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TECHNICAL REPORT OF EFSA

Proposed template to be used in drafting scientific opinion on flavouring substances (explanatory notes for guidance included)

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The proposed template is expected to facilitate the drafting and the harmonization of scientific opinions on flavouring substances.

At the 13th CEF Plenary held on 10 May 2010, the Panel adopted an Opinion on data needed for the evaluation of flavourings in accordance with Regulation (EC) No 1334/2008. This Opinion has been used by the Commission for the preparation of the implementing measures (Regulation (EC) No 234/2011), which lay down amongst other aspects, the content, drafting and presentation of the applications for the evaluation and authorisation of flavourings.

In order to assist the application process, the CEF Unit was invited by EFSA to prepare, together with the CEF Flavouring Working Group, the current note for guidance giving explanatory examples of scientific data needed for the risk assessment established in the EFSA Guidance. The explanatory notes have been incorporated into the proposed template to be used in drafting opinions on flavourings substances.

The reader is recommended to go through the EFSA Scientific Opinion (EFSA Journal 2010;8(6): 1623) on "Guidance on data required for the risk assessment of flavourings to be used in or on food" to have a detailed insight into data to be incorporated in this technical report.

KEY WORDS

(Flavouring substances, guidance, template, note for guidance)

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BACKGROUND

On the 13th CEF Plenary, 20 May 2010, the Panel adopted an Opinion on data required for the risk assessment of flavourings in accordance with Regulation (EC) No 1334/2008. This Opinion has been used by Commission for preparation of the implementing measure (Regulation (EC) No 234/2011), which lay down amongst other aspects, the content, drafting and presentation of the applications for the evaluation and authorisation of flavourings.

Based on comments from the Public Consultation on the draft Guidance on the data required for the risk assessment of flavourings it became obvious that, in order to avoid misinterpretations of the requested scientific data in the guidance document, a document giving explanatory examples is needed.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The CEF Unit is asked to prepare, with assistance from the Flavouring Working Group, a technical report on "Explanatory Notes for Guidance".

1. IDENTIFICATION OF THE SUBSTANCE

Note for Guidance: e.g. chemical name, structure, CAS number, any other registration number if exists

2. EXISTING AUTHORISATIONS AND EVALUATIONS

3. MANUFACTURING PROCESS

3.1. 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. impurities or contaminants).

Note for Guidance: Data on source material should allow making a link to the specifications of the final product, in the light of the production process.

3.1.1. Genetic 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.

3.2. 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.

4. Specifications

The following information has to be provided for the flavouring substance; descriptive information should be reported here (e.g. information on impurities and/or on configuration) with numerical information reported in the Summary table:
- 4.1 Chemical name (IUPAC name, synonyms).
- 4.2 CAS-, E-, EINECS-, CoE-, JECFA-, FLAVIS- and FEMA numbers (if assigned).
- 4.3 Chemical and structural formula, molecular weight.
- 4.4 Physical form/odour.
- 4.5 Solubility data.
-4.6 Identity tests (infra red-, nuclear magnetic resonance- and/or mass spectrum, gas chromatographic retention indices).
- 4.7 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.

Note for Guidance: By-products, impurities and contaminants can be mentioned in percentage ranges without decimal places.

- 4.8 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.
- 4.9 Physical parameters related to purity: boiling point (for liquids), melting point (for solids), refractive index (for liquids), and specific gravity (for liquids).
- 4.10 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.).

Note for Guidance: Percentage for a defined mixture of isomers should be as precise as possible. Generally, a 10% range for the individual isomers is considered acceptable.

- 4.11 Stability and decomposition products, if relevant.
- 4.12 Interaction with food components, if relevant.
- 4.13 Any other relevant information, if applicable.

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

Table 1: Specifications

Chemical name	Registration numbers	Chemical formula	Structural formula	Physical form/odour	Solubility data	ID test	Purity	Impurities	Physical parameter	Information on the configuration of the flavouring substance
	CAS E- EINECS CoE JECFA FLAVIS FEMA								Boiling point Melting point Refractive index Specific gravity	

5. EXPOSURE ASSESSMENT (Details are reported in Annex 2).

Note for Guidance. All data necessary for the calculation of normal and maximum occurrence levels for refined sub categories of foods and beverages should be reported in Annex 2 (see Appendix 1 and 2 and Table 1 in the flavouring guidance). Combined APET will rarely be the sum of occurrence levels from added flavourings and occurrence levels from other sources. In many cases, as stated in the flavouring guidance, the likelihood of addition of a flavouring in products that would already contain it from other sources will be a matter of assessment (e.g. expert judgment). This expert judgment will be included as a footnote text to the table in Annex 2.

5.1. Non-food sources of exposure

Note for Guidance: Information on non-food sources of exposure as the one submitted to ECHA under REACH framework would is acceptable. Other possible recommended sources are SCCNFP and SCCS.

5.2. Chronic Dietary Exposure

5.2.1. Adult APET

Table 2 Adult APET

	Added (mg/kg/bw)		Other dietary sources (mg/kg/bw)		Combined (mg/kg/bw)	
	Normal	Maximum	Normal	Maximum	Normal	Maximum
Substance						

5.2.2. Children APET

Table 3 Children APET

	Added (mg/kg/bw)		Other dietary sources (mg/kg/bw)		Combined (mg/kg/bw)	
	Normal	Maximum	Normal	Maximum	Normal	Maximum
Substance						

5.2.3. Infants APET

Note for Guidance: Only maximum combined APET exposure should be reported here for infants

Table 4 Infants APET

Substance	Maximum Combined APET

5.3. Acute Dietary Exposure

Note for Guidance: Information on acute dietary exposure should be provided on a case by case basis, depending on potential acute toxic properties of the flavouring substance and the acute dietary exposure to the flavouring substance.

5.3.1. Adult APET

Table 5 Acute Adult APET

	Added (mg/kg/bw)		Other dietary sources (mg/kg/bw)		Combined (mg/kg/bw)	
	Normal	Maximum	Normal	Maximum	Normal	Maximum
Substance						

5.3.2. Children APET

Table 6 Acute Children APET

	Added (mg/kg/bw)		Other dietary sources (mg/kg/bw)		Combined (mg/kg/bw)	
	Normal	Maximum	Normal	Maximum	Normal	Maximum
Substance						

5.4. Cumulative Dietary Exposure

5.4.1. Structurally and metabolically related flavouring substances (see Annex 3 and section 7 of this document for group allocation)

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. 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 (see section 7) 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. 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" to that of the newly submitted substance and expressed in mg/kg bw per day.

Note for Guidance: The same principle used to assign substances to (sub) groups applies to the estimation of the cumulative exposure. Applicant should identify here the five structurally and metabolically related substances with the highest intake based on available data (i.e. MSDI). Poundage data as provided by applicants so far would be adequate if no new surveys have been conducted. Poundage data for already assessed substances can be calculated from the published MSDI values. For substances already evaluated, added use levels can be retrieved in published opinions; for JEFCA evaluated substances, normal use levels have to be collected. A summary table on MSDI data for structurally and metabolically related flavouring substances should be reported in the Annex 3.

Table 6 Structurally and Metabolically Related Flavouring Substances with Highest MSDI Values

Identified flavouring substance	MSDI data

Table 7 Added and Combined APET for Structurally and Metabolically Related Flavouring Substances with Highest MSDI Values

Substance	Added APET (mg/kg/bw)	Other dietary sources (mg/kg/bw)	Combined APET (mg/kg/bw)

6. GENOTOXICITY

6.1. Genotoxicity studies (Details on results and study designs are reported in Annex 4)

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:
- 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

Note for Guidance: All three genetic endpoints (i.e. gene mutations, structural chromosomal aberrations and numerical chromosomal aberrations) have to be explored in vitro. This independently of the outcome of the in-vitro tests (e.g. in cases where one in-vitro test would result positive for one endpoint, the remaining endpoints have still to be explored).
Note for Guidance: In cases where genotoxicity testing may be deemed not necessary (e.g. FGE group evaluation, see section 7) the strength of the data used to evaluate genotoxicity of the substances/representatives contained in that subgroup (i.e. the coverage of the three genetic endpoints) will be considered as a key criteria.

Note for Guidance: A new Scientific Opinion adopted by the EFSA Scientific Committee (Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment) is now in force and the reader should refer to this opinion for the required tests and recommended strategies

6.1.1. In vitro assessment

6.1.2. In vivo assessment

6.1.3. Conclusion on genotoxicity assessment

Key aspects: A concise conclusion on genotoxicity results should be reported in the conclusion section, clearly indicating that all endpoints for genotoxicity have been properly explored. Study details should be reported in Annex 4.

7. EXAMINATION FOR STRUCTURAL/METABOLIC SIMILARITY TO FLAVOURING SUBSTANCES IN AN EXISTING FGE (Annex 5)

The applicant should provide a proposal for the assignment of the new flavouring substance to an existing FGE. 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.

7.1. Experimental data

7.2. Literature data

7.3. Conclusion

8. PROCEDURE FOR ASSESSMENT

Two alternatives exist. 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). See Figure 2 and text in the flavouring guidance and Annex 1 of this document.
Alternatively, 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. A scheme outlining the principles of this evaluation is shown in Figure 3 of the flavouring guidance and Annex 1 of this document.

8.1. Group based evaluation

Introductory Note: Description of the decision made at the respective steps of the procedure should be made in this section and summarized in Tables as Annex (Annex 5 and 6).
Key aspects should be considered and any step should have a conclusive part.
Study details and a summary of each study report (i.e. Report Summary) and/or the abstract from the relevant literature quoted should be reported as part of Annex 5 and 6. A concise and integrated summary of available data should be reported here. Toxicity data should be described by target organ toxicity or endpoints.

Step 1 Decision tree structural class

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).

Note for Guidance: Provided that toxicological data available have been evaluated and considered to be sufficient in the existing FGE, a summarising description is considered adequate

Conclusion

Step 2 Can the substance be predicted be metabolised to innocuous products? (Annex 5)

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. The assessment of the metabolites has to be substantiated by appropriate experimental data or relevant evidence from the literature.

Note for Guidance: If the metabolic similarity used for the assignment of the new flavouring substance to a (sub) group of an existing FGE has been demonstrated on the basis of experimental data or relevant evidence from literature, this set of data may also be used at this step of the Procedure.

Note for Guidance: If hydrolysis cannot be substantiated by using experimental data (e.g. hydrolysis in food or simulated gastro-intestinal tract), evidence from literature and read-across from other similar structures could be also accepted. Metabolites expected to result from hydrolysis should at least be quantitatively estimated.

Conclusion

If the candidate substance is expected to be metabolised to innocuous products, evaluation will be carried out through the A side of the procedure. If metabolism to innocuous products cannot be substantiated, evaluation will be carried out through the B side of the Procedure

Step A3/B3. Intake data

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" and of the "intended use" should be based on the exposure resulting from the proposed addition of the flavouring substance to foods (See Chapter II of the flavouring guidance).

Conclusion

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*".

For candidate substances that are evaluated through the Aside of the Procedure, if the condition of use of the candidate substance result in an intake greater than the threshold of concern for the structural class, the safety evaluation will move to step A4 of the Procedure.

For candidate substances that were evaluated through the B side of the Procedure, if the level of intake is greater than the threshold of concern for the structural class, data must be available on the substance or closely related substances to perform a safety evaluation. If the level of intake is not greater than the threshold of concern for the structural class, the candidate substance will move to step B4 of the Procedure.

Table 8 Step A3/B3

Substance	Structural class	Add APET	Threshold of Concern

Step A4 Is the substance or are its metabolites endogenous?"

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.

Note for Guidance: This information should be provided by the applicant

Conclusion

Step A5/B4 Required Toxicological data (Annex 6)

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 this step is "Additional data required", more information is needed, e.g. from further studies on toxicity.
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 of the flavouring guidance) 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

Table 9 Step A5/B4

Study (e.g.90 day study)	NOAEL	Add APET	Margin of safety

Conclusion

8.2. Individual evaluation

Describe the decisions made according to the decision tree described in figure 3 of the flavouring guidance document (see also Annex 1 in this document)
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.

Note for Guidance: If hydrolysis cannot be substantiated by using experimental data (e.g. hydrolysis in food or simulated gastro-intestinal tract), evidence from literature and read-

across from other similar structures could be also accepted. Metabolites expected to result from hydrolysis should at least be quantitatively estimated.
The experimental data for the various tests 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.
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) is 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. 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.

Note for guidance: In absence of any specific reproductive effect (e.g. histological changes in male seminipherous epthelium) observed in the general toxicity study i.e. 90 day study), default developmental toxicity study would be a teratogenesis study in accordance with the most recent guidance (OECD Guideline 414) .

Key aspects should be considered in the text and any step should have a conclusion part.

Table 10 Individual evaluation

Substance	Structural class	Add APET	Threshold of Concern

8.2.1. Required Toxicity data (Annex 6)

If the candidate substance cannot be demonstrated to be metabolised to innocuous products or in case where data can demonstrate that metabolites can be considered innocuous but the dietary exposure is greater than the threshold of concern for the structural class, additional toxicity data are required (see Fig 3 of the flavouring guidance or Annex 1 of this document).

Study details and a summary of each study report (i.e. Report Summary) and/or the abstract from the relevant literature quoted should be reported in Annex 6. A concise and integrated summary of available data should be reported here. Toxicity data should be described by target organ toxicity or endpoints.

Table 11 Summary table on calculated margins of safety by toxicity studies

Study (e.g.90 day study)	NOAEL / BMDL	AddAPET	Margin of Safety

Conclusions

9. 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 former sections, 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.

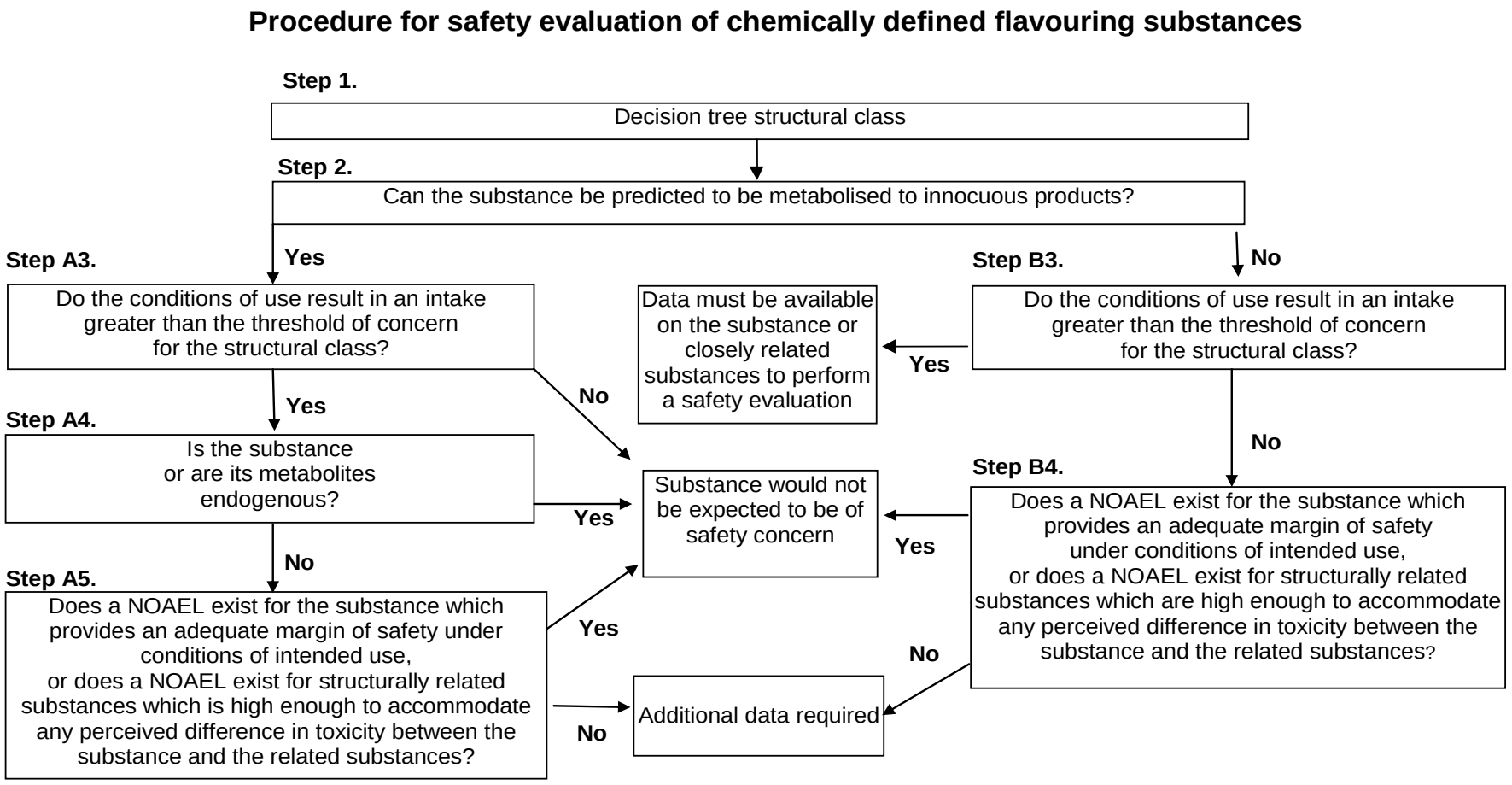
10. OVERALL CONCLUSION

APPENDIX/APPENDICES [AS APPROPRIATE]

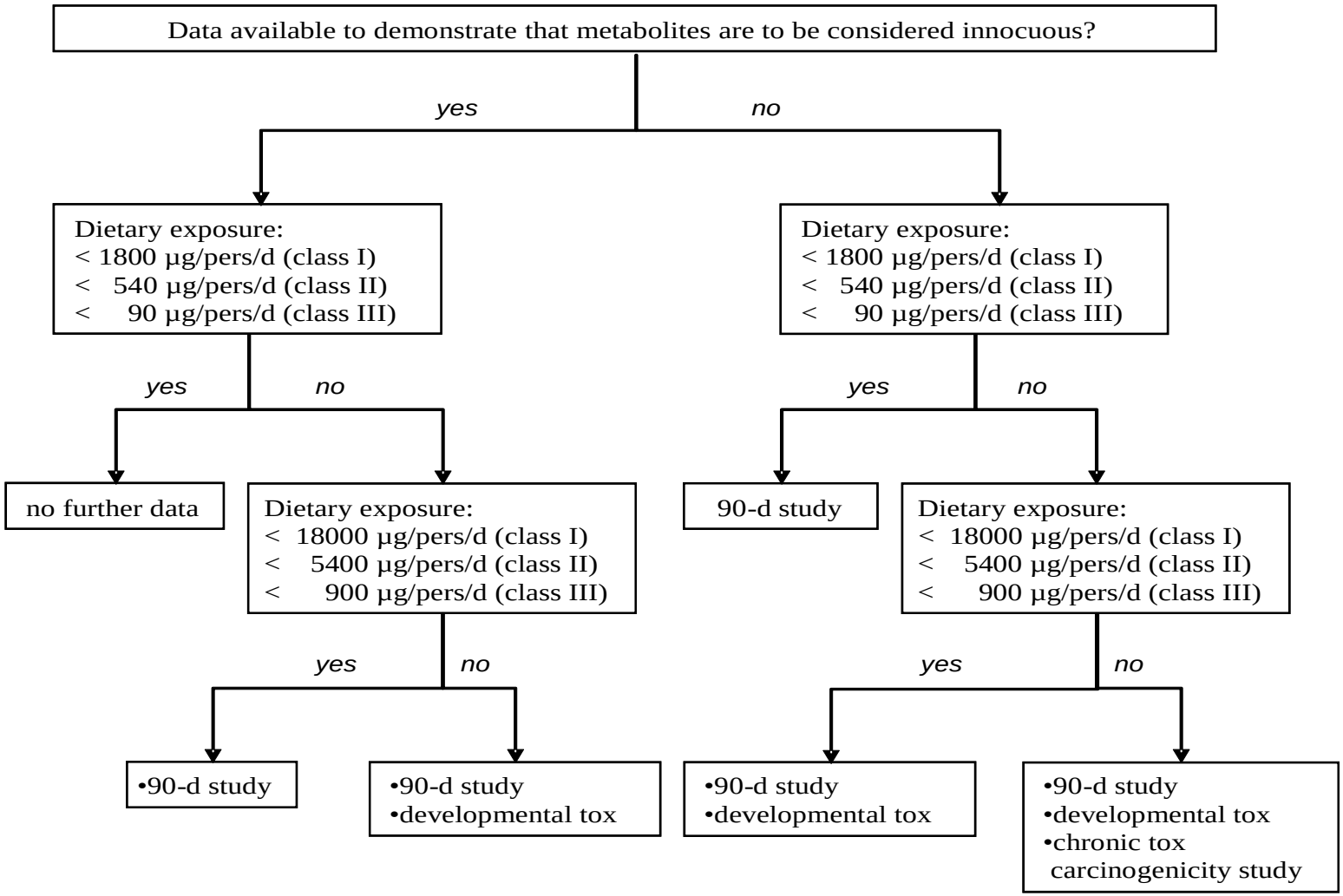
Note: Each appendix should start on a new page.

Annex 1

Decision trees for safety evaluation of chemically defined flavouring substances following the Procedure and decision tree of individual evaluation of the flavouring substance



Individual evaluation of the flavouring substance



Annex 2

TABLE 1 - NORMAL AND MAXIMUM OCCURRENCE LEVELS FOR REFINED SUB CATEGORIES OF FOODS AND BEVERAGES

Group CODEX code	Food categories §	Standard portions * (g)	Occurrence level as added flavouring substance (mg/kg)		Occurrence level from other sources @ (mg/kg)		Combined occurrence level from all 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						
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 wares), toppings (non-fruit) and sweet sauces	35
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
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
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
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	
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
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.

* For Adults. 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.

@ As natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed

$ 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).

As added flavouring or from other sources. 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.

Annex 3

Structural similarities (structurally and metabolically related substances)

Table 12 Supporting Substances Summary

FL-no	EU Unit list name	Structural Formula	EFSA status	Cramer class	MSDI (EU) µg/capita/day	Comments

Annex 4

Genotoxicity

Table 13a Summary of *in vitro* genotoxicity studies

FL-no JECFA-no	Unit list name / test material	Test System	Test Object	Concentration	Result	Reference	Comments

Table 13b Summary of *in vivo* genotoxicity studies

FL-no JECFA-no	Unit list name / test material	Test System	Test Object	Route	Dose	Result	Reference	Comments

Annex 5

Evaluation of metabolic products

Table 14

FL-no JECFA-no	Unit list name	Structural formula	Estimated amount	EFSA status	Cramer class	Comments

Annex 6

Toxicity

Table 15 Summary table of toxicity studies

FL-no JECFA-no	Unit list name / test material	Species; Sex No/group	Route of Administration	Dose Level mg/kg bw/day	Duration	LD_{50} /NOAEL/BMDL (mg/kg bw/day)	Reference	Comments

CONCLUSIONS [AND/OR] RECOMMENDATIONS

CONCLUSIONS

RECOMMENDATIONS

DOCUMENTATION PROVIDED TO EFSA

1. Dossier name. Month YYYY. Submitted by [name of company].

REFERENCES

EFSA (2010) Guidance on the data required for the risk assessment of flavouring to be used in or on foods. The EFSA Journal 2010; 8 (6): 1623

EFSA (2011) Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. The EFSA Journal 2011; 9(9): 2397

GLOSSARY [AND/OR] ABBREVIATIONS

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