Draft Statement on Exposure Assessment of Food Enzymes

EFSA Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF)

Abstract
Following a request from EFSA, the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) was asked to explain the principles of the refinement of exposure estimates for food enzymes. Its guidance document on the submission of a dossier on food enzymes for safety evaluation suggests that the 'potential human exposure to the food enzyme and to any other constituent or by-product of concern should be assessed considering all proposed uses, and that a conservative technique such as the 'Budget method' should be used. The margin of exposure (MoE) between the estimated dietary exposure from use of the food enzyme and the no-observed-adverse-effect level (NOAEL) should be calculated'. Since then, the CEF Panel has taken note of the difficulties in the application of the budget method to estimating exposure to food enzymes and proposes refined stepwise approach. © European Food Safety Authority, 2015

Keywords: food enzymes, exposure assessment, budget method, refinement

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1. Introduction

1.1. Background and Terms of Reference as provided by EFSA

The CEF guidance on food enzymes (CEF EFSA, 2009) which was adopted in 2009 stipulates that the 'Potential human exposure to the food enzyme and to any other constituent or by-product of concern should be assessed considering all proposed uses. A conservative technique such as the "budget method" should be used ... assuming that they (i.e. foods and beverages) always contain the food enzyme at its proposed upper use level.'

The CEF Panel has taken note of the difficulty to apply the budget method to food enzymes in general as they are added during processing of food and food ingredients. Based on the experience acquired in the last months, the CEF Panel considered the need to evaluate the exposure to enzymes through more realistic scenarios applying a tiered approach.

This is in line with the advice of EFSA to use ‘a stepwise or tiered approach in which the initial steps rely on conservative screening methods to minimise estimation costs and focus resources on the most important issues for which there is a potential health concern’. (EFSA, 2011)

In accordance with Article 29(1) of Regulation (EC) No 178/2002, the European Food Safety Authority asks its scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) to explain the principles of the refinement of exposure estimates for food enzymes in a scientific statement. This statement shall be presented to stakeholders/applicants before adoption by the CEF Panel.

2. Data and Methodologies

In 2009 CEF Panel adopted a guidance document on the submission of a dossier on food enzymes for safety evaluation. This document aims to assist applicants in the preparation and submission of applications and lays down the data requirements for the safety evaluation of food enzymes (EFSA CEF Panel, 2009). The guidance suggests that the ‘potential human exposure to the food enzyme and to any other constituent or by-product of concern should be assessed considering all proposed uses, and that a conservative technique such as the ‘budget method’ should be used’ (Hansen, 1966, 1979; Douglass et al., 1997; European Commission, 1998; FAO/WHO, 2008).

It stipulates also that information on 'the type of foodstuffs in which the food enzyme is intended to be used‘ as well as ‘the amount of food enzymes to be added to specific foods (recommended use levels and maximum use levels)’ shall be provided in the dossier. “Furthermore, that information should be provided on the fate of the food enzyme during the food processing.”

Finally the margin of exposure (MoE) should be calculated based on the estimated dietary exposure from use of the food enzyme and the no-observed-adverse-effect level (NOAEL).
Most of the applications submitted to EFSA to date contain an estimate of exposure based on the budget method without further refinement. Maximum and/or normal use levels are provided by applicants. However, in most cases detailed information on the type of foodstuffs as consumed in which the food enzyme can be present is not provided. Instead, food processes are described and non-exhaustive examples of food categories are given, not allowing for the refinement of exposure.

3. Assessment

Food enzymes are typically not added to the final food rather they are added during processing of food and food ingredients; therefore, assessing exposure to food enzymes is complex and requires particular consideration.

In the application of the budget method, initially designed and used as a screening method for food additives, several assumptions are made regarding:

- a) food and beverage intake;
- b) percentage of food and beverage that are processed; and
- c) percentage of processed food and beverage containing the food additive.

The levels of consumption of foods and beverages considered are based on assumptions regarding the physiological requirements for energy and liquids of a 2-year old child (Hansen, 1979) - i.e. the daily consumption of 0.1 L/kg bw of liquid and the daily energy intake of 100 kcal/kg bw from foods (equivalent to 0.05 kg/kg bw based on an estimated energy density of 2 kcal/g food). These levels correspond to the daily consumption of 6 litres of non-milk beverages and 3 kg of food by a person with a body weight of 60 kg (typical adult) and a daily consumption of 1.5 litres of non-milk beverages and 750 grams of food by a child with a body weight of 15 kg (typical 3-year old child) (FAO/WHO, 2009). The Panel confirmed the conservativeness of these assumptions by means of comparing the data with food consumption summary statistics from the EFSA Comprehensive European Food Consumption Database.

As previously mentioned under points b) and c), the budget method makes assumptions with regard to the percentage of foods/beverages that are processed and the percentage of the latter containing a given food additive. A number of standard factors (typically 12.5%, 25% and 50%) have been applied in the assessment of additives, the choice of which is based on the type and importance of the food group(s) in which the additive is permitted, in relation to overall food/beverage intake. The assumptions underlying the budget method and their suitability to assess food additive intake have previously been examined (Douglas et al, 1997; ILSI, 1997), however, this has not been done in the case of food enzymes. Therefore, the appropriateness of using such standard factors in the exposure assessment to food enzymes requires further consideration, in particular since application of the budget method and associated factors can lead to a considerable overestimation of exposure (Douglas et al, 1997). In such cases a refinement of exposure as recommended in the EFSA report (EFSA, 2011) is deemed necessary.

As a consequence the CEF Panel agreed to adopt a tiered approach (as outlined in Annex A) for the assessment of exposure to food enzymes.

**Tier 1:** As a first initial screening step, the budget method will be used for all enzymes under evaluation without the use of above described standard factors. If the MoE derived from this exposure estimate is sufficiently high (s. Annex A), no further assessment is required.

For those cases where the calculated MoE according to Tier 1 is insufficient (s. below), the exposure assessment will be refined through one of two possible alternative evaluation steps (s. Annex A), as follows:

**Tier 2a:** For those cases where information on the occurrence of the enzyme in food/beverages as consumed is available and allows for a calculation of the exposure using specific food categories in the EFSA Comprehensive European Food Consumption Database, the latter will be used. The so derived exposure estimates will be based on individual food consumption reported for the European populations.

**Tier 2b:** For all other cases, the budget method will be used with factors specific to the respective enzyme. Such factors will be derived using all available information (e.g. the use of the enzyme during food processing, the proportion of processed food and the presence of the food enzyme therein).

The use levels provided by the applicants often are expressed as food enzyme on a per substrate basis (e.g. enzyme activity per amount of dry matter starch) or for a raw material (e.g. enzyme activity per amount of grain used in beer production). In both cases, the provided use level of the enzyme does not refer to the food/food ingredient as consumed. Therefore the amount of substrate or raw material in relation to the amount of food as consumed has to be taken into account in the exposure calculation independent of any tier applied in form of a conversion factor.

As each safety assessment is performed on a case-by-case basis requiring expert judgement of the entire toxicological database and information related to the intrinsic properties of specific food enzyme, no generally acceptable value can be established for MoE. As a first indication, a MoE of 300 (Factor 10 for inter-species difference, factor 10 for intra-species difference and factor 3 for the extrapolation from short-term studies to chronic studies, EFSA Scientific Committee, 2012) may be regarded as sufficient provided the data are complete and the quality of the data is acceptable.
References


Hansen SC, 1966, Acceptable daily intake of food additives and ceiling on levels of use. Food and Cosmetics Toxicology, 4, 427-432.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CEF</td>
<td>Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids</td>
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<td>EFSA</td>
<td>European Food Safety Authority</td>
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<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect level</td>
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<td>MoE</td>
<td>Margin of Exposure</td>
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Annex A – Flowchart of the tiered approach for the exposure assessment of food enzymes

**TIER 1**

- Budget method\(^1\)\(^2\) → MoE\(^3\) sufficient → No safety concern under proposed conditions of use and use levels
- MoE not sufficient\(^4\)

**TIER 2**

2a. EFSA Comprehensive Food Consumption Database\(^5\)

2b. Budget method with specific factors\(^6\)\(^7\)

- MoE sufficient\(^4\)
- No safety concern under proposed conditions of use and use levels
- MoE not sufficient\(^4\)
- Safety cannot be established at the proposed use and use levels

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1) In tier 1: without the factors mentioned in section 3b) and 3c).
2) In tier 1 and 2: including conversion factors as appropriate.
3) Specific factors see in Section 3.
4) A generally accepted value for the Margin of Exposure (MoE) cannot be established as each safety assessment is performed on a case-by-case basis requiring expert judgement of the entire toxicological database and information related to the intrinsic properties of a specific food enzyme, no generally acceptable value can be established for MoE. As a first indication, a MoE of 200 (factor 10 for inter-species difference, factor 10 for intra-species difference and factor 3 for the extrapolation from short-term studies to chronic studies, EFSA Scientific Committee, 2012) may be regarded as sufficient provided the data are complete and the quality of the data is acceptable.

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MoE – Margin of Exposure