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**SCIENTIFIC OPINION**

# Guidance on the data required for the risk assessment of flavourings to be used in or on foods

**EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids**

European Food Safety Authority (EFSA), Parma, Italy

This guidance was originally adopted by the Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) Panel on 20 May 2010; the present revision was endorsed by the Food Additives and Flavourings (FAF) Panel on 2 July 2020[1].

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The present guidance has been revised and it is republished with editorial changes: the chapter "Submission of an application" has been replaced by the "Administrative guidance on the preparation of applications on food improvement agents (food enzymes, food additives and food flavourings)" (EFSA, 2021) following the new provisions defined by Regulation (EC) 178/2002 ('GFL Regulation'), as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain, applicable as from 27 March 2021. The scientific content of this guidance related to the data required for the risk assessment of flavourings to be used in or on foods has been left unchanged and it is expected to be updated at a later stage. The current scientific guidance applies until further notice*.

[1] The current version of the document was endorsed by the EFSA FAF Panel (Panel on Food Additives and Flavourings) on 2 July 2020. FAF Panel members: Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Rainer Gürtler, Ursula Gundert-Remy, Trine Husøy, Melania Manco, Wim Mennes, Peter Moldeus, Sabina Passamonti, Romina Shah, Ine Waalkens-Berendsen, Detlef Woelfle, Matthew Wright, Maged Younes.

* This revised version of the guidance contains new text compared to the previous version. The new text has been inserted in boxes to be easily identifiable.

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## ABSTRACT

This Opinion follows a request from the European Commission for the data required for the risk assessment of flavourings.

The Panel considered that the elaboration of a proposal concerning the data required for the risk assessment of new flavouring substances should build upon the experience gained in the course of the evaluation of flavouring substances included in the Union list.

A general principle of this Opinion is that new flavouring substances that can be assigned to one of the existing Flavouring Group Evaluations (FGEs) on the basis of structural and metabolic similarities should be evaluated according to the scientific principles and to the group-based approach underlying the former evaluation programme.

In addition, the proposal provides a Procedure for the evaluation of flavouring substances which cannot be assigned to one of the existing FGEs. This should allow an individual evaluation of the new flavouring substance.

The proposal also covers flavourings other than flavouring substances for which an evaluation and an approval is required according to Article 9 (b) – (f) of the Regulation (EC) No 1334/2008.

In general, information on the following issues has to be provided: Identity of the source materials, manufacturing process, specifications, assessment of dietary exposure and toxicological data. Requirements covering aspects specific for the risk assessment of the different flavouring categories have been compiled.



## KEY WORDS

Flavourings, Guidelines, risk assessment, dietary exposure.

## SUMMARY

Following a request from the Commission, the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids was asked to provide scientific advice regarding the data required for the evaluation of flavourings.

Part A of these Guidelines provides a proposal concerning the data required for the risk assessment of flavouring substances, i.e. chemically defined substances with flavouring properties.

Part B of these Guidelines provides a proposal concerning the data required for the risk assessment of categories of flavourings other than flavouring substances for which an evaluation and an approval is required according to Article 9 (b) – (f) of the Regulation (EC) No 1334/2008 of the European Parliament and of the Council on flavourings and certain food ingredients with flavourings properties for use in and on foods.


This guidance was originally adopted by the Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) Panel on 20 May 2010; the revised version was endorsed by the Food Additives and Flavourings (FAF) Panel on 2 July 2020.

## TABLE OF CONTENTS

## BACKGROUND AS PROVIDED BY THE COMMISSION in 2009

On 16 December 2008 the following Regulations of the European Parliament and of the Council were adopted:

Regulation (EC) No 1332/2008 on food enzymes[2],

Regulation (EC) No 1333/2008 on food additives[3],

Regulation (EC) No 1334/2008 on flavourings and certain food ingredients with flavouring properties[4] and

Regulation (EC) No 1331/2008 on a common authorisation procedure for food additives, food enzymes and food flavourings[5].

The Regulations entered into force on 20 January 2009.

Regulation (EC) No 1334/2008 on flavourings and certain food ingredients with flavouring properties applies to flavourings which are used or intended to be used in or on foods, food ingredients with flavourings properties, food containing flavourings and/or food ingredients with flavouring properties and source materials for flavourings and/or source materials for food ingredients with flavouring properties.

The Regulation requires an evaluation by EFSA and an approval by the Commission for the following types of flavourings:

a) flavouring substances;

b) flavouring preparations obtained from material other than food;

c) thermal process flavourings where ingredients for the production of thermal process flavourings are from source material other than food or the production conditions set in Annex V of the Regulation are not met;

d) flavour precursors obtained from source material other than food;

e) other flavourings;

f) source materials other than food.

In order to ensure consistency amongst the new Regulations on food additives, food enzymes and food flavourings, the procedural aspects of approval of substances (such as handling of applications within well-defined deadlines, evaluation of substances by EFSA and decision making by the Commission), are provided in Regulation (EC) No 1331/2008 on the common authorisation procedure on food additives, food enzymes and food flavourings. This Regulation also provides that an implementing measure (Article 9) shall be adopted by the Commission, within 24 months from the adoption of the Regulation on flavourings, which shall concern in particular the content, drafting and presentation of the application for the evaluation and authorisation of flavourings. With a view to the adoption of this implementing measure the Commission consulted EFSA, which, within six months of the date of entry into force of the Regulation on flavourings, i.e. by 20 July 2009, shall present a proposal concerning the data required for risk assessment of flavourings.

[2] OJ L 354, 31.12.2008, p. 7
[3] OJ L 354, 31.12.2008, p. 16
[4] OJ L 354, 31.12.2008, p. 34
[5] OJ L 354, 31.12.2008, p. 1

## TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION in 2009

The European Food Safety Authority (EFSA) is asked to provide the Commission with a proposal concerning the data required for the risk assessment of flavourings with a view to including it in the implementing measure, which will lay down amongst other aspects, the content, drafting and presentation of the application for the evaluation and authorisation of flavourings.

## INTRODUCTION

According to the Regulation (EC) No 1334/2008 (European Commission, 2008), hereafter referred to as "the Regulation," The European Food Safety Authority (EFSA) is asked to provide the Commission with a proposal concerning the data required for the risk assessment of flavourings with a view to including it in the implementing measure, which will lay down amongst other aspects, the content, drafting and presentation of the application for the evaluation and authorisation of flavourings.

The Regulation shall apply to:

(a) flavourings which are used or intended to be used in or on foods, without prejudice to more specific provisions laid down in Regulation (EC) No 2065/2003;

(b) food ingredients with flavouring properties;

(c) food containing flavourings and/or food ingredients with flavouring properties;

(d) source materials for flavourings and/or source materials for food ingredients with flavouring properties.

The Guidance was submitted to a Public Consultation from 15 October to 14 December 2009 on Part A and Part B was discussed with Stakeholders in a Workshop 4 and 5 March 2010.

**Note:** The present guidance has been revised and it is republished with editorial changes: the chapter "Submission of an application" has been replaced by the "Administrative guidance on the preparation of applications on food improvement agents (food enzymes, food additives and food flavourings)" (EFSA, 2021) following the new provisions defined by Regulation (EC) 178/2002 ('GFL Regulation'), as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain, applicable as from 27 March 2021. The scientific content of this guidance related to the data required for the risk assessment of flavourings to be used in or on foods has been left unchanged and it is expected to be updated at a later stage. The current guidance document applies until further notice.

# PART A: FLAVOURING SUBSTANCES

## I. GENERAL PRINCIPLES OF THE SAFETY ASSESSMENT OF FLAVOURING SUBSTANCES INTENDED TO BE USED IN OR ON FOODS

### 1. Background

Regulation (EC) No 2232/96 of the European Parliament and the Council (European Commission, 1996) laid down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all others in the EU. In application of that Regulation, a Register of flavouring substances used in or on foods in the Member States was adopted by Commission Decision 1999/217/EC (European Commission, 1999), as last amended by Commission Decision 2009/163/EC (European Commission, 2009). Each flavouring substance was attributed a FLAVIS- number (FL-number) and all substances were divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common. These chemical groups are covered in Flavouring Group Evaluations (FGEs).

The substances listed in the Register have been evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (European Commission, 2000), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999). It is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 44$^{th}$, 46$^{th}$ and 49$^{th}$ meetings (JECFA, 1995; JECFA, 1996; JECFA, 1997; JECFA, 1999).

After the completion of the evaluation programme, but at the latest by 31 December 2010, the Union list of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96) (European Commission, 1996).

In the mandate for the current Opinion, the Commission suggests that the European Food Safety Authority (EFSA) takes into account the experience from this evaluation programme.

### 2. General approach

Flavouring substances in the Community Register have been evaluated in accordance with Commission Regulation (EC) No 1565/2000 (European Commission, 2000). This Regulation lays down a general approach for the evaluation.

The Panel considered that the elaboration of a proposal concerning the data required for the risk assessment of new flavouring substances should build upon the experience gained in the course of the evaluation of flavouring substances included in the Union list.

A general principle of this Opinion is that new flavouring substances that can be assigned to one of the existing Flavouring Group Evaluations (FGEs) (See the EFSA web-site) on the basis of structural and metabolic similarities should be evaluated according to the scientific principles and to the group- based approach underlying the former evaluation programme.

In addition, the proposal provides a Procedure for the evaluation of flavouring substances which cannot be assigned to one of the existing FGEs. This should allow an individual evaluation of the new flavouring substance.

The overall strategy for the risk assessment of flavouring substances is outlined in Figure 1.

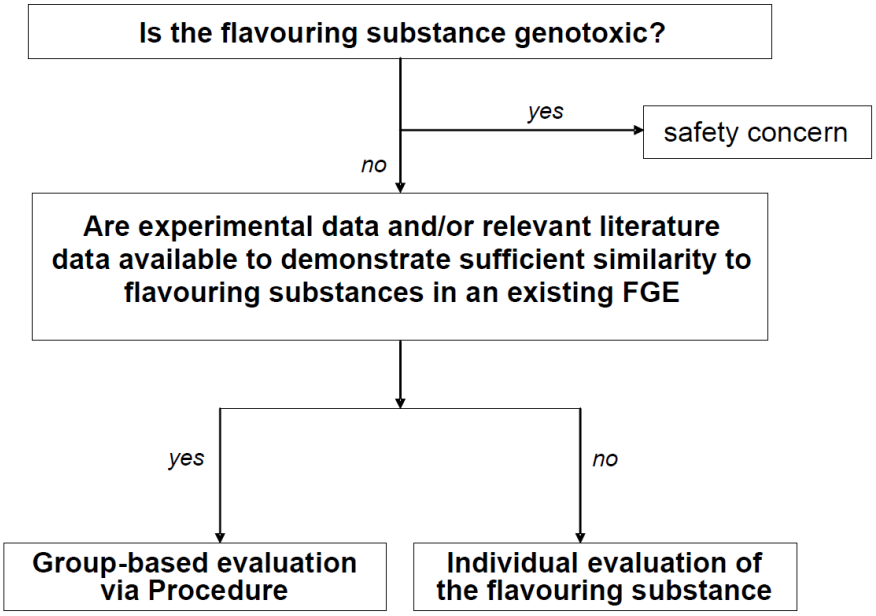


**FIGURE 1: OVERALL STRATEGY FOR THE RISK ASSESSMENT OF FLAVOURING SUBSTANCES.**

The Procedure applied for the group-based evaluation is shown and explained in Chapter V (see also Figure 2), the individual evaluation of a flavouring substance is outlined in Chapter VI (see also Figure 3).

# II. INFORMATION TO BE SUPPLIED WITH AN APPLICATION FOR THE AUTHORISATION OF FLAVOURING SUBSTANCES

## 1. Manufacturing process

### 1.1 Source material

The source material(s) used in the production of the flavouring substance must be described in sufficient detail to allow an adequate characterisation of the flavouring substance as well as an estimation of the likelihood of the presence of undesirable substances (e.g. contaminants).

#### 1.1.1 Genetically modified organisms

If a flavouring substance is produced by or from genetically modified organisms (GMOs), the respective legal requirements (Commission Regulation (EC) No 1829/2003) have to be fulfilled. Additionally, information should be provided according to the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Microorganisms and their derived Products Intended for Food and Feed Use" (EFSA, 2006a) and the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and derived Food and Feed" (EFSA, 2006b), respectively.

## 1.2 Production Process

The process employed to produce the flavouring substance (e.g. chemical synthesis, enzyme-catalysis, fermentation or isolation from a natural source) should be described. The information should specifically focus on the potential of the applied process to result in by-products, impurities or contaminants.

## 2. Specifications

The following information has to be provided for the flavouring substance:

- Chemical name (IUPAC name, synonyms).

- CAS-, E-, EINECS-, CoE-, JECFA-, FLAVIS- and FEMA numbers (if assigned).

- Chemical and structural formula, molecular weight.

- Physical form/odour.

- Solubility data.

- Identity tests (infra red-, nuclear magnetic resonance- and/or mass spectrum, gas chromatographic retention indices).

- Purity/Minimum assay value: Normally the purity should be at least 95 %; otherwise, information on the identities and the quantities of the by-products has to be provided.

- Impurities: The applicant shall identify and quantify chemical and microbial impurities, substances with toxic or other undesirable properties that are not intentionally added or do not contribute to the activity of the flavouring substance. Any substance produced via fermentation should be free of antimicrobial activities relevant to the use of antibiotics in humans. In addition, the absence of production organisms should be confirmed.

- Physical parameters related to purity: boiling point (for liquids), melting point (for solids), refractive index (for liquids), specific gravity (for liquids).

- Information on the configuration of the flavouring substance: It is recognised that geometrical and optical isomers of substances may have different properties. Their organoleptic properties may be different, and they may have different chemical properties resulting in differences in their absorption, distribution, metabolism, elimination and toxicity. Thus, information must be provided on the configuration of the flavouring substance, i.e. whether it is one of the geometrical/optical isomers, or a defined mixture of stereoisomers. The available specifications of purity will be considered in order to determine whether the safety evaluation carried out for candidate substances for which stereoisomers may exist can be applied to the material of commerce. Flavouring substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number, etc.).

- Stability and decomposition products, if relevant.

- Interaction with food components, if relevant.

- Any other relevant information.

The specifications provided should be sufficient to demonstrate that the flavouring substance tested toxicologically is representative for the material of commerce.

# 3. Data on dietary and non-dietary sources

## 3.1 Occurrence levels in food (as added flavouring substances and from other sources)

In order to assess total dietary exposure to the flavouring substance from all sources, for each of the categories reported in Table 1, the applicant needs to provide:

- Normal and maximum occurrence levels as added flavouring substance (first two empty columns of Table 1).
  For each specific food/beverage category, "normal occurrence level", expressed in mg/kg of product, is intended as the median of anticipated concentration values of added flavouring substance for products belonging to the category. On the other hand, "maximum use level", expressed in mg/kg of product, is intended as the concentration of added flavouring substance that, according to the applicant, will not be exceeded in any product belonging to the category.

- Normal and maximum occurrence levels of the substance from other sources: as natural constituent, as substance developed during the processing of foods (such as Maillard products or products resulting from hydrolysis or oxidation reactions), as carry-over originating from their use in animal feed or as residues of packaging (medium two columns of Table 1). The applicant will illustrate in an accompanying text the different dietary sources of the substance.
  In order to assign normal occurrence levels to each category, only foods and beverages in which the substance has been identified will be considered. The normal occurrence level is aimed at providing an indication of central tendency, based on occurrence levels available in the literature. Thus, the median of all occurrence levels determined in all kinds of fruit where the flavouring substance is known to occur will be assigned to the category "Fresh fruit" 04.1.1. If only a range of values is available, the mid of the range will be selected as "normal occurrence level".

- Normal and maximum combined occurrence levels of the substance, taking into account all sources; as added flavourings and from other sources (last two columns of Table 1).

Most categories reported in Table 1 correspond to the sub-categories of the Codex GSFA (General Standard for Food Additives available at http://www.codexalimentarius.net/gsfaonline/CXS_192e.pdf that were used by the JECFA in the "Single Portion Exposure Technique" (SPET) technique (FAO/WHO, 2008). No use levels are requested for the category infant formulae and follow-on formulae since, based on the Commission Directive 2006/141/EC of 22 December 2006, flavouring substances are not expected to be added to these products[6]. For the category 13.2 (complementary foods for infants and young children), further refined categories have been added so that a specific assessment of dietary exposure can be performed for infants and small children.

When occurrence levels as added flavourings are not provided by the applicant for one or more sub-categories, it will be made clear that the output of the safety evaluation is related only to the use of the substance in those sub-categories for which use levels have been provided. In particular, if use levels are not provided for category 13.2, it will be made clear that the safety of the substance in products specifically designed for infants and young children has not been evaluated.

In case of foods marketed as powder or as concentrates, occurrence levels must be reported for the reconstituted product, considering the instructions reported on the product label or one of the standard dilution factors established by the JECFA (FAO/WHO 2008).

[6] If the addition of flavouring substances to these formulae should be considered, a specific assessment of dietary exposure should be performed in infants fed with these products.

Occurrence levels as added flavouring substance (first two columns of Table 1) must be provided at the same level of detail as in the International Organization of the Flavour Industry (IOFI) provision of use levels to the Joint FAO/WHO Expert Committee on Food Additives (IOFI, 2008). Obviously, for new substances that are not yet in use in the EU no industry survey can be performed in the EU. In this case, refined use levels will need to be provided from industry surveys performed in other areas of the world. For new flavouring substances that would not have been used in other areas of the world, "recommended" use levels will be provided by the applicant for the main GSFA food categories listed in Table 2, based on internal application trials on samples/products representative for the various food categories. The conclusion of the safety evaluation may then be revised in the future to take into account modifications in terms of use levels and/or in terms of categories in which the substance is intended to be used.

Occurrence levels from other sources (as natural constituent and/or as substance developed during the normal processing of foods) will be retrieved by the applicant from all available databases. In particular, all quantitative data present in databases listed in Appendix 1 need to be considered.

A flavouring substance can be concomitantly present in a product as an added flavouring and from other sources (thus a substance may be present in a fruit-based beverage both as added flavouring substance and as a natural constituent of the fruit ingredient). The last two columns of Table 1 ("Combined occurrence level from all sources") can be filled by the applicant by adding up the columns "Occurrence level as added flavouring substance" and "Occurrence level from other sources". Alternatively, these columns can be filled based on an expert judgment of the likelihood of the concomitant presence of the substance from the two sources. This will be done both for normal use levels and for maximum use levels.

### 3.2 Non-food sources of exposure

The applicant needs to indicate the non-food uses of the flavouring substance. Available information on annual volumes of production in the EU for non-food uses (e.g. in cosmetics, medicines and detergents), the content of the substance in these products and its absorption rates via skin and/or inhalation should be provided by the applicant to identify non-food sources of exposure.

The Panel is aware that for many flavouring substances, quantitative data on their occurrence in non-food sources may be limited. Any available information on potential non-food sources, i.e. the exposure via dermal or inhalational routes, should be provided.

## 4. Assessment of dietary exposure

In the evaluation of flavouring substances to be included in the Union list, the dietary exposure considered by EFSA within the Procedure to assess their safety has been a per capita estimate, the "Maximised Survey-Derived Daily Intake" (MSDI), based on the annual volume of production reported by the applicant. In addition, the "modified Theoretical Added Maximum Daily Intake" (mTAMDI) was calculated, based on the normal added use levels of the substances as reported by the applicant in the 18 food categories of Annex III of Commission Regulation (EC) No 1565/2000 (European Commission, 2000). The mTAMDI value was not considered in the Procedure but was only used as a tool to screen and prioritise the flavouring substances according to the need for refined intake data (EFSA, 2004). Both the MSDI and the mTAMDI approach take into consideration the dietary exposure of a 60 kg adult. For flavouring substances that are also naturally present in foods or beverages, qualitative and quantitative information related to natural occurrence was reported by the applicant but was not considered for the assessment of dietary exposure.

The limitations of the MSDI approach have been frequently reiterated by the Scientific Committee for Food (SCF), the former Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) of the EFSA and the JECFA.

In particular, the use of the MSDI value calculated on the basis of anticipated volumes of production (for flavouring substances that were not yet on the market at the time of the safety evaluation) is not currently accepted by the JECFA as a basis for safety evaluation (FAO/WHO, 2008).

A complementary method was developed by the JECFA (FAO/WHO, 2008) to assess dietary exposure to flavouring substances: the SPET (Single Portion Exposure Technique). The SPET is calculated by combining, in each food category, average (or usual) added use levels for a flavouring substance with standard portion sizes of flavourable foods. For flavouring substances with usages in multiple food categories (most cases), only the food category resulting in the highest potential dietary exposure is considered. This dietary exposure is taken to represent that of a 60 kg adult, regular consumer of a flavoured food, who is loyal to a specific product containing the specific flavouring of interest.

The Panel considered the need for a better harmonization of the present Guidelines in line with existing exposure assessment procedures. The Panel noted that different procedures are used in the assessment of exposure to the different classes of chemical substances in the remit of EFSA (e.g. contaminants, food additives, packaging residues, etc.). These differences are due to the different assumptions made to compensate for the lack of food consumption and occurrence data in relation to the specific requirements of the class of substances under evaluation. The development of exposure assessment procedures harmonized across the different classes of substances is a long-term objective supported by the Panel. However, this objective can only be achieved when refined and accurate food consumption and occurrence information will be available at European level.

Therefore, the Panel developed a new approach for dietary exposure assessment for new flavourings which is in line with the methods that have been used until now for flavourings but takes into account some of their limitations.

The following issues should be covered:

## 4.1 Chronic dietary exposure to flavouring substances from the consumption of flavoured foods and beverages in adults and children

Dietary exposure should be assessed in adults and children consuming foods and beverages containing the substance of interest. The highest of these values among adults and children, expressed per kg body weight (bw), should be used as the basis for the safety evaluation of the substance.

Poundage data are not considered to be useful for the quantitative assessment of dietary exposure to new flavourings. Surveyed poundage data of new flavourings used in foods and beverages could be provided only for non-EU regions (e.g. in the case of flavouring substances currently used in the United States) and these data may not be relevant for the EU situation. On the other hand, "anticipated annual production volumes" in the EU cannot be used since they bear a very high uncertainty.

The new method used to estimate the dietary exposure for adults and children is an adaptation of the TAMDI method called the "Added Portions Exposure Technique" (APET). This new method makes use of the standard portions established for each food category when the JECFA developed the SPET. More variability in potential dietary exposure can be captured with this technique than with the TAMDI. Thus, the dietary exposure estimated with the APET will be lower when a flavouring substance is intended to be used in food categories consumed in smaller portions. On the other hand, the APET is more conservative than the SPET since it retains the assumption, used under the TAMDI, that the consumer will daily consume a fixed amount of both flavoured solid foods and flavoured beverages. No data are currently available showing that such an assumption is unrealistic. In a conservative prospective for the consumer safety and to be in line with other existing conservative exposure assessment procedures used for the different classes of chemical substances in the remit of EFSA, this assumption was confirmed.

The APET is calculated based on the occurrence levels provided by the applicant in each of the food sub-categories reported in Table 1, with the exclusion of categories 13.2 (complementary foods for infants and young children):

1) on the basis of normal occurrence level from added flavourings. The data obtained will be an estimate of dietary exposure deriving solely from the addition of flavouring substances to foods and beverages;

2) on the basis of normal occurrence level from other dietary sources. The data obtained will be an estimate of dietary exposure deriving from all dietary sources, excluding flavourings added to foods and beverages;

3) on the basis of normal combined occurrence levels. The data obtained will be an estimate of total dietary exposure deriving from both the addition of flavouring substances to foods and beverages and other dietary sources.

Sub-categories are classified in two groups: "Beverages", including all sub-categories of the category 14.0 ("Beverages, excluding dairy products") and "Solid foods", including all others sub-categories. For both, "Beverages" and "Solid foods", only the food sub-category resulting in the highest potential dietary exposure is considered. This latest procedure is the same as that used by the SPET method. For both "Beverages" and "Solid foods", the dietary exposure is taken to represent that of a regular consumer of one flavoured product among the group. This consumer would be loyal to a product containing the specific flavour of interest at the normal combined occurrence level.

The APET is calculated by summing the highest potential dietary exposure within each of the two groups ("Beverages" and "Solid foods"). Such an estimate, based on daily consumption of one single standard portion of beverage and one single standard portion of solid food, is likely to provide a conservative assessment of long-term average dietary exposure for consumers of flavoured products. The APET is expressed in mg/kg bw per day. For an adult a body weight of 60 kg is considered, and the portions are those established by the JECFA (FAO/WHO, 2008) when developing the SPET technique.

A child of 3 years of age will be considered in order to provide a conservative scenario for all children aged more than 3, since the consumption of foods and beverages per kg bw decreases with age. In the 3-year old child, a 15 kg bw is considered. Moreover, the sub-categories 14.2.1, 14.2.2, 14.2.3 and 14.2.4 ("Alcoholic beverages") and the sub-category 13.4 ("Dietetic formulae for slimming purposes and weight reduction") are excluded a priori since it can be assumed that these products are not consumed by children. Ad hoc standard portions are used for each of the other sub-categories. These are derived from the adult standard portions. A correction factor was calculated to take into account their lower consumption of foods and beverages, based on their lower energy requirement. On average, a 3-year old child weighing 15 kg requires 6 MJ of energy whereas on average a sedentary adult requires 9.5 MJ (mean of 10.7 MJ in males and 8.3 MJ in females aged 30-59 years) (Commission for the European Communities, 1993). Standard portion sizes for children are therefore obtained by multiplying the adult standard portion sizes by a factor of 0.63 (6/9.5). The value of 15 kg bw is then used to assess exposure in mg/kg bw in a 3-year old child.

The APET in the adult could be higher than the APET in the child only in few cases: if the highest dietary exposure from one portion of beverages is found in the sub-categories 14.2 or if the highest dietary exposure from one portion of solid food is found in the sub-category 13.4.

## 4.2 Dietary exposure to flavouring substances that may be used in foods specifically designed for infants and young children

The age class to which "infants" (0-12 months) and "young children" (12-36 months) refer are defined in the Commission Directive 2006/125/EC on processed cereal-based foods and baby foods for infants and young children (European Commission, 2006). Flavouring substances may be used in products specifically designed for these consumer subgroups. The potential dietary exposure to flavourings per kg bw is likely to be higher than that of adults in these two age classes. Dietary exposure will be assessed taking into consideration only the consumption of foods specifically designed for these two subgroups.

The diets of infants and young children tend to be less varied than those of older children and adults; an ad hoc method is therefore needed for estimating the exposure in this age group.

A specific exposure assessment will be performed based on the model diet of a 12-month young child fed milk and a variety of processed baby foods flavoured with the substance of interest.

Due to the high brand loyalty in young children the maximum combined occurrence levels will be considered in this exposure assessment.

Details on how dietary exposure will be assessed in the 12-month young child are reported in Appendix 2.

## 4.3 Acute dietary exposure

Data on acute toxicity and acute dietary exposure will not be needed on a regular basis.

However, if the estimated level of dietary exposure may raise any concern about acute adverse effects of a flavouring substance, the Panel may need to consider safety aspects in terms of acute exposure, as exemplified by camphor (EFSA, 2008). Then, the assessment must be based on maximum concentration of flavouring substances in foods and beverages and on an estimate of the largest quantities (high percentiles) of foods or beverages that can be consumed by a subject within one day. These bolus doses will be compared to those resulting in acute adverse effects.

The General Standard for Food Additives (GSFA) category leading to the highest potential dietary exposure in one day will be identified and this value will be used as an estimate of acute dietary exposure. To this aim, the maximum occurrence levels from all sources, as reported in Table 1, will be used.

"Large portions", representing the 97.5$^{th}$ percentile of consumption observed on a single day in national surveys, are reported in the Global Environment Monitoring System (GEMS) diet to assess acute dietary exposure to pesticides in adults and children (WHO, 2008) but are referred to agricultural commodities and not directly applicable. Large portions per kg bw were developed in the EFSA Opinion on camphor (EFSA, 2008) for a limited number of foods and beverages, based on the large single day amounts of commodities (observed 97.5$^{th}$ percentile in one day among eaters only) in the INCA French individual consumption survey (Volatier et al., 2006). The observed levels of consumption correspond, in a 60 kg bw adult to the consumption within one day of 840 g of soft drink, 96 g of candies, 144 g of cheese or 72 g of sauces. These values are about three times as high as the standard portions used in the APET for the corresponding categories (respectively 300 g, 30 g, 40 g and 30 g). Based on this observation, the acute dietary exposure will be assessed considering as large portions three standard portions, for either a solid food or a beverage listed in Table 1.

The same will be done for 3-year old children with the use of their specific portions for all relevant foods and beverages categories. The highest value obtained among adults and children will be used in the safety evaluation as an estimate of potential acute dietary exposure.

Therefore, in both adults and 3-year-old children, the acute exposure is represented by the consumption of three portions of either a solid food or a beverage, containing the flavouring substance at its maximum occurrence levels.

These estimates of large portions may be refined by EFSA in the future on the basis of the databases of food consumption in EU countries that will be made available to the Data Collection and Exposure (DATEX) unit of EFSA.

No specific assessment of acute dietary exposure is required for young children since the model diet used to assess dietary exposure in this age class already takes into account maximum occurrence levels and a high level of consumption of flavoured foods specifically designed for them. Due to the low day to day variability in consumption patterns in young children, the model used to assess chronic dietary exposure is also adequate to assess acute dietary exposure.

## 4.4 Cumulative dietary exposure

Cumulative dietary exposure to flavouring substances structurally and metabolically related to the substance under study is assessed in order to ensure that the concomitant dietary exposure to all flavouring substances belonging to the same group does not exceed the capacity of the organism to metabolise them. To this aim, an assessment of cumulative dietary exposure within one day is needed. Until now it was assessed by adding up MSDIs (the so called "combined intake"). A technique based on occurrence levels in foods is needed for new flavourings. In order to assess potential cumulative dietary exposure within one day the applicant shall provide occurrence levels not only for the new substance but also for structurally and metabolically related substances which have already been evaluated in an FGE.

Potential cumulative dietary exposure within one day to flavouring substances structurally and metabolically related to the new substance will be assessed.

The applicant shall identify all flavouring substances structurally and metabolically related to the new substance and shall retrieve the most recent EU poundage data (total annual volumes of production at EU level) for these substances. Substances will be ordered according to their poundage data. The five substances with the highest poundage data will be identified ("high poundage substances"). The applicant shall retrieve normal occurrence levels for these substances used as added flavouring substances and use them to calculate the APET in adults, as described above. The APET of the 5 "high poundage substances" will be added up and used as an estimate of potential cumulative dietary exposure within one day, expressed in mg/kg bw per day, in adults.

The APET of the "high poundage substances" and of the new substance will be added up and used as an estimate of potential cumulative dietary exposure within one day, expressed in mg/kg bw per day, in adults and children, respectively.

For young children, the potential cumulative dietary exposure within one day will be calculated by adding up the dietary exposure to the "high poundage substances" (assessed with the techniques described in Appendix 2) to that of the newly submitted substance and expressed in mg/kg bw per day.

The EFSA Scientific Committee, in its Opinion on exposure assessment (EFSA, 2005), recommended that all sources of exposure should be taken into account, including non-food sources of exposure.

Any information on potential non-food sources, i.e. the exposure via dermal or inhalational routes should therefore be considered on the basis of data as described in Section 3.2. The Panel is aware that at present for most flavouring substances quantitative data on their occurrence in non-food sources are rather limited. Nevertheless, the applicant should provide all available information on the exposure to the flavouring substance from consumer products allowing the estimation of the overall exposure and an evaluation of potential health risks arising from the addition of the flavouring substance to food.

# III. ASSESSMENT OF THE GENOTOXIC POTENTIAL OF THE FLAVOURING SUBSTANCE

For any new flavouring substance its genotoxic potential has to be assessed in the first step of the evaluation. This assessment should start with *in vitro* tests, covering all three genetic endpoints, i.e. gene mutations, structural and numerical chromosomal aberrations. The following three *in vitro* tests would normally be required[7]:

- a test for induction of gene mutations in bacteria (Ames test; OECD Guideline 471);
- a test for induction of gene mutations in mammalian cells (preferably the mouse lymphoma *tk* assay with colony sizing; OECD Guideline 476);
- an *in vitro* chromosomal aberration test (OECD Guideline 473) or an *in vitro* micronucleus assay (Draft OECD Guideline 487).

There may be circumstances under which it may be justified to deviate from the above-mentioned core set. In such cases a scientific justification should be provided, and additional types of considerations or mechanistic studies may be needed. In some cases, genotoxicity testing may be even deemed unnecessary, e.g. for substances which are strictly related and share the same metabolic fate as previously evaluated flavouring substances which do not raise concern for genotoxicity.

One or more positive *in vitro* tests normally require follow-up by *in vivo* testing, unless it can be adequately demonstrated that the positive *in vitro* findings are not relevant for the *in vivo* situation. This is in line with the general strategy elaborated in the updated WHO/IPCS Harmonised Scheme on mutagenicity testing (Eastmond et al., 2009). In rare cases there may be scientific grounds (e.g. insufficient metabolic activation *in vitro* or structural similarity with known mutagens/carcinogens) for requiring *in vivo* testing even in case of negative results *in vitro*.

The choice of the appropriate *in vivo* test is critical, due to different sensitivities, different endpoints and other variables. It requires expert judgement based on all available information, to be applied case-by-case. For this reason, a flexible approach is preferable to a fixed decision tree.

Guidance for the follow-up on positive results from *in vitro* assays could be taken from a guidance document issued recently by the European Chemicals Agency (ECHA, 2008), which recommends that any of the following tests may be conducted:

- a rodent bone marrow or mouse peripheral blood micronucleus test (OECD Guideline 474) or a rodent bone marrow clastogenicity study (OECD Guideline 475);
- a Comet (single cell gel electrophoresis) assay;
- a test for gene mutations in a transgenic rodent model, *e.g.* using *lacI*, *lacZ* or *cII* as reporter gene;
- a rat liver Unscheduled DNA synthesis (UDS) test.

According to this ECHA guidance (ECHA 2008), "the nature of the original *in vitro* response(s) (i.e. gene mutation, structural or numerical chromosome aberration) should be considered when selecting the *in vivo* study. For example, if the test substance showed evidence of *in vitro* clastogenicity, then it would be most appropriate to follow this up with either a micronucleus test or chromosomal aberration test or a Comet assay.

[7] The composition of the test battery may be revised following the outcome of ongoing discussion on genotoxicity test strategies in the EFSA Scientific Committee.

However, if a positive result were obtained in the *in vitro* micronucleus test, the rodent micronucleus test would be appropriate to best address clastogenic and aneugenic potential. The rat liver UDS test may be appropriate for substances that appear preferentially to induce gene mutations, although the Comet and transgenic tests are also suitable (Kirkland and Speit, 2008). These latter test systems offer greater flexibility, most notably the possibility of selecting a range of tissues for study on the basis of what is known of the toxicokinetics and toxicodynamics of the substance. It should be realised that the UDS and Comet tests are indicator assays detecting putative DNA lesions. In contrast, the transgenic test measures permanent mutations."

A combination of the *in vivo* micronucleus assay and the Comet assay in a single study as suggested by Pfuhler et al. (2007) would also be acceptable.

Other studies (e.g. DNA adduct studies) could also be relevant in order to clarify the mechanism of genotoxicity.

It should also be taken into account that the sensitivity (ability to detect carcinogens as positive) and specificity (ability to give negative results with non-carcinogens) of such assays have recently been analysed by Kirkland and Speit (2008).

Studies should be conducted using internationally agreed protocols. Test methods described by OECD or in European Commission Directives are recommended. The most up-to-date edition of any test Guidelines should be followed. Studies should be carried out according to the principles of Good Laboratory Practice (GLP) described in Council Directives 87/18/EEC and 88/320/EEC and accompanied by a statement of GLP compliance. Use of any methods differing from internationally agreed protocols should be justified. An OECD Guideline is not yet available for the Comet assay. However, recommendations for an appropriate performance of the assay using OECD Guidelines for other *in vivo* tests have been published and a standard protocol and acceptance criteria for this assay have been developed through the International Workshop on Genotoxicity Working Parties and international Comet assay workshops (Tice et al., 2000; Hartman et al., 2003; Burlinson et al., 2007). Additional information could be taken from a website on the Comet assay (http://cometassay.com).

## IV. EXAMINATION FOR STRUCTURAL/METABOLIC SIMILARITY TO FLAVOURING SUBSTANCES IN AN EXISTING FGE

The applicant should provide a proposal for the assignment of the new flavouring substance to an existing FGE (see EFSA website). This proposal has to be substantiated by appropriate experimental data or relevant evidence from the literature in order to demonstrate the structural/metabolic similarity to the substances in this FGE. The Panel will decide on these proposals on a case-by-case basis.

## V. GROUP-BASED EVALUATION VIA THE PROCEDURE

If sufficient structural/metabolic similarity of the flavouring substance to flavouring substances in an existing FGE has been demonstrated, a group-based evaluation using the Procedure can be performed. The Procedure, referred to as the approach for a safety evaluation of chemically defined flavouring substances in Commission Regulation (EC) No 1565/2000 (European Commission, 2000), is shown in Figure 2 and explained in the following text.

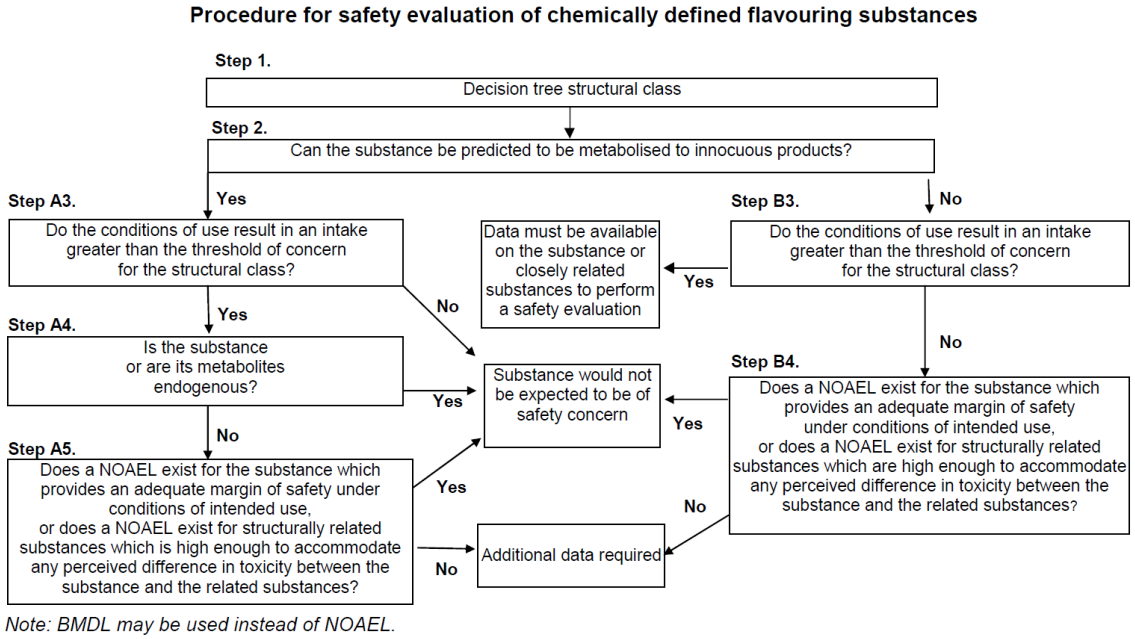


**FIGURE 2: PROCEDURE FOR THE SAFETY EVALUATION OF CHEMICALLY DEFINED FLAVOURING SUBSTANCES.**

The Procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II, III) for which thresholds of concern (human exposure thresholds), that are not considered to present a safety concern, have been specified. Class I contains flavouring substances that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavouring substances that have structural features that are less innocuous but are not suggestive of toxicity. Class III comprises flavouring substances that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1800, 540 or 90 microgram/person/day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996).

In addition to the data provided for the flavouring substance to be evaluated (candidate substance), toxicological background information available for compounds structurally related to the candidate substance is considered (supporting substances).

The Panel is of the opinion that the principles of the above-described Procedure should be applied to the evaluation of new flavouring substances if the substance can be assigned to one of the existing FGEs on the basis of structural and metabolic similarities.

Based on the experience gained from the evaluation of flavouring substances to be included into the Union list, particular attention should be paid to the following issues when applying the Procedure:

### *Step 2 of the Procedure*

At Step 2 of the Procedure, the question "Can the substance be predicted to be metabolised to innocuous products?" has to be answered.

"Innocuous products" are defined as metabolites that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring substance. The application of this definition requires that quantitative aspects related to the anticipated chronic exposure should be taken into account at this step of the Procedure (see Section 4.1). The assessment of the metabolites has to be substantiated by appropriate experimental data or relevant evidence from the literature.

### *Step A4 of the Procedure*

At step A4 of the Procedure, the question "Is the substance or are its metabolites endogenous?" has to be answered.

"Endogenous" substances are intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included.

The dietary exposure to flavouring substances that are, or are metabolised to, endogenous substances should be sufficiently low not to be expected to give rise to perturbations outside the physiological range.

### *Required toxicological data (Steps A5 and B4)*

At step A5 and B4 of the Procedure, the question "Does a No Observed Adverse Effect Level (NOAEL) or a Benchmark Dose Lower Confidence Limit (BMDL) exist for the substance which provides an adequate margin of safety under conditions of intended use, or does a NOAEL or BMDL value exist for structurally related substances which are high enough to accommodate any perceived difference in toxicity between the substance and the related substances?" has to be answered.

Regarding the first part of this question, generally, the minimum toxicological data required to establish a NOAEL or BMDL to be used at these steps of the Procedure should be based on a repeated-dose oral (usually dietary) study in rodents of at least 90 days duration on the candidate substance or on an appropriate structurally and metabolically related substance in accordance with the most recent OECD Guidelines.

The second part of the question envisages the situation where there is a NOAEL or BMDL value and a dietary exposure estimate, and the margin of safety under the conditions of intended use, resulting from these two parameters, is inadequate. Under these circumstances the default position would be that there is a safety concern.

If the outcome at step B4/A5 of the Procedure is "Additional data required", more information is needed, e.g. from further studies on toxicity. For substances evaluated via the B-side, such toxicity studies may not be necessary if adequate (new) biotransformation studies demonstrate that the substance is metabolised to innocuous products and that therefore, in a reconsideration of all data, the substance can be evaluated via the A-side of the Procedure.

If multiple structurally/metabolically related flavouring substances refer to a NOAEL or BMDL value from the same chemical at step A5 or B4, these structurally/metabolically related flavouring substances should be identified, and the applicant shall retrieve for all of them the most recent EU poundage data. The "high poundage substances" (See Section 4.4) will be selected and the applicant shall retrieve their normal use levels as added flavourings so as to calculate their APET. The APET of the high poundage substances will be added up for comparison with the NOAEL or BMDL value.

***Intake data (Steps A3/B3 and A5/B4)***

When applying the decision tree to the safety evaluation of a chemically defined flavouring substance used as a food improvement agent, the assessment of the "intake" as referred to at steps A3/B3 and of the "intended use" as referred to at steps A5/B4 should be based on the exposure resulting from the proposed addition of the flavouring substance to foods (See Chapter II). The conclusion drawn in this first part of the safety evaluation has to clearly reflect the underlying approach by stating, for example: "*The proposed use is not expected to be of safety concern at the estimated level of dietary exposure arising from its addition as a flavouring substance to foods*".

## VI. INDIVIDUAL EVALUATION OF A FLAVOURING SUBSTANCE

If a new flavouring substance cannot be assigned to one of the existing FGEs on the basis of structural and metabolic similarities, an individual evaluation has to be performed, given no safety concern with respect to genotoxicity (See Figure 1). A scheme outlining the principles of this evaluation is shown in Figure 3.

The type of toxicological data required depends on:

(i) whether there are experimental data available for the substance to demonstrate that the metabolites can be considered as innocuous and

(ii) whether the chronic dietary exposure, based on added use levels, is below or above the threshold of concern of the structural class to which the flavouring substance belongs.

Experimental data on the flavouring substance as such or on closely structurally related substances can be used as a basis to provide evidence that the metabolites of the flavouring substance are to be considered as innocuous.

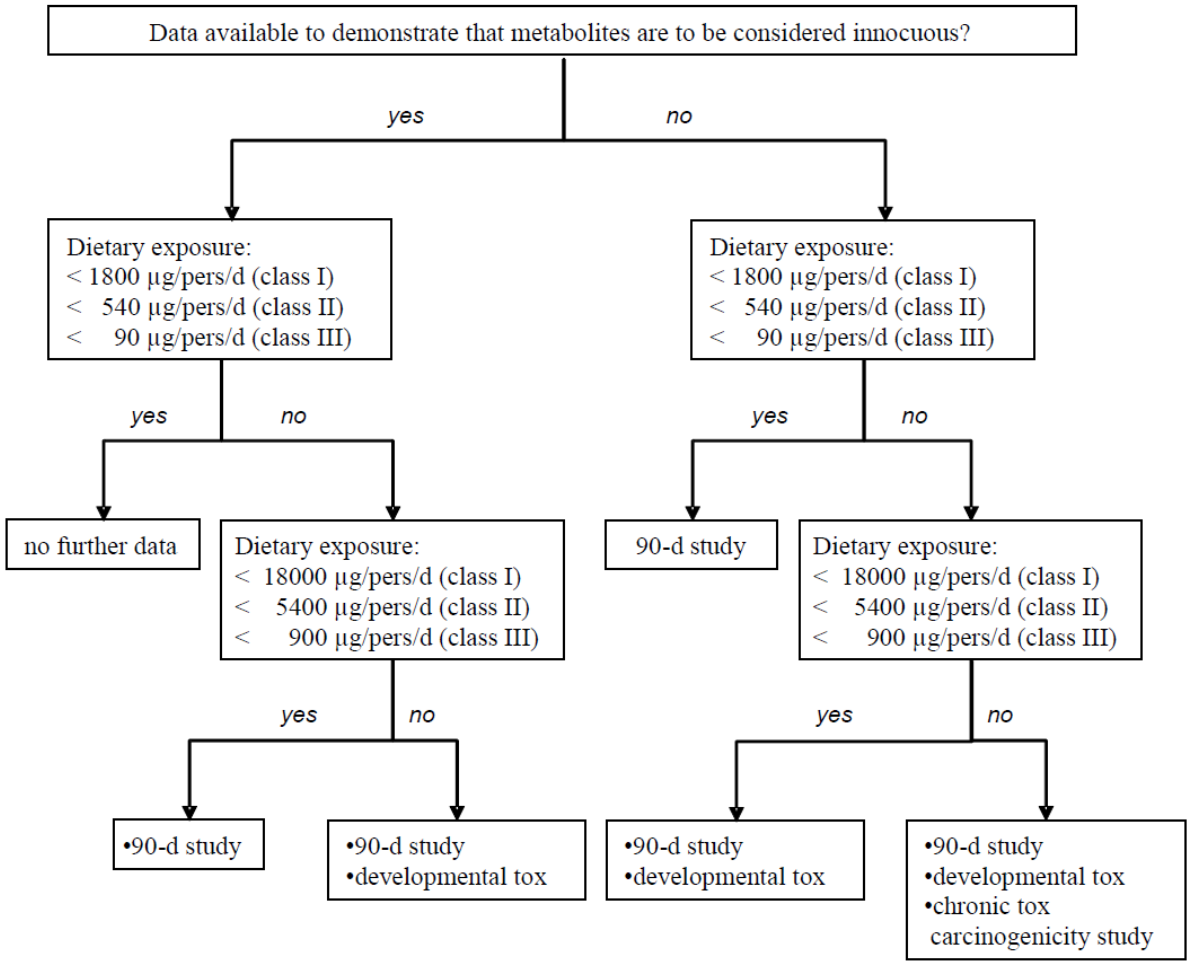


**FIGURE 3: INDIVIDUAL EVALUATION OF THE FLAVOURING SUBSTANCE.**

The experimental data for the various tests, as indicated in Figure 3, should be provided for the parent flavouring substance. Such data would implicitly cover the toxicity of the putative metabolites. When studies from the past are available, such studies can be taken into consideration, but their acceptability will depend upon their quality and the quality of the respective study report. New studies must be performed according to current OECD or EU Guidelines and must be in compliance with GLP.

As can be seen from Figure 3, the requirements for further toxicity data depend on the level of exposure in comparison with the respective Cramer class threshold. For exposures below the respective Cramer class threshold, no additional toxicity data (innocuous metabolites) or a 90-day toxicity study (metabolites not innocuous) are requested. The next higher exposure level requiring a more extensive data package was set by applying a default factor of 10 to the thresholds for the Cramer classes. These exposure levels approach those observed for food additives, and therefore it is not unreasonable to require toxicity data in line with the requirement for additives. For exposures up to 10-fold above the Cramer class threshold, a 90-day study or a 90-day study and a developmental toxicity study would suffice, depending on whether metabolites are considered innocuous or not. For higher exposures (i.e. more than 10-fold the respective class threshold) a more extensive data package will be required. For substances which will be converted to noxious metabolites the data requirements include also chronic toxicity and carcinogenicity data.

Detailed considerations underlying the toxicological requirements outlined in this Chapter as well as in Chapter V have been elaborated in the Annex to the guidance on submissions for food additive evaluations by the Scientific Committee on Food (SCF, 2001).

Other studies may also be helpful or necessary for certain flavouring substances. Decisions on whether other studies are needed should be taken on a case-by-case basis. Examples of other areas of investigation which might be appropriate include, but are not limited to immunotoxicity, allergenicity, intolerance reactions, neurotoxicity, human volunteer studies and predictive mechanistic studies.

There are also other toxicity studies that are not required for evaluation of the safety of flavouring substances, but which may have been conducted for other purposes, such as worker safety (e.g. acute toxicity, irritation and sensitisation studies). If such studies are available, they should be submitted as they may provide useful background information.

## VII. CONSIDERATION OF THE NATURAL OCCURRENCE OF A FLAVOURING SUBSTANCE AND THE TOTAL EXPOSURE FROM FOOD AND NON-FOOD SOURCES

Total dietary exposure to flavouring substances should be assessed based on the overall concentrations of flavouring substances in foods and beverages derived from all possible sources (either naturally present, added as flavouring substance or present as residue from other uses) and the value obtained should be considered in the safety evaluation. Moreover, other non-food sources of exposure to flavouring substances will have to be considered.

As an important part of the overall safety assessment, the estimated level of exposure arising from the proposed addition of the flavouring substance to food should therefore be put into the context of any other dietary source of exposure. On the basis of the data described in sections II.3.1 and II.3.2, total exposure to the substance should be estimated. The Panel is aware that at present for most flavouring substances quantitative data on their natural occurrence in foods and on their occurrence in non-food products are rather limited. In its evaluation, the Panel will take into account the amount of information made available and the level of uncertainty in the data. If the estimates of total exposure are high or if the estimates have a high level of uncertainty, the Panel may, on a case-by-case basis, request further information on total exposure or may ask for more toxicological data, in order to finalise the safety evaluation.

# PART B: FLAVOURINGS OTHER THAN FLAVOURING SUBSTANCES

In addition to flavouring substances, Article 9 of Regulation (EC) No 1334/2008 of the European Parliament specifies other categories of flavourings for which an evaluation and approval is required.

## I. INFORMATION TO BE SUPPLIED WITH AN APPLICATION FOR THE AUTHORISATION OF FLAVOURING PREPARATIONS

This chapter applies to "flavouring preparations" referred to in Article 3(2)(d)(ii) of Regulation (EC) No 1334/2008:

> *a product, other than a flavouring substance, obtained from material of vegetable, animal or microbiological origin, other than food, by appropriate physical, enzymatic or microbiological processes, the material being taken as such or prepared by one or more of the traditional food preparation processes listed in Annex II of the Regulation.*

The following information has to be supplied with an application for the authorisation of such a flavouring preparation:

### 1. Manufacturing process

### 1.1 Source material

The source material(s) used in the production of the flavouring preparation must be described in sufficient detail to allow an adequate characterisation of the principle components in the flavouring preparation as well as an estimation of the likelihood of the presence of undesirable substances (e.g. contaminants).

#### 1.1.1 Genetically modified organisms

If a flavouring preparation contains, consists of or is produced from genetically modified organisms (GMOs), the respective legal requirements (Commission Regulation (EC) No 1829/2003) have to be fulfilled. Additionally, information should be provided according to the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Microorganisms and their derived Products Intended for Food and Feed Use" (EFSA, 2006a) and the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and derived Food and Feed" (EFSA, 2006b), respectively.

### 1.2 Production Process

The process(es) employed in the production of the flavouring preparation should be described in sufficient detail to allow the evaluators to understand the key steps involved in the production of the flavouring preparation and to demonstrate its reproducibility. In addition, the description should also allow to estimate the likelihood of the presence of undesirable substances (e.g. contaminants) in the final flavouring preparation. This will help guiding the choice of the most appropriate analytical techniques employed for the assessment of the flavouring preparation.

## 2. Identity of the flavouring preparation

### 2.1 Trade name

### 2.2 Description of physical state

### 2.3 Chemical composition

The flavouring preparation should be chemically characterised as far as it is necessary to describe and define its identity, e.g. by gas chromatography (GC), liquid chromatography (LC), mass spectrometry (MS), IR-spectroscopy.

Information on the fraction of unidentified constituents should be provided. Any other information on chemical composition considered to be relevant for the evaluation should also be given.

Information should be provided on the batch-to-batch variability in all the measured parameters for chemical composition, as well as on the stability of the flavouring preparation during storage, including potential degradation products.

The sample(s) tested for chemical composition should be the same as or identical to the sample(s) tested toxicologically. This should be stated explicitly in the dossier. If the samples are not identical a justification should be provided. However, the sample(s) tested should at any rate be in accordance with the specifications.

## 3. Specifications

Specifications used to describe the flavouring preparation to be placed on the market should be provided.

## 4. Exposure to the flavouring preparation

### 4.1 Intended use of the flavouring preparation

Intended use and anticipated use levels of the flavouring preparation should be reported at the level of second tier categorisation of the GSFA (as for the APET method, described in Part A of these Guidelines).

### 4.2 Dietary exposure

As a first step, dietary exposure should be assessed as described in Part A of the present Guidelines.

Dietary exposure to individual components and/or to groups of components should be determined based on the intake of the preparation and the level of each component present in the preparation (determined by analytical characterisation). In this case total dietary exposure to individual components and/or to groups of components will also need to be assessed as in Part A.

Information on non-food sources of exposure to individual components and/or to groups of *components should also be provided as in Part A.*

## 5. Toxicological data

Since these preparations may be anticipated to consist of mixtures of chemicals, which may include considerable amounts of materials for which the chemical identity may be unknown, extensive toxicity data are needed.

As a default, information on genotoxicity and toxicity should be provided, as described below.

### 5.1 Genotoxicity

Information on the ability of the flavouring preparation to induce gene mutations as well as structural and numerical chromosomal aberrations should be provided according to the guidance given in Part A of these Guidelines.

### 5.2 Repeated-dose studies

#### 5.2.1 Subchronic toxicity

A 90-day feeding study in rodents, preferably in rats, should be submitted.

#### 5.2.2 Developmental toxicity

A developmental study in rodents should be submitted.

Deviations from the requirements in Section 5.1 and Section 5.2 are acceptable if adequate scientific justifications are provided. Such deviations may include different testing strategies and/or approaches.

Data on related flavouring preparations may be used in a weight of evidence approach in the safety assessment of the submitted preparation.

As clarified in Part A of these Guidelines, newly performed studies should be carried out according to current international Guidelines for toxicity testing (e.g. OECD Guidelines) and under GLP quality assurance.

### 5.3 Other studies

If available, other studies relevant for the safety evaluation of the flavouring preparations should be submitted.

The Panel may request further toxicity testing if a need for additional testing would arise from the submitted data.

# II. INFORMATION TO BE SUPPLIED WITH AN APPLICATION FOR THE AUTHORISATION OF FLAVOURING PRECURSORS

This chapter applies to "flavour precursors" referred to in Article 3(2)(g)(ii) of Regulation (EC) No 1334/2008:

> *a product, not necessarily having flavouring properties itself, intentionally added to food for the sole purpose of producing flavour by breaking down or reacting with other components during food processing; it is obtained from source material other than food.*

The following information has to be supplied with an application for the authorisation of such a flavour precursor:

## 1. Manufacturing process

### 1.1 Source material

The source material(s) used in the production must be described in sufficient detail to allow adequate characterisation of the flavour precursor as well as an estimation of the likelihood of the presence of undesirable substances (e.g. contaminants). This type of information may vary depending whether the flavour precursor is a chemically defined substance or a non-food complex matrix.

#### 1.1.1 Genetically modified organisms

If a flavour precursor contains, consists of or is produced from genetically modified organisms (GMOs), the respective legal requirements (Commission Regulation (EC) No 1829/2003) have to be fulfilled. Additionally, information should be provided according to the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Microorganisms and their derived Products Intended for Food and Feed Use" (EFSA, 2006a) and the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and derived Food and Feed" (EFSA, 2006b), respectively.

### 1.2 Production process

The process(es) employed in the production of the flavour precursors (e.g. syntheses or extractions) should be described in sufficient detail to allow the evaluators to understand the key steps involved in the production of the flavour precursor and to demonstrate its reproducibility. In addition, the description should also allow to estimate the likelihood of the presence of undesirable substances (e.g. contaminants) in the final flavour precursor. This will help guiding the choice of the most appropriate analytical techniques for the assessment of the flavour precursor.

## 2. Identity of the flavour precursor

### 2.1 Trade name

### 2.2 Description of physical state

### 2.3 Chemical composition

### 2.3.1 Information on the flavour precursor

The flavour precursor should be chemically characterised as far as necessary to describe and define its identity, e.g. by means of GC, LC, MS, IR.

If the flavour precursor is a chemically defined substance, data on its identity (e.g. CAS nr structure, common names) and data on minimum assay value and purity should be given.

If the flavour precursor is or is contained in a complex non-food matrix, data on proximate composition and analytical characterisations (e.g. GC, LC, MS) should be provided. The actual content of the flavour precursor in the non-food matrix should be reported. Information on the fraction of unidentified constituents should be provided.

Any other information on chemical composition relevant for the evaluation should also be given.

Information should be provided on the batch-to-batch variability in all the measured parameters for chemical composition, as well as on the stability of the flavouring precursor during storage, including potential degradation products.

### 2.3.2 Information on the components obtained by transformation of the flavour precursor

Data should be submitted showing the extent of transformation of the flavour precursor. In particular, the influence of transformation conditions under the intended applications (e.g. matrix, temperature, pH) should be described.

If the flavour precursor is a chemically defined substance, information on the identity of the transformation products should be provided (e.g. alcohols and aldehydes released from acetals).

If the flavour precursor is or is contained in a complex non-food matrix, the data available to characterise the transformation products are expected to vary; they may range from the identification of single compounds to a mere chromatographic profiling of major / minor transformation products.

The sample(s) tested for chemical composition (flavour precursor and/or transformation products) should be the same as or identical to the sample(s) tested toxicologically. This should be stated explicitly in the dossier. If the samples are not identical a justification should be provided. However, the sample(s) tested should at any rate be in accordance with the specifications.

## 3. Specifications

Specifications used to describe the flavour precursor to be placed on the market should be provided.

## 4. Exposure to flavour precursor and to transformation products

### 4.1 Intended use of the flavour precursor

Intended use and anticipated use levels of the flavour precursor should be reported at the level of second tier categorisation of the GSFA (as for the APET method described in Part A of the present Guidelines).

The exposure assessment should address the flavour precursors, the transformation products and, if the flavour precursor is (contained in) a non-food complex matrix also other non-flavouring components. If no precursors or components thereof are left to be present in the food product, assessment of exposure to the flavour precursor can be omitted.

## 4.2 Dietary exposure to flavour precursor and to transformation products

As a first step, dietary exposure should be assessed as described in Part A. Dietary exposure should be determined based on the intake of the flavour precursor and of the transformation products.

Information on non-food sources of exposure to individual components and/or to groups of components should also be provided as in Part A.

## 5. Toxicological data

The toxicological data submitted for the safety assessment of flavour precursors should address at least the following aspects: genotoxicity, repeated dose toxicity (prolonged exposure) and developmental toxicity. Several cases can be distinguished which will require different approaches (see Table below):

| **Type of flavour precursor** | **Extent of transformation** | |
|---|---|---|
| | **I:** *complete* | **II:** *incomplete* |
| **A:** *Chemically defined substance* | Assessment of reaction products | Assessment of reaction products + precursor |
| **B:** *Non-food complex matrix* | Assessment of reaction products | Assessment of reaction products + precursor |

**Case A-I:** If the flavour precursor is a chemically defined substance, which is shown to be completely transformed under the intended conditions of application into identified (chemically defined) products, the safety assessment of these transformation products can be carried out according to the Procedure for chemically defined flavouring substances as described in Part A of these Guidelines. As in this case no exposure to the flavour precursor itself is anticipated, the toxicity of the flavour precursor does not need to be addressed.

**Case A-II:** If the flavour precursor is a chemically defined substance, which is expected to be incompletely transformed under the intended conditions of application into identified (chemically defined) products, the safety assessment of the flavour precursor as well as of the transformation products can be carried out according to the principles described for chemically defined flavouring substances in Part A of these Guidelines. In this case, both the safety of the flavour precursor as well as the safety of the transformation products has to be evaluated.

It is noted that in the two cases A-I and A-II described above, it is assumed that the transformation products can be identified. If additional transformation products or products resulting from the reaction with other food constituents are generated, the identities of which might not be established, no straightforward guidance for the toxicological data requirements for the safety assessment can be given. The safety evaluation should cover at least genotoxicity, repeated dose toxicity and developmental toxicity. The applicant should go into a process of exchange of information with Commission and EFSA to determine the most suitable way to go forward. This process should be started as soon as the data-requirements described in sections II.1, II.2.3.1, II.3 and II.4 can be submitted.

**Case B-I:** If the flavour precursors is or is contained in a non-food complex matrix, which is shown to be completely transformed in the food, no exposure to the flavour precursor itself will occur and therefore the safety of the precursor as such does not need to be addressed. However, a safety assessment of the transformation products will be necessary.

**Case B-II:** If the flavour precursor is or is contained in a non-food complex matrix, which is incompletely transformed in the food, the safety of both the flavour precursor as well as of the transformation products has to be assessed.

It is noted that in the two cases B-I and B-II described above, whether the flavour precursor is fully identified or not, it is very likely that the exposure will always be to mixtures of substances, including the remaining components of the non-food matrix, and often the identities of the transformation products will be unknown. Therefore, for these two cases no straightforward guidance on the method of safety assessment can be given, and the applicant should go into a process of exchange of information with Commission and EFSA to determine the most suitable way to go forward. This process should be started as soon as the data- requirements described in sections II.1, II.2.3.1, II.3 and II.4 can be submitted.

# III. INFORMATION TO BE SUPPLIED WITH AN APPLICATION FOR THE AUTHORISATION OF THERMAL PROCESS FLAVOURINGS

According to Article 3(2)(e) of Regulation (EC) No 1334/2008, "thermal process flavouring" shall mean a product obtained after heat treatment from a mixture of ingredients not necessarily having flavouring properties themselves, of which at least one contains nitrogen (amino) and another is a reducing sugar; the ingredients for the production of the thermal process flavourings may be (i) food and/or (ii) source material other than food.

This chapter applies to "thermal process flavourings" referred to in Article 9(c) of Regulation (EC) No 1334/2008:

> *thermal process flavourings obtained by heating ingredients which fall partially or totally within Article 3(2)(e)(ii), i.e. source materials other than food, and/or for which the conditions for the production of thermal process flavourings and/or the maximum levels for certain undesirable substances set out in Annex V of the Regulation are not met.*

The following information has to be supplied with an application for the authorisation of such a thermal process flavouring:

## 1. Manufacturing Process

### 1.1 Source material

The source material(s) used in the production of the thermal process flavouring, i.e. the source of nitrogen, the reducing sugar, or other ingredients used for the production must be described in sufficient detail to allow an adequate characterisation of the flavouring preparation as well as an estimation of the likelihood of the presence of undesirable substances (e.g. contaminants).

#### 1.1.1 Genetically modified organisms

If a thermal process flavouring is produced by or from genetically modified organisms (GMOs), the respective legal requirements (Commission Regulation (EC) No 1829/2003) have to be fulfilled.
Additionally, information should be provided according to the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Microorganisms and their derived Products Intended for Food and Feed Use" (EFSA, 2006a) and the "Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and derived Food and Feed" (EFSA, 2006b), respectively.

### 1.2 Production process

The process(es) by which the raw materials are converted to a thermal process flavouring should be described in sufficient detail to allow the evaluators to understand the key steps involved in the production of the thermal process flavourings and to demonstrate its reproducibility. The description shall include process parameters such as time-temperature condition, pH and other relevant process conditions (e.g. oxygen, pressure). In addition, the description should also allow to estimate the likelihood of the presence of undesirable substances (e.g. contaminants) in the final thermal process flavouring. This will help guiding the choice of the most appropriate analytical techniques employed for the assessment of the thermal process flavouring.

## 2. Identity of the thermal process flavouring

### 2.1 Trade names

### 2.2 Description of physical state

### 2.3 Chemical composition.

The thermal process flavouring should be chemically characterised as far as necessary to describe and define its identity, for example by GC, LC, MS, IR.

Information on the fraction of unidentified constituents should be provided. Any other information on chemical composition considered to be relevant for the evaluation should also be given.

Information should be provided on the batch-to-batch variability in all the measured parameters for chemical composition, as well as on the stability of the thermal processed flavouring during storage, including potential degradation products.

The sample(s) tested for chemical composition should be the same as or identical to the sample(s) tested toxicologically. This should be stated explicitly in the dossier. If the samples are not identical a justification should be provided. However, the sample(s) should be in accordance with the specifications.

### 2.4 Constituents of concern

As minimal requirement analyses of the following constituents of concern should be performed:

2-Amino-1-methyl-6-phenylimidazol [4,5-*b*] pyridine (PhIP)
2-Amino-3,8-dimethylimidazo [4,5-*f*] quinoxaline (MeIQx)
2-Amino-3-methylimidazo [4,5-*f*] quinoline (IQ)
2-Amino-3-methylimidazo [4,5-*f*] quinoxaline (IQx)
2-Amino-3,4,8-trimethylimidazo [4,5-*f*] quinoxaline (4,8-DIMeIQx)
Acrylamide
4-Methylimidazole
2-Acetyl-4-tetrahydroxy-butylimidazole.

In addition, the analysis of other possible undesirable substances should also be considered, depending upon the source material(s) and the production process.

## 3. Specifications

Specifications used to describe the thermal processed flavouring to be placed on the market should be provided.

## 4. Exposure to thermal process flavouring

### 4.1 Intended use of the thermal process flavouring

Intended use and anticipated use levels should be reported at the level of second tier categorisation of the GSFA (as for the APET method described in Part A of the present Guidelines).

## 4.2 Dietary exposure

As a first step, dietary exposure to the preparation should be assessed as described in Part A of the present Guidelines.

If needed, dietary exposure to individual components and/or to groups of components should be determined based on the intake of the preparation and the level of each component present in the preparation (determined by analytical characterisation).
In this case total dietary exposure to individual components and/or to groups of components will also need to be assessed as in Part A. For this type of flavourings non-oral routes of exposure are not expected to be of relevance.

# 5. Toxicological data

Since thermal process flavourings may be anticipated to consist of mixtures of chemicals which may include considerable amounts of materials for which the chemical identity may be unknown, extensive toxicity data are needed.

As a default, information on the genotoxicity and toxicity should be provided, as described below.

## 5.1 Genotoxicity

Information on the ability of the thermal processed flavouring to induce gene mutations as well as structural and numerical chromosomal aberrations should be provided according to the guidance given in Part A of these Guidelines.

## 5.2 Repeated-dose studies

### 5.2.1 Subchronic toxicity

A 90-day feeding study in rodents, preferably in rats, should be submitted.

### 5.2.2 Developmental toxicity

A developmental study in rodents, should be submitted.

Deviations from the requirements in Section 5.1 and Section 5.2 are acceptable if adequate scientific justifications are provided. Such deviations may include different testing strategies and/or approaches.

Data on related thermal process flavouring may be used in a weight of evidence approach in the safety assessment of the submitted thermal process flavouring.

As clarified in Part A of these Guidelines, newly performed studies should be carried out according to current international Guidelines for toxicity testing (e.g. OECD Guidelines) and under GLP quality assurance.

## 5.3 Other studies

If available other studies relevant for the safety evaluation of the thermal processed flavouring should be submitted.

The Panel may request further toxicity testing if a need for additional testing would arise from the submitted data.

# IV. INFORMATION TO BE SUPPLIED WITH AN APPLICATION FOR THE AUTHORISATION OF OTHER FLAVOURINGS

This chapter applies to "other flavourings" referred to in Article 3(2)(h) of Regulation (EC) No 1334/2008:

> *a flavouring added or intended to be added to food in order to impart odour and/or taste and which does not fall under the definitions of Article 3(2)(b) – (g) of Regulation (EC) No 1334/2008.*

From this definition it remains unclear what "Other Flavourings" might consist of; it is, therefore, of paramount importance to go into a process of inter- and pro-active exchange of information between Commission, Applicant and EFSA before the actual submission of data.
It is difficult to anticipate what kind of materials will undergo an evaluation as "Other Flavourings", which suggests that the standard evaluation template is flexible.

At this point in time, only some key aspects can be identified in terms of information to be supplied with an application for the authorisation of "Other Flavourings". As a general approach, the following data should be provided:

- Full description of the production process, with emphasis on the parameters that might influence the composition of the flavouring;
- identification and quantification of the substances present in the flavouring;
- specifications of the flavouring;
- exposure and toxicological data required to perform a risk assessment of the flavouring.

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# APPENDICES

## APPENDIX 1.

Databases to be used by petitioners to assess normal and maximum occurrence levels of flavourings from other sources in the different categories of foods and beverages (the list is not exhaustive):

Anonymous (1999). Volatile Compounds in Food (VCF). Boelens Aroma Chemical Information Service, Huizen. The Netherlands. http://www.vcf-online.nl/VcfHome.cfm.

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## APPENDIX 2

*Dietary exposure in a 12-month young child*

The method that needs to be used to estimate the dietary exposure is a model diet which uses standard portions sizes specific for young children. The USDA document that was used by the JECFA as a basis for the development of standard portion sizes in the adult also provides standard portions sizes for infants and toddlers up to 4 years (http://edocket.access.gpo.gov/cfr_2001/aprqtr/21cfr101.12.htm).
The portions expressed as "ready to serve" were considered and an additional category was considered: milk for young children (one baby bottle).

Dry instant cereals (with or without milk), including pasta: 110 g

Biscuits and cookies: 20 g.

Fruit purée: 110 g.

Fruit juice, herbal tea: 120 g.

Meat based or fish-based meal: 170 g.

Dairy based dessert: 110 g.

Vegetables, potatoes, broth, soups, pulses: 170 g.

Milk for young children, ready to serve: 200 g.

Dietary exposure will be assessed by adding up the exposure from one standard portion of each of these foods and beverage categories at the maximum combined occurrence level as reported by the applicant in Table 1. The value obtained will represent the dietary exposure in a 12-month young child consuming every day products containing the flavouring substance at its maximum use level. A standard bw of 10 kg will be used to assess dietary exposure in mg/kg bw per day. The average weight of children aged 12 months is 9.5 kg in females and 10 kg in males (Commission of the European Communities, 1993).

**TABLE 1 - NORMAL AND MAXIMUM OCCURRENCE LEVELS FOR REFINED SUBCATEGORIES OF FOODS AND BEVERAGES**

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 01.1 | Milk and dairy-based drinks | 200 | | | | | | |
| 01.2 | Fermented and renneted milk products (plain), excluding food category 01.1.2 (dairy-based drinks) | 200 | | | | | | |
| 01.3 | Condensed milk and analogues (plain) | 70 | | | | | | |
| 01.4 | Cream (plain) and the like | 15 | | | | | | |
| 01.5 | Milk powder and cream powder and powder analogues (plain) | 30 | | | | | | |
| 01.6 | Cheese and analogues | 40 | | | | | | |
| 01.7 | Dairy-based desserts (e.g., pudding, fruit or flavoured yoghurt) | 125 | | | | | | |
| 01.8 | Whey and whey products, excluding whey cheeses | 200 | | | | | | |
| 02.1 | Fats and oils essentially free from water | 15 | | | | | | |
| 02.2 | Fat emulsions mainly of type water-in-oil | 15 | | | | | | |
| 02.3 | Fat emulsions mainly of type water-in-oil, including mixed and/or flavoured products based on fat emulsions | 15 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 02.4 | Fat-based desserts excluding dairy-based dessert products of category 1.7 | 50 | | | | | | |
| 03.0 | Edible ices, including sherbet and sorbet | 50 | | | | | | |
| 04.1.1 | Fresh fruit | 140 | | | | | | |
| 04.1.2 | Processed fruit | 125 | | | | | | |
| 04.1.2.5 | Jams, jellies, marmalades | 30 | | | | | | |
| 04.2.2 | Processed vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g. peanut butter) and nuts and seeds | 200 | | | | | | |
| 04.2.2.5 | Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g. peanut butter) | 30 | | | | | | |
| 05.1 | Cocoa products and chocolate products, including imitations and chocolate substitutes | 40 | | | | | | |
| 05.2 | Confectionery, including hard and soft candy, nougats, etc., other than 05.1, 05.3 and 05.4 | 30 | | | | | | |
| 05.3 | Chewing gum | 3 | | | | | | |
| 05.4 | Decorations (e.g. for fine bakery | 35 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| | wares), toppings (non-fruit) and sweet sauces | | | | | | | |
| 06.1 | Whole, broken or flaked grain, including rice | 200 | | | | | | |
| 06.2 | Flours and starches (including soya bean powder) | 30 | | | | | | |
| 06.3 | Breakfast cereals, including rolled oats | 30 | | | | | | |
| 06.4 | Pastas and noodles and like products (e.g. rice paper, rice vermicelli, soya bean pastas and noodles) | 200 | | | | | | |
| 06.5 | Cereal and starch-based desserts (e.g. rice pudding, tapioca pudding) | 200 | | | | | | |
| 06.6 | Batters (e.g. for breading or batters for fish or poultry) | 30 | | | | | | |
| 06.7 | Pre-cooked or processed rice products, including rice cakes (Oriental type only) | 200 | | | | | | |
| 06.8 | Soya bean products (excluding soya bean products of food category 12.9 and fermented soya bean products of food category 12.10) | 100 | | | | | | |
| 07.1 | Bread and ordinary bakery wares | 50 | | | | | | |
| 07.2 | Fine bakery wares (sweet, salty, savoury) and mixes | 80 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 08.1 | Fresh meat, poultry and game | 200 | | | | | | |
| 08.2 | Processed meat, poultry and game products in whole pieces or cuts | 100 | | | | | | |
| 08.3 | Processed comminuted meat, poultry and game products | 100 | | | | | | |
| 08.4 | Edible casings (e.g. sausage casings) | 1 | | | | | | |
| 09.1.1 | Fresh fish | 200 | | | | | | |
| 09.1.2 | Fresh molluscs, crustaceans and echinoderms | 200 | | | | | | |
| 09.2 | Processed fish and fish products, including molluscs, crustaceans and echinoderms | 100 | | | | | | |
| 09.3 | Semi-preserved fish and fish products, including molluscs, crustaceans and echinoderms | 100 | | | | | | |
| 09.4 | Fully preserved, including canned or fermented, fish and fish products, including molluscs, crustaceans and echinoderms | 100 | | | | | | |
| 10.1 | Fresh eggs | 100 | | | | | | |
| 10.2 | Egg products | 100 | | | | | | |
| 10.3 | Preserved eggs, including alkaline. salted and canned eggs | 100 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 10.4 | Egg-based desserts (e.g. custard) | 125 | | | | | | |
| 11.1 | Refined and raw sugar | 10 | | | | | | |
| 11.2 | Brown sugar excluding products of food category 11.1 | 10 | | | | | | |
| 11.3 | Sugar solutions and syrups, and (partially) inverted sugars, including molasses and treacle, excluding products of food category 11.1 | 30 | | | | | | |
| 11.4 | Other sugars and syrups (e.g. xylose, maple syrup, sugar toppings) | 30 | | | | | | |
| 11.5 | Honey | 15 | | | | | | |
| 11.6 | Table-top sweeteners, including those containing high-intensity sweeteners | 1 | | | | | | |
| 12.1 | Salt and salt substitutes | 1 | | | | | | |
| 12.2 | Herbs, spices, seasonings and condiments (e.g. seasoning for instant noodles) | 1 | | | | | | |
| 12.3 | Vinegars | 15 | | | | | | |
| 12.4 | Mustards | 15 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 12.5 | Soups and broths | 200 | | | | | | |
| 12.6 | Sauces and like products | 30 | | | | | | |
| 12.7.1 | Salads 120 g (e.g. macaroni salad, potato salad) excluding cocoa- and nut-based spreads of food categories | 120 | | | | | | |
| 12.7.2 | Sandwich spreads (20 g), excluding cocoa- and nut-based spreads of food categories | 20 | | | | | | |
| 12.8 | Yeast and like products | 1 | | | | | | |
| 12.9 | Protein products | 15 | | | | | | |
| 12.10 | Fermented soya bean products | 40 | | | | | | |
| 13.2. a | Complementary foods for infants and young children: Dry instant cereals (with or without milk), including pasta | | | | | | | |
| 13.2. b | Complementary foods for infants and young children: Meat based or fish based dinner | | | | | | | |
| 13.2. c | Complementary foods for infants and young children: Dairy based dessert | | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 13.2. d | Complementary foods for infants and young children: Vegetables, potatoes, broth, soups, pulses | | | | | | | |
| 13.2. e | Complementary foods for infants and young children: Biscuits and cookies | | | | | | | |
| 13.2. f | Complementary foods for infants and young children: Fruit purée | | | | | | | |
| 13.2. g | Complementary foods for infants and young children: Fruit juice | | | | | | | |
| 13.2. h | Milk for young children | | | | | | | |
| 13.3 | Dietetic foods intended for special medical purposes (excluding food products of category 13.1) | 200 | | | | | | |
| 13.4 | Dietetic formulae for slimming purposes and weight reduction | 200 | | | | | | |
| 13.5 | Dietetic foods (e.g. supplementary foods for dietary use), excluding products of food categories 13.1–13.4 and 13.6 | 200 | | | | | | |
| 13.6 | Food supplements | 5 | | | | | | |
| 14.1 | Non-alcoholic (“soft”) beverages | 300 | | | | | | |
| 14.2.1 | Beer and malt beverages | 300 | | | | | | |
| 14.2.2 | Grape wines | 150 | | | | | | |
| 14.2.3 | Mead | 150 | | | | | | |
| 14.2.4 | Spirituous beverages | 30 | | | | | | |

| Group CODEX code | Food categories § | Standard portions for adults* (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 15.1 | Snacks, potato-, cereal-, flour- or starch-based (from roots and tubers, pulses and legumes) | 30 | | | | | | |
| 15.2 | Processed nuts, including coated nuts and nut mixtures (with e.g. dried fruit) | 30 | | | | | | |
| 15.3 | Snacks – fish based | 30 | | | | | | |
| 16.0 | Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15 | 300 | | | | | | |

§ Most of the categories reported are the sub-categories of Codex GSFA (General Standard for Food Additives, available at http://www.codexalimentarius.net/gsfaonline/CXS_192e.pdf) used by the JECFA in the SPET technique (FAO/WHO, 2008). In the case of category 13.2 (complementary foods for infants and young children), further refined categories have been created so that a specific assessment of dietary exposure can be performed in young children.

* In case of foods marketed as powder or as concentrates, occurrence levels must be reported for the reconstituted product, considering the instructions reported on the product label or one of the standard dilution factors established by the JECFA (FAO/WHO 2008):

- 1/25 for powder used to prepare water-based drinks such as coffee, containing no additional ingredients,
- 1/10 for powder used to prepare water-based drinks containing additional ingredients such as sugars (ice tea, squashes, etc.),
- 1/7 for powder used to prepare milk, soups and puddings,
- 1/3 for condensed milk.

$ In order to estimate normal values in each category, only foods and beverages in which the substance is present in significant amount will be considered (e.g. for the category “Fresh fruit” 04.1.1., the normal concentration will be the median concentration observed in all kinds of fruit where the flavouring substance is known to occur).

# The normal and maximum combined occurrence levels of the substance will be assessed by the applicant either by adding up occurrence levels from added use to that from other sources or by expert judgment based on the likelihood of their concomitant presence. This will be done both for normal use levels and for maximum use levels.

**TABLE 2 - NORMAL AND MAXIMUM OCCURRENCE LEVELS IN THE MAIN GSFA FOOD CATEGORIES**

| Group CODEX code | Main GSFA food categories § | Standard portions for adults * (g) | Occurrence level as added flavouring substance (mg/kg) | | Occurrence level from other sources: as natural constituent and/or developed during the processing and/or as residue from animal feed (mg/kg) | | Combined occurrence level from all sources (as added flavouring or from other sources) # (mg/kg) | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Maximum | Normal[$] | Maximum | Normal | Maximum |
| 01.0 | Dairy products and analogues, excluding products of category 02.0 | 200 | | | | | | |
| 02.0 | Fats and oils and fat emulsions | 50 | | | | | | |
| 03.0 | Edible ices, including sherbet and sorbet | 50 | | | | | | |
| 04.0 | Fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes and aloe vera), seaweeds, and nuts and seeds | 200 | | | | | | |
| 05.0 | Confectionery | 40 | | | | | | |
| 06.0 | Cereals and cereal products derived from cereal grains, roots and tubers, and pulses and legumes, excluding bakery wares of food category 07.0 | 200 | | | | | | |
| 07.0 | Bakery wares | 80 | | | | | | |
| 08.0 | Meat and meat products, including poultry and game | 200 | | | | | | |
| 09.0 | Fish and fish products, including molluscs, crustaceans and echinoderms | 200 | | | | | | |
| 10.0 | Eggs and egg products | 125 | | | | | | |
| 11.0 | Sweeteners, including honey | 30 | | | | | | |
| 12.0 | Salts, spices, soups, sauces, salads, protein products (including soya bean protein products) and fermented soya bean products | 200 | | | | | | |
| 13.0 | Foodstuffs intended for particular nutritional uses | 200 | | | | | | |
| 14.0 | Beverages, excluding dairy products | 300 | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15.0 | Ready-to-eat savouries | 30 | | | | | | |
| 16.0 | Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15 | 300 | | | | | | |

§ The categories reported are the main categories of Codex GSFA (General Standard for Food Additives, available at http://www.codexalimentarius.net/gsfaonline/CXS_192e.pdf).
* The standard portions reported in the present table are, for each of the main GSFA category, the largest standard portion size among its sub-category. They will be used to estimate dietary exposure if the applicant cannot provide occurrence data at the level of sub-categories as listed in Table 1. In case of foods marketed as powder or as concentrates, occurrence levels must be reported for the reconstituted product, considering the instructions reported on the product label or one of the standard dilution factors established by the JECFA (FAO/WHO 2008).
$ In order to estimate normal values in each category, only foods and beverages in which the substance is present in significant amount will be considered (e.g. for the category "Fruit and vegetables" 04.0., the normal concentration will be the median concentration observed in all kinds of fruit and vegetables where the flavouring substance is known to occur).
# The normal and maximum combined occurrence levels of the substance will be assessed by the applicant either by adding up occurrence levels from added use to that from other sources or by expert judgment based on the likelihood of their concomitant presence. This will be done both for normal use levels and for maximum use levels.

## ABBREVIATIONS

| | |
|---|---|
| AFC | Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food |
| APET | Added Portions Exposure Technique |
| BMDL | Benchmark Dose Lower Confidence Limit |
| BW | Body Weight |
| CAS | Chemical Abstract Service |
| CEF | Panel on Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids |
| CoE | Council of Europe |
| DATEX | Data Collection and Exposure unit, EFSA |
| DG SANCO | Directorate General for Health and Consumers |
| EC | European Commission |
| ECHA | European Chemicals Agency |
| EFFA | European Flavour and Fragrance Association |
| EFSA | European Food Safety Authority |
| EINECS | European INventory of Existing Commercial chemical Substances |
| EP | European Parliament |
| EU | European Union |
| FAO | Food and Agriculture Organization of the United Nations |
| FEMA | Flavor and Extract Manufacturers Association |
| FGE | Flavouring Group Evaluation |
| FLAVIS | Flavour Information System database |
| GC | Gas Chromatography |
| GEMS | Global Environment Monitoring System |
| GLP | Good Laboratory Practice |
| GMO | Genetically Modified Organisms |

| | |
|---|---|
| GSFA | General Standard for Food Additives |
| INCA | Individuelle et Nationale sur les Consommations Alimentaires |
| IOFI | The International Organization of the Flavor Industry |
| IR | Infra Red |
| IUPAC | International Union of Pure and Applied Chemistry |
| JECFA | The Joint FAO/WHO Expert Committee on Food Additives |
| JEFMA | Japanese Flavour and Fragrance Material Association |
| LC | Liquid Chromatography |
| MS | Mass Spectrometry |
| MSDI | Maximised Survey-derived Daily Intake |
| mTAMDI | Modified Theoretical Added Maximum Daily Intake |
| NOAEL | No Observed Adverse Effect Level |
| OECD | Organisation for Economic Co-operation and Development |
| SCF | Scientific Committee on Food |
| SPET | Single Portion Exposure Technique |
| TAMDI | Theoretical Added Maximum Daily Intake |
| TGD | Technical Guidance Document on Risk Assessment of Chemical Substances and Biocides |
| UDS | Unscheduled DNA Synthesis |
| USDA | United Stated Department of Agriculture |
| WHO | World Health Organisation |