense for governmental bodies controlling e.g. imports of seeds and release into the environment. Since the microorganism is not a reference material for the food enzyme put on the market, it would not allow the authorities to check whether a food enzyme was produced by a particular microorganism strain. Finally, the deposit of the production micro-organism would de facto render the evaluations and the authorizations product-specific, whereas this is not systematically justified from a scientific point of view. Because of the above reasons, we propose to delete lines 416 till 420.
Amfep	3.2.1. Source Materials	316 and 345 The list “animal, plant, fungal or microbial sources” is somehow confusing. Food enzymes can be made by extraction from plant or animal tissues, or by fermentation using micro-organisms such as: yeasts, bacteria or filamentous fungi. Therefore “fungi” should not be a separate item but instead be implicitly part of “micro-organisms” – as is the case for yeasts and bacteria. Moreover, the definition in Regulation 1332/2008 does not distinguish between fungi and micro-organisms. 368 We believe that “certain microbial fungi […] can produce […]” should read instead: “individual strains of certain microbial fungal species […] may produce […]”. 378 We believe that this should read: “The taxonomic identity…”. 386-389 We welcome the use of the EFSA GMM Guidance document and the simultaneous evaluation by the GMO Panel. This process is already successfully used for enzyme feed additives produced by genetically modified micro-organisms and will prevent unnecessary delays. 391-394 This section forms part of the EFSA GMM Guidance document and hence should be deleted here to prevent duplication.

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SYNPA	3.2.2. Manufacturing Process	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
AFSSA	3.2.2. Manufacturing Process	i. Line 452 : The following sentence must be added "Elements of the enzyme formulation such as charge component, stabilizers or diluters should be provided". ii.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		Line 458 : pH may complete temperature.
Amfep	3.2.2. Manufacturing Process	434-472 (general comments on this section) A very detailed description of the manufacturing process, including fermentation parameters and degree of purity achieved, may not provide the optimum data for assessing the safety of a food enzyme. What is relevant for the safety of the manufacturing process is that: - the fermentation is performed under strict hygiene conditions, in pure culture; - the whole process is controlled using key parameters and control points. 451 We propose to delete the requirement of providing the degree of purity. The degree of purity is not really relevant for the safety evaluation. A very impure food enzyme could be perfectly safe (if for instance the production micro-organism is QPS) whereas a highly purified one could still contain significant amounts of mycotoxins if the strain is able to produce those in large amounts. The latter is, however, already covered by the required purity specifications in Section 3.1.2.2. To compare the purity of various batches one should use the ratio [enzyme activity / TOS]. 453 A “statistically relevant number” will be a problem for new food enzymes, which by definition have not yet been produced in large amounts. We propose to limit this number in all cases to 3 batches. 460-463 Requirements in section (iii) are already fulfilled by the manufacturer’s compliance with the General Food Law (Regulation 178/2002) and the Food Hygiene Regulation (852/2004) and should be covered in the authorization dossier only by a statement to this effect. Furthermore, some dossiers will cover food enzymes that will be authorized in a generic way. It would be unfair in these cases to oblige the applicants to document compliance for a large number of batches, whereas subsequent operators putting the same food enzyme on the market would bear no such requirement at all. It is therefore proposed to rephrase this Section.
Amfep	3.2.2. Manufacturing Process	434-472 (general comments on this section) A very detailed description of the manufacturing process, including fermentation parameters and degree of purity achieved, may not provide the optimum data for assessing the safety of a food enzyme. What is relevant for the safety of the manufacturing process is that: - the fermentation is performed under strict hygiene conditions, in pure culture; - the whole process is controlled using key parameters and control points. 451

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		We propose to delete the requirement of providing the degree of purity. The degree of purity is not really relevant for the safety evaluation. A very impure food enzyme could be perfectly safe (if for instance the production micro-organism is QPS) whereas a highly purified one could still contain significant amounts of mycotoxins if the strain is able to produce those in large amounts. The latter is, however, already covered by the required purity specifications in Section 3.1.2.2. To compare the purity of various batches one should use the ratio [enzyme activity / TOS]. 453 A "statistically relevant number" will be a problem for new food enzymes, which by definition have not yet been produced in large amounts. We propose to limit this number in all cases to 3 batches. 460-463 Requirements in section (iii) are already fulfilled by the manufacturer's compliance with the General Food Law (Regulation 178/2002) and the Food Hygiene Regulation (852/2004) and should be covered in the authorization dossier only by a statement to this effect. Furthermore, some dossiers will cover food enzymes that will be authorized in a generic way. It would be unfair in these cases to oblige the applicants to document compliance for a large number of batches, whereas subsequent operators putting the same food enzyme on the market would bear no such requirement at all. It is therefore proposed to rephrase this Section.
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	3.3. Reaction and Fate in Food	CIAA is concerned that this requirement could lead to unnecessary restrictions in the use of food enzymes to only those foods for which data on interactions with the food matrix have been provided. This does not appear to be risk-based or at to the safety of the final food, particularly when most of the food enzymes have history of safe food use.
SYNPA	3.3. Reaction and Fate in Food	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	3.3. Reaction and Fate in Food	475-490 (the whole section) This section largely deals with very hypothetical considerations. Most food enzymes and/or their reaction products already exist in the food matrix. Therefore we do not believe that this would give rise to safety concerns. The "fate of the food enzyme during food processing" is a regulatory consideration – does the enzyme exert its function in the final food? And hence we question whether this should be part of the safety evaluation. Based on the above, we propose that lines 477-482 are rephrased in such a way that it is clear that this applies only for enzyme activities which have never been used in food. Moreover, we propose to delete lines 484-490.
SYNPA	3.4. Case of Need and proposed Conditions of Use	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
Danish Veterinary and Food Administration	3.5. Dietary Exposure	In general the NOAEL is high for food enzymes and the intake is low. Based on many years of experience of risk assessment of food enzymes in Denmark, we think that the Budget Method is far sufficient for evaluation of the dietary exposure for food enzymes.
ELC - Federation of European Food Additives, Food Enzymes and Food Cultures Industries	3.5. Dietary Exposure	ELC supports the comments made by its member association AMFEP, in particular as regards the calculation of consumer dietary exposure for which more flexibility is needed. Issue Section 3.5 of the draft guidelines describes how to evaluate the consumers' dietary exposure to a given food enzyme. The very sophisticated, refined and detailed approach taken fits well substances with high toxicity levels / low NOAELs (No Adverse Effect Levels). However, this approach is not warranted for the vast majority of food enzymes: indeed, the NOAELs for enzymes are generally very high (typically in the order of magnitude of 500 mg TOS / kg body weight / day) and typically the highest dosage of the test substance that can be administered to the test animal. Furthermore, the food enzyme doses are generally very low (typically no more than 50 mg TOS / kg food materials). Impact Should this approach be kept in the guidelines, it would result in unnecessary work and costs for the industry, as well as time spent by the risk assessor. EU institutions and EFSA are already well aware of the complexity and the time involved collecting scientifically trustworthy information on the consumption patterns in EU Member States. Proposal A calculation of the consumer exposure using the Budget Method normally suffices to define a very high safety margin – even using an exaggerated maximum intake approach, supposing that all processed food was manufactured with the enzyme under consideration and that all enzyme remains in the final food. In line with AMFEP, ELC suggest to use the above method – and to resort to more refined calculations only in the case where it would not provide a high-enough safety margin.
SYNPA	3.5. Dietary Exposure	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Enzyme Technical Association	3.5. Dietary Exposure	LINES 507-517 Issue Section 3.5 of the draft guidelines describe how to evaluate the consumers' dietary exposure to a given food enzyme. The very sophisticated, refined and detailed approach taken fits well for substances with high toxicity levels / low NOAELs (No Adverse Effect Levels). However, this approach is not warranted for the vast majority of food enzymes: indeed, the NOAELs for enzymes are generally very high (typically in the order of magnitude of 500 mg TOS / kg body weight / day) and typically the highest dosage of the test substance that can be administered to the test animal. Furthermore, the food enzyme doses are generally very low (typically no more than 50 mg TOS / kg food materials). Impact Should this approach be kept in the guidelines, it would result in unnecessary work and costs for the industry, as well as time spent by the risk assessor. Proposal A calculation of the consumer exposure using the Budget Method normally suffices to define a very high safety margin – even using an exaggerated maximum intake approach, supposing that all processed food was manufactured with the enzyme under consideration and that all enzyme remains in the final food. We suggest to use the above method – and to resort to more refined calculations only in the case where it would not provide a high-enough safety margin.
Amfep	3.5. Dietary Exposure	507-517 (the whole section) Using refined or ad hoc exposure estimates, as well as taking into account special groups of consumers, is an approach that fits substances with relatively low NOAELs.

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		This approach is not warranted for the vast majority of food enzymes: indeed, the NOAELs for enzymes are generally very high (typically in the order of magnitude of 500 mg TOS / kg body weight / day) and typically the highest dosage of the test substance that can be administered to the test animal. Furthermore, the food enzyme doses are generally very low (typically no more than 50 mg TOS / kg food materials). As a consequence, a calculation of the consumer exposure using the Budget Method normally suffices to define a very high safety margin – even using an exaggerated maximum intake approach, supposing that all processed food was manufactured with the enzyme under consideration and that all enzyme remains in the final food. In order not to burden industry with unnecessary work and costs, we propose to rephrase lines 509 till 517 in such a way that the very conservative budget method generally can be used.
Amfep	3.5. Dietary Exposure	507-517 (the whole section) Using refined or ad hoc exposure estimates, as well as taking into account special groups of consumers, is an approach that fits substances with relatively low NOAELs. This approach is not warranted for the vast majority of food enzymes: indeed, the NOAELs for enzymes are generally very high (typically in the order of magnitude of 500 mg TOS / kg body weight / day) and typically the highest dosage of the test substance that can be administered to the test animal. Furthermore, the food enzyme doses are generally very low (typically no more than 50 mg TOS / kg food materials). As a consequence, a calculation of the consumer exposure using the Budget Method normally suffices to define a very high safety margin – even using an exaggerated maximum intake approach, supposing that all processed food was manufactured with the enzyme under consideration and that all enzyme remains in the final food. In order not to burden industry with unnecessary work and costs, we propose to rephrase lines 509 till 517 in such a way that the very conservative budget method generally can be used.
DGCCRF- bureau C2	3.6. Information on Existing Authorisations and Evaluations	Faut il se référer uniquement aux évaluations réalisées dans le cadre de l"Union européenne voire de l"EEE ou bien ces informations peuvent elles aussi intégrer les informations issues des pays tiers ? Dans le cadre des procédures d'autorisation de certains Etats membres, des évaluations récentes ont été réalisées selon les lignes directrices établies par le Comité scientifique de l'alimentation humaine (« guidelines for the presentation of date on food enzymes » (opinion expressed 11/04/91) EUR 14181 EN, 1992). Les autorités françaises souhaiteraient qu'il en soit tenu compte par l'AESA sous la forme d'une procédure d'évaluation simplifiée afin d'accélérer la publication de la liste positive initiale des enzymes autorisées.
Danish Veterinary and Food Administration	3.6. Information on Existing Authorisations and Evaluations	The Danish Veterinary and Food Administration welcome that EFSA will look at previous authorisations and evaluations for a food enzyme. However, it is not clear to what extent they will be used in the risk assessments of the individual enzymes. The Danish Veterinary and Food Administration encourage EFSA to clarify how and to what extent, previous authorisations and evaluations will influence the risk assessments by EFSA.
SYNPA	3.6. Information on Existing Authorisations and Evaluations	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
SYNPA	3.6. Information on Existing Authorisations and Evaluations	Comments of lines 520-523 : France has implemented a authorisation procedure (risk assessment + risk management) for food enzymes for 1983.

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		The draft guidelines which are proposed by EFSA, are consistent with the guidelines used by the French food safety agency (Afssa). Therefore, we would like to suggest for an efficient use of EFSA"s ressources and to avoid the unappropriate repetition of animals studies, to apply the proportionality principle for food enzymes which are already authorised in France.
CIAA-Confederation of the Food and Drink manufacturing industries of the EU	4. Toxicological Data	CIAA would like to see the work already carried out by the Danish and French authorities and JECFA taken into account to reduce the workload on EFSA and avoid duplication of effort. CIAA suggests that the data waiving criteria when using the Qualified Presumption of Safety (QPS) and safe strain lineage concepts are spelled out in the guidelines. When these concepts are used, the identity section of the guidelines makes room for this by requiring a much less product specific set of documentation elements.
ELC - Federation of European Food Additives, Food Enzymes and Food Cultures Industries	4. Toxicological Data	ELC supports the comments made by its member association AMFEP, in particular as regards the lack of proportionality and decision criteria. We believe that more flexibility to deviate from the core set of safety studies is needed. Issue Section 4 of the draft guidelines describe the toxicological requirements. While some room is left to the waiving of part of the toxicological studies (for instance when the production microorganism has a QPS – Qualified Presumption of Safety – status), it remains that: - no certainty is provided that the QPS concept (developed by EFSA itself) will be used to its full extent by the CEF Panel; - the safe strain lineage concept described by Pariza & Johnson (2001) is not mentioned; - the amount of documentation to provide in the case the food enzyme has already been evaluated by the Danish, French or JECFA experts is not specified. Overall, the approach taken by the draft guidelines tends towards a shopping list more than towards sound, scientific proportionality. Impact The applicant would have very limited regulatory predictability on the fate of his dossier, if he chooses to waive part of the toxicological data, based on the use of the QPS or safe strain lineage concepts. Unnecessary animal testing may be performed as a consequence. Resources will be wasted at applicant, risk assessor, risk manager. Proposal In line with AMFEP, ELC suggest that the data waiving criteria when using the QPS and safe strain lineage concepts are spelled out in the guidelines. ELC suggest that when these concepts are used, the identity section of the guidelines makes room for this by requiring a much less product-specific set of documentation elements.
SYNPA	4. Toxicological Data	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Enzyme Technical Association	4. Toxicological Data	LINES 525-603 LACK OF PROPORTIONALITY AND DECISION CRITERIA Issue Section 4 of the draft guidelines describes the toxicological requirements. While there may be some flexibility when toxicological testing may not be needed including waiving of part of the toxicological studies (for instance when the production microorganism has a QPS – Qualified Presumption of Safety – status), there is

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		- no certainty is provided that the QPS concept (developed by EFSA itself) will be used to its full extent by the CEF Panel; - no consideration of a decision tree analysis based on the safe strain lineage concept described by Van Dijck et al (year); - the amount of documentation to provide in the case the food enzyme has already been evaluated by national authorities in Europe (Denmark, France), America (US, Canada) or JECFA experts is not specified. Overall, the approach taken by the draft guidelines resembles a long shopping list of standard requirements rather than a logical approach of sound, scientific proportionality that takes into account any history of safe use or safe testing for either the enzyme in question or the production organism used to manufacture the enzyme. Impact The applicant would have very limited regulatory predictability on the fate of the dossier, if one chooses to waive part of the toxicological data, based on the use of the QPS or safe strain lineage concepts. Unnecessary animal testing will be performed as a consequence. Resources will be wasted at many levels, including that of the applicant, the risk assessor, and the risk manager. Proposal We suggest that the data waiving criteria for production organisms with QPS status or belonging to a safe strain lineage are spelled out in the guidelines. In this context, we urge EFSA to consider using a comprehensive safety evaluation decision tree to identify the focal points for data requirements. One such decision tree is outlined in Pariza and Johnson (2001), which provides decision criteria for enzymes from all microbial sources, including both unmodified and genetically modified microorganisms (see attached figure). We suggest that when these concepts are used, the identity section of the guidelines would allow for much less product-specific set of documentation requirements.
SYNPA	4.1. Toxicological Testing	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	4.1. Toxicological Testing	526-529 We welcome the introduction of flexibility in the toxicological testing requirements. Indeed, depending on the enzyme source organism, the whole set of tests is frequently not relevant (cf. our comments to the toxicological requirements below).
SYNPA	4.1.1. The toxicological Data Set	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
General Chemical State Laboratory	4.1.1. The toxicological Data Set	II Assessment of systemic toxicity. Although lines 572-575 provide for a deviation from the toxicological core set, the required toxicological data for enzymes which will be active in the final food (main use as an additive) should be differentiated from the required toxicological data for enzymes which are inactive (or not present) in the final food (main use as a processing aid). Furthermore, in order to distinguish between potential toxic effects due to enzymatic activity and due to the protein itself, enzyme should also be administered in a form similar to that found in the final food (e.g. together with its substrate and co-factors)
AFSSA	4.1.1. The toxicological Data Set	Line 555 : The sentence “Differences between results obtained on the test sample and the reference should be explained” must be added.
Amfep	4.1.1. The toxicological Data Set	552 The words “represent a carcinogenic hazard” are purely speculative and we propose that they are deleted. 554 Selection of an in vivo genotoxicity assay should follow the recommendations in the draft ICH Guidance of Genotoxicity Testing and Data Interpretation S2(R1), March 2008.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		572 We suggest to slightly reword the first sentence, into: "There may be circumstances under which it may be appropriate to deviate". We suggest to reword the second sentence into: "Such deviations include exemption from certain tests, or use of alternative protocols, or use of alternative assays or tests." 583 See comments in section 4.2 on allergenicity.
SYNPA	4.1.2. When toxicological Testing may not be needed	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
DSM Food Specialties	4.1.2. When toxicological Testing may not be needed	4.1.2 When toxicological Testing may not be needed: line 586 - 603 Many enzymes on the European market as processing aids have been evaluated by the National Scientific Committees and approved by Authorities in France and/or Denmark. Some of these enzymes are approved based on less toxicity studies than required according these EFSA Guidelines. This reduced package of studies was scientifically justified and accepted. The EFSA Guidelines indicates that the requirements for toxicological may be reduced or completely waved. However, clear criteria are not given and only two examples are given. Also the value of approvals in France and/or Denmark is uncertain. By absence of clear criteria or a more extended list of examples and clarity on existing approvals our industry is confronted with a dilemma: 1. Carry out additional safety studies, which is undesirable and unjustified extra use of laboratory animals or 2. Accept the commercial risk that an enzyme preparation is not approved by EFSA and should be withdrawn temporally from the market until the additional study (or studies) has (have) been carried out and the product is re-evaluated by EFSA.
AFSSA	4.1.2. When toxicological Testing may not be needed	Lines 587-603 : This paragraph should be modified: While administrative and technical data shall be provided for all notified food enzymes, the requirements for toxicological data may in some cases be reduced or completely waived; the justification for not supplying toxicological data may include examples of cases for whose toxicological testing may not be needed include : – A document history on the safety of the source of the enzyme, the composition and the properties of the enzymes as well as its use in food, demonstrating no adverse effects on human health when consumed in a comparable way, supported by any existing toxicological studies. In such cases, a detailed rationale must be provided to EFSA for evaluation, e.g. edible parts of animals and (non GM) plants. A demonstrated history of safe use according to Constable (2008) of the source materials, the manufacturing processing, the food enzyme composition including specifications and properties as well as its use in food. The history of safe use should be accurately documented and unambiguously supported by relevant safety data including human data. – On a case by case basis, food enzymes produced by non genetically modified micro-organisms that have been given a status of Qualified Presumption of Safety (QPS), providing the manufacturing processing, the enzyme composition including specifications and properties as well as its use in food can be demonstrated as no safety concerns if it can be demonstrated that there are no concerns related to any residues, degradation products or substances originating from the total production process (EFSA, 2005). Obviously, the safety assessment should consider the whole criteria described in the part 3 of this document (Technical data). Furthermore, the lack of toxicological testing should be accurately justified in the dossier. The detailed justification shall be provided in the dossier. However, EFSA may request further clarification and any additional data if necessary.
University of Wisconsin	4.1.2. When toxicological Testing may not be needed	Sections 3.2 and 4; lines 366-694 and lines 586-603 In addition to not using the Safe Strain Lineage concept appropriate for the safety evaluation of food enzymes, the EFSA guidance document also does not refer to an overall decision tree mechanism such as the one in Pariza and Johnson (2001) for microbially derived enzymes, or anything similar, in which the concept of Safe Strain Lineage can be an integral component. Decision trees such as that in Pariza and Johnson (2001) are not limited to GMM-derived enzymes. For example, in the case of non-GMM (or non-rDNA) derived enzymes, this decision tree allows the safety assessment by merely by-passing a few GMM (or rDNA) specific steps in the decision tree (questions 2 to 5 or 3 and 4, respectively) followed by several additional steps that are common for all enzymes regardless of their source or development method. It is noteworthy that the decision tree published in 2001 was expanded from a basic decision tree for traditional enzymes that has been in use since the early 1980s (Pariza and Foster, 1983) to evaluate enzymes

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		derived from natural isolates and improved traditional strains. Use of a comprehensive decision tree would be an invaluable tool in the overall food enzyme safety evaluation by EFSA; its use could be incorporated in section 3.2 and also in section 4 to establish the need for new toxicology data.
Amfep	4.1.2. When toxicological Testing may not be needed	586-603 We welcome the criteria for defining when toxicological data can be waived, and in particular the use of the EFSA QPS concept. We suggest in addition to this that the safe strain lineage concept as described by Pariza and Johnson (2001) is also a valid tool for defining the nature and extent of toxicological testing on food enzymes produced by conventional as well as genetically modified microorganisms (GMMs). 597-600 The correct reference for the QPS concept dates from 2007 and is: Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA Opinion of the Scientific Committee (Question No EFSA-Q-2005-293) Adopted on 19 November 2007 The EFSA Journal (2007) 587, 1-16. The EFSA opinion states (p. 4) that no further studies are necessary for a QPS micro-organism (except the demonstration of its compliance with the possible qualifications): “Thereafter any strain of microorganism the identity of which could be unambiguously established and assigned to a QPS group would be freed from the need for further safety assessment other than satisfying any qualifications specified. Those strains failing to satisfy a qualification would be considered hazardous and, in the absence of mitigating circumstances, unfit for purpose. Microorganisms not considered suitable for QPS would remain subject to a full safety assessment.” Therefore the sentence “[…] if it can be demonstrated that there are no concerns […] (EFSA, 2005)” seems superfluous. One should ensure, in compliance with section 3.2.2, that the manufacturing process is not creating safety concerns through e.g. lack of hygiene.
SYNPA	4.1.3 Data reporting	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	4.1.3 Data reporting	609 We do not believe that compliance to general purity specifications (3.1.2.2) will assist in demonstrating that the test material is still representative. We therefore suggest deleting the part of the sentence saying “and supported by analytical data for the specification as defined in section 3.1.2.2”.
SYNPA	4.1.4. Review of the toxicological and exposure data and conclusions	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	4.1.4. Review of the toxicological and exposure data and conclusions	612 Enzymes produced by non toxigenic micro-organisms are of very low toxicity (high NOAEL) and it is therefore necessary to use very high doses when performing oral toxicity studies. Because of this, effects not related to the toxicity of the test material itself can in certain cases be observed (e.g. due to high salt concentration). When such effects appear, they lead to a NOEL which is artificially lower than the NOAEL but has no significance by itself. Such effects are of course reported in the toxicological studies – however we recommend that the requirement for a NOEL is deleted.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
SYNPA	4.2. Allergenicity	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	4.2. Allergenicity	618-634 (the whole section) As evidenced by Bindslev-Jensen et al. (2006), food enzymes in general are not a concern for allergenicity by ingestion. Indeed, a very large number of enzyme proteins have been used for decades without any reliably reported incident that would purely be related to allergenicity by ingestion. We therefore propose that this requirement, as well as the determination of the enzyme amino-acid sequence, is deleted altogether. 630-634 This section should be deleted. As stated higher up in the draft guidelines, occupational safety is not in the scope of this document. In addition, although enzymes are respiratory sensitizers, this is a totally unrelated type of phenomenon to the allergenicity by ingestion.
SYNPA	5. Conclusion	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
SYNPA	6. Dossier Bibliography	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	6. Dossier Bibliography	642-643 The requirement to submit all literature references as “full length paper” is in general an unnecessary administrative burden. This requirement can only be justified in the case of unpublished work, books or proceeding papers that are not easily accessible. It should be limited to those papers that are essential to the safety evaluation.
Amfep	6. Dossier Bibliography	642-643 The requirement to submit all literature references as “full length paper” is in general an unnecessary administrative burden. This requirement can only be justified in the case of unpublished work, books or proceeding papers that are not easily accessible. It should be limited to those papers that are essential to the safety evaluation.
SYNPA	Abbreviations	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
SYNPA	References	SYNPA represents the interests of the French food enzymes producers. SYNPA supports the comments made by AMFEP.
Amfep	References	The Bindslev-Jensen paper should be part of the bibliography, reference as follows: Investigation on possible allergenicity of 19 different commercial enzymes used in the food industry. Carsten Bindslev-Jensen, Per Stahl Skov, Erwin L. Roggen, Peter Hvass, Ditte Sidelmann Brinch. Food and Chemical Toxicology 44 (2006) 1909–1915. 745 The Pariza and Johnson paper is in our opinion one of the most useful and meaningful references and should be kept in the list of references.