TECHNICAL REPORT

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Public consultation on the draft scientific guidance on the data required for the risk assessment of flavourings to be used in or on foods

European Food Safety Authority (EFSA)

Abstract

This technical report presents the outcome of the public consultation carried out by the European Food Safety Authority (EFSA) to receive input from all interested parties on the draft scientific guidance for the preparation of applications on flavourings to be used in or on foods. The guidance document was prepared by the EFSA Panel on Food Additives and Flavourings (FAF), supported by the Working Group on Guidance Update on Flavourings, and endorsed for public consultation at the 29th plenary meeting of the FAF Panel, held on 30 March – 1 April 2022. The public consultation for this document was open from 25 April until 19 June 2022. On 25 May 2022, EFSA also organised a technical hearing with interested parties with the aim to present the content of the draft guidance document and to collect preliminary comments and input on its clarity and completeness ahead of the closing date of the public consultation. During the public consultation EFSA received written comments from 4 different interested parties. EFSA and its FAF Panel wish to thank all stakeholders for their contributions. The present report contains the comments received and explains the way they have been considered for the finalisation of the guidance on flavourings. The guidance was adopted at the FAF Panel plenary meeting on 8-10 November and published in the EFSA Journal.

Key words: food flavourings, guidance, public consultation

Requestor: EFSA

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1. Introduction

1.1. Background as provided by the requestor

In the European Union, flavourings are subject to Regulation (EC) No 1334/2008[1] on flavourings and certain food ingredients with flavouring properties for use in and on foods. This Regulation lays down among other elements the general requirements for the safe use of flavourings and defines different types of flavourings, amongst which the following categories are identified: flavouring substances, flavouring preparations, thermal process flavourings, flavour precursors, other flavourings, and source materials. It also sets out flavourings for which an evaluation and approval is required.

The flavourings for which an evaluation and approval are required are listed in Article 9 (a) - (f) of the Regulation (EC) No 1334/2008. Although Regulation (EC) No 1334/2008 specifies those flavourings for which an evaluation and an approval prior to being placed on the market is not required according to its Article 8 (a) – (d), under certain circumstances, the European Food Safety Authority (EFSA) can also be asked to evaluate these flavourings.

EFSA was asked in 2009 to provide the Commission with a document concerning the data required for the risk assessment of flavourings laying down amongst other aspects, the content, drafting and presentation of the application for the evaluation and authorisation of flavourings.

EFSA prepared the guidance in response to this request, which is essentially based on the two following main EFSA documents:

- Guidance on the data required for the risk assessment of flavourings to be used in or on foods of the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA CEF Panel, 2010)

and

- Proposed template to be used in drafting scientific opinions on flavouring substances (explanatory notes for guidance included) (EFSA, 2012).

EFSA is asked to update the above mentioned guidance documents and compile them in a single comprehensive document describing the data required for the risk assessment of new applications on flavourings submitted under Regulation (EC) No 1334/2008 and Regulation (EC) No 1331/2008[2] on the Common Authorisation Procedures for food additives, food enzymes and food flavourings and its implementing Commission Regulation (EC) No 234/2011[3]. The updated guidance is also expected to take into account the latest cross-sectional documents relevant for flavouring evaluations that have been developed by EFSA since the adoption of the current guidance documents on the risk assessment of flavourings.

Regulatory aspects

EFSA should also take into account the legislation on Food for Special Groups, Regulation (EU) 609/2013[4] in particular as regards infants and young children as well as the EFSA Scientific Committee's

[1] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34–50.

[2] Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 354, 31.12.2008, p. 1–6.

[3] Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 64, 11.3.2011, p. 15–24.

[4] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35–56.

guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017a) so that the updated guidance addresses possible use and consumption of flavourings by that population group.

Whenever possible and appropriate the updated EFSA guidance should be consistent with the relevant guidance documents on food additives, as the two areas are closely related, taking also into account their differences in legislative aspects and safety requirements and the fact that both food additives and food flavourings are assessed by the same EFSA panel, the FAF panel.

In preparing this updated guidance, EFSA should take into account Regulation (EC) No 178/2002[5] and Regulation (EC) No 1331/2008, as amended by Regulation (EU) No 2019/1381[6] of the European Parliament and of the Council on the transparency and sustainability of the EU risk assessment in the food chain as well as Commission Regulation 234/2011 as amended by Commission Implementing Regulation (EU) 2020/1823[7]. Consistency should be ensured with other sectors where similar updates will be done.

Scientific and technical developments

When updating the guidance, EFSA should take into account the scientific and technical progress. For example, there have been significant developments in considerations on Threshold of Toxicological Concern related to flavourings. The so-called JECFA procedure for the assessment of flavouring substances has been modified at the 82nd JECFA meeting (JECFA, 2016). New methods for the dietary exposure assessment, as well as for the acceptability of the read across are now available for flavourings. New developments in the assessment of genotoxicity of substances and mixtures should be considered, together with new and/or updated OECD test guidelines.

There have also been developments in the techniques/approaches applied in the manufacturing of food flavourings and improvements in the performances of the analytical methods, which allow an in-depth characterisation of the final product, and its source materials. It also allows defining more accurately specifications for the material of commerce.

In addition, EFSA has gained very substantial experience as regards the safety assessment of flavouring substances and other flavourings both, on so-called existing flavouring substances under the old evaluation program and new flavouring substances.

Concerning dietary exposure assessment, the updated guidance should take into account that a number of substances and products can be, in addition to their use as flavourings, also be used in foods for other purposes. For example, they can be used, as food additives (e.g. sorbates, neohesperidin), food ingredients with physiological effects (e.g. caffeine), and food contact materials (e.g. ethyl acrylate), or may be related to plant protection products or cosmetics.

In the dietary exposure assessment specific consideration should be given to infants and young children, representing a particular vulnerable part of the population. Where relevant, this should reflect not only the consumption of foods intended for infants and young children defined in Regulation (EU) 609/2013, but also foods typically consumed by adults that may be consumed by infants and young children from a certain age.

The updated guidance should also take into consideration the scientific guidance from the EFSA Scientific Committee applicable for the assessment of substances intentionally added to foods intended for use by infants below 16 weeks of age.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[6] 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 and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC. OJ L 231, 6.9.2019, p. 1–28.

[7] Commission Implementing Regulation (EU) 2020/1823 of 2 December 2020 amending Regulation (EU) No 234/2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 406, 3.12.2020, p. 43–50.

Furthermore, EFSA should also take into account that the food categories used for regulatory purposes in flavourings are those mentioned in Part D of Annex II of Regulation 1333/2008[8] on food additives. This may be particularly relevant when carrying out more refined dietary exposure assessments based on actual use levels and detailed food consumption data across different population groups and scenarios.

Besides the safety aspects derived from the general requirements for flavourings, the protection of the environment should also be considered, where appropriate. In particular, experience shows that persistence in the environment may be a relevant issue for some products.

Smoke flavourings

Although smoke flavourings are a category of flavourings covered by Regulation 1334/2008, there are specific provisions, specific conditions of use and also specific EFSA guidance documents for this category of flavourings. The guidance on flavourings should therefore consider the specific guidance for smoke flavourings to ensure consistency but not to address their safety requirements as these are covered by specific guidance documents developed by EFSA (EFSA, 2021; EFSA FAF Panel, 2021).

1.2. Terms of Reference as provided by the requestor

In accordance with Article 29 of Regulation (EC) No 178/2002, the Commission requests EFSA to update the Guidance on the data required for the risk assessment of applications on flavourings to be used in or on foods submitted under Regulation (EC) No 1331/2008.

It should take into account the information provided in the background and the experience gained with the assessment of the currently authorised flavourings. Where possible, EFSA should ensure consistency with guidance documents in other sectors.

The Commission requests EFSA to carry out this updating within 18 months from the receipt of this letter.

2. Data and Methodologies

2.1. Data

In line with its policy on openness and transparency, EFSA engages in public consultations on key issues in order to receive comments on its work from the scientific community and stakeholders.

Accordingly, the draft guidance on the data required for the risk assessment of flavourings to be used in or on foods was published on EFSA's website for comments. The online public consultation was made available, after the endorsement of the draft document, for the period from 25 April 2022 to 19 June 2022.

During the public consultation EFSA also organised a technical hearing with interested parties, which was held on 25 May 2022 as virtual meeting (a post-meeting announcement for this event is available here), with the aim to present the content of the draft guidance document and to collect preliminary comments and input on its clarity and completeness ahead of the closing date of the public consultation.

This technical report presents the comments received on the draft guidance during the public consultation and the technical hearing and it provides responses to these comments explaining how they have been considered in the finalisation of the guidance. The FAF Panel, supported by the Working Group on Guidance Update on Flavourings, prepared an updated version of the guidance, taking into account the comments received. The guidance document was discussed and endorsed at the 32nd FAF Plenary meeting on 9 November 2022 and is published in the EFSA Journal (EFSA FAF Panel, 2022).

[8] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.

2.2. Methodologies

All the comments received were tabulated with reference to their author(s) and the section of the draft guidance to which they refer. References to sections and appendices in the comments or the answers to the comments refer to the draft guidance as published at the time of the consultation https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l7U0000011Yej/pc0168

Four interested parties submitted 76 comments via the EU survey online tool. The comments submitted formally on behalf of an organisation appear with the name of that organisation. Table 1 provides an overview of the interested parties that have submitted comments during the public consultation.

Table 1: Comments received on the draft guidance per interested party

Interested party	Category [(a)]	Country
Sciensano	Public research institutes	BE
EFFA (European Flavour Association)	International organisation	BE
International Organization of the Flavor Industry (IOFI)	International organisation	US
Specialised Nutrition Europe (SNE)	International organisation	BE

(a): As specified by the commenter.

3. Comments received and responses from EFSA

The comments received were duly evaluated by the FAF Panel, supported by the Working Group on Guidance Update on Flavourings, and wherever appropriate, taken into account in the finalisation of the guidance document. Tables 2 and 3 provide a detailed list with all comments as received from interested parties from the public consultation and during the technical hearing, together with EFSA responses and explanations how the comments were considered for the finalisation of the guidance document.

Table 2: Full list of comments received from the public consultation on the draft scientific guidance on the data required for the risk assessment of flavourings to be used in or on foods and responses from EFSA (the line numbers mentioned in the answers refer to those of the draft guidance submitted for public consultation, available at this link.

#	Section of the Guidance	Name of affiliation/organisation and/or First Name, Last Name	Comment	EFSA Response
1	**1.1.5 Reaction and fate in foods**	Séverine Goscinny (Sciensano) - Belgium	Page 14, 1.1.5 Reaction and fate in foods: Concerning the analytical method the applicant should provide, it is not specified if the method should be validated. If the method provided should be validated, then to have consistent data, maybe the Guidance document should specify under which validation criteria the analytical method performance should be evaluated (e.g. The Commission decision of 14 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results (2002/657/EC)). Furthermore, it is not specified to provide the flavouring substance fate in the final food product. The applicant could consider that its flavouring substance will only be used in food (e.g. strawberry syrup), which is used as a raw ingredient in complex dishes (e.g. ice creams, cakes, dairy products). In line 595, it is mentioned "respective foods", but this is quite vague. How to ensure the whole food spectrum will be taken into consideration?	- "A method" has been replaced by "Validated methods" in line 584 of the draft guidance. - "categories" has been deleted in line 585 of the draft guidance[9]. - "respective foods" has been replaced by "intended final foods" in line 595 of the draft guidance.

[9] The line numbers mentioned in the answers refer to those of the draft guidance submitted for public consultation, available at this link.

2	**3.1 Data needed for the assessment of the dietary exposure to food flavourings**		Page 24, 3.1 Data needed for the assessment of the dietary exposure to food flavourings, Lines 990-994: Next to the food categories listed in Annex II of Regulation (EC) No 1334/2008, applicants are encouraged to use also FoodEx classification. This is a very useful exercise. Nevertheless, it would be useful for any further assessment whether this suggested food classification was followed by EFSA or whether the applicant has accepted the correction suggested by EFSA in case of misalliance of the classifications. In conclusion, the final classification of the food in which a new flavouring is suggested should be known. For post-market monitoring (analysis and exposure assessment), the compound food samples will be purchased and analysed as such. The concentration will be for the entire food, and back calculating the concentration per ingredient is complex and not always possible. Therefore, using the FAIM tool for these samples is usually not possible. The DietEx tool will probably have to be used to consider the results for compound food samples. Exposure results will be difficult to compare. Would you have any recommendations for post-market monitoring on that issue?	Qualitative and quantitative information on the use levels of flavourings in the ingredients of a composite food and the respective recipe information would be required in order to perform the exposure assessment as part of post market monitoring. No detailed information on this issue is provided in this document, as post market monitoring falls outside the scope of this guidance.

3	**3.3 Exposure assessment**		Page 25, 3.3 Exposure assessment: It could be recommended to provide the data when the exposure assessment was performed using any of the EFSA tools (FAIM-obligatory or DietEx-optional). By providing the date of consultation, it will help the transparency and conclusion of knowing which consumption data has been used. This is to be deduced by the version of the consumption data available at that moment. Also the (suggested) food categorisation should be seen from the analysis. In the lines 1068-1069 it is only stipulated that dietary exposure results should be reported whereas we consider that it may be suggested what could be reported (date, food categorisation and exposure results).	The text has been modified as follows (lines 1068-1069 of the draft guidance): "Dietary exposure results obtained with the tools, including the food categories considered and the date of the assessment, should be included in the dossier submitted by applicants. Data should be provided by exporting each spreadsheet in the tool to an excel file (an excel file for each tool, i.e. FAIM and DietEx)."

4	**3.3.3 Exposure assessment to the food flavouring coming from other sources**		It is stipulated applicants should provide exposure estimates of the food flavouring substances for each intended dietary source. Additionally, exposure assessment from other dietary sources and also non-dietary sources should be provided. Whereas it is stipulated in the document that aggregate exposure will be performed by EFSA on case-by-case basis for oral routes only (lines 1150-1151) it is also said that non-oral sources will not be included. However, the attempts to consolidate the hazard/safety assessment of the substances across Europe may also be anticipated that some of the flavourings would become a part of such an aligned approach. In order to anticipate this and additional recommendation that applicant provides also any notion of exposure assessment of that flavouring by different agencies/instances can be added.	The following sentence has been inserted into the text, in line 1150 of the draft guidance document: "If information is available on exposure assessments resulting from non-oral sources (e.g., 'e-cigarettes') performed by other bodies, this may also be provided."
5	**Appendix B - Tiered toxicity testing of flavouring substances**		We fully agree that the assessment of genotoxicity and toxicokinetics are the logical elements of TIER I. We also agree with the approach and studies comprised in TIER III. However, we identified several issues in the way TIER II is designed. First of all, the criterion of "negligible absorption" is poorly defined (line 1663). The toxicokinetics study (OECD TG 417) will provide information about the absorption, but what is "negligible"? Is it zero, i.e. below limit of detection? Is there a threshold (limit of quantification, 1%, 5%, 10%?)? Without further clarifications, the "negligible absorption" criterion does not provide a clear way forward, especially in the case of complex mixtures for which an ADME study is not a default requirement. Moreover, the guidance creates confusion by stating on line 1662 and following "If, the absorption of the flavouring substance is considered negligible, and in case only local effects are observed in the subchronic oral toxicity study (i.e. in the gastrointestinal tract), or when systemic effects are directly related to such local effects	- The assessment of negligible absorption has to consider both the efficiency of absorption plus the dosage and therefore this would have to be considered on a case-by-case basis and no generic cut-off value for negligible absorption can be given. However, some additional guidance on how to evaluate relevance of absorption has now been added to the guidance document in section "4.5.1.3.1 Toxicokinetics (absorption, distribution,

			(e.g. weight loss as a result of malabsorption of nutrients from the gastrointestinal tract or dehydration), an MOE?" and on line 1675 and following "On the other hand, when data indicate that there will be a relevant absorption of the substance, or when despite negligible absorption still systemic effects (i.e. other than in the gastrointestinal tract) are observed, more extensive toxicity data should be generated by conducting an Extended One Generation Reproductive Toxicity study (EOGRTS), according to OECD TG 443 (OECD, 2018)." How can the underlined elements be known with only having the information obtained in TIER I at disposal? We consider this as a sub-optimal situation considering that a choice is required to be made between the conduct of a 90-day repeated dose toxicity study (OECD 408, at least 80 animals) and an extended one generation reproductive toxicity study (EOGRTS, OECD 443).	metabolism, excretion (ADME))". - The decision whether only a 90-day study will suffice, without the need for EOGRTS, is not solely based on the information from Tier I, but can only be made in Tier II, after completion of the 90-day study (see Appendix C - Tier II Scheme A). For clarification of the procedure the request for ADME studies has been moved from Tier I to Tier II – Scheme A and has been described in the revised text (see answer to comment #33). - For flavourings that are complex mixtures (excluding flavour precursors), absorption would have to be assumed since a lack of absorption of the entire mixture cannot be demonstrated. Therefore, for such mixtures the TTC approach and the data-requirements and lines–of–thought under Tier I and II (see Appendix C – Tier II Scheme A) are not applicable and (apart from genotoxicity) only the data requirements and lines–of–thought as depicted in Appendix C - Tier

				II Scheme B and Tier III are applicable.
6	**Abstract**	Sean Taylor (International Organization of the Flavor Industry (IOFI)) - Belgium	19 June 2022 TO: EFSA Secretariat SUBJECT: Comments from the International Organization of the Flavor Industry (IOFI) regarding the EFSA Scientific Committee Draft Guidance on Flavourings Dear EFSA Secretariat, The International Organization of the Flavor Industry (IOFI) is the global trade association that works in service of our members to promote sound science and the safe use of flavourings. IOFI works with internationally recognized safety assessment bodies to ensure the industry meets their needs for sound scientific data. For a number of years, we have worked with our member association the European Flavour Association (EFFA), to provide in vitro and in vivo genotoxicity, toxicity and other data in response to requests from the EFSA Panels that evaluate flavouring substances. We are now pleased to provide comments in response to the 1 April 2022 Draft Guidance on Flavourings. Where possible, we have included references or links to references immediately after the paragraph in which they are cited. Our specific comments are lengthy, and so we have attached them in one compendium file to the abstract, and then also uploaded individual pdfs for each main section[10]. We are resubmitting these comments, as it was not clear to us that our comments were posted to the EFSA Portal. Apologies for any duplication.	Noted.

[10] The comments included in the pdf files by IOFI have been extracted and included in this table.

7	**General principles**		General Comments on the Guidance: IOFI advances the global trade of safe, responsibly produced flavourings that respect the environment and enrich the lives of consumers. This is achieved through state-of-the-art and reliable science to support the safety assessments of flavouring ingredients. Additionally, IOFI and its members have endeavoured to provide all the data necessary for risk assessors to pursue and complete these safety assessments. However, the significant increase in animal testing that is a major element of this draft scientific guidance is not in step with current advances in toxicology and risk assessment. IOFI suggests that EFSA, perhaps both the FAF Panel and the Scientific Committee, should re-evaluate the necessity of performing and ultimately submitting data from animal-intensive experiments. IOFI further notes that numerous recent concept papers have been commissioned by EFSA that describe frameworks to embrace alternatives to animal testing, including the application of so-called "new approach methods" (EFSA, 2022a, 2022b, Escher et al., 2022). https://www.efsa.europa.eu/en/supporting/pub/e200502; https://www.efsa.europa.eu/en/supporting/pub/en-7341; https://www.efsa.europa.eu/en/supporting/pub/e200507	The mentioned external reports under EFSA contract provide recommendations for further work to endorse New Approach Methodologies (NAMs) in chemical risk assessment, but do not really specify how NAMs at the moment can already be implemented. NAMs may be used as supporting information, but cannot systematically replace the more conventional way of toxicological risk assessment (see Rovida et al, 2020).
8	**1.1.1 Identity**		**Page 10, Lines 402-403**: *"Flavouring substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number, etc.)"* IOFI understands the need for appropriate identification of all configurations of flavouring substances; however, not all isomers have individual registry numbers, such as CAS, assigned to them. It would be helpful for EFSA to provide guidance as to how to approach such instances.	On page 10, line 403 of the draft guidance, the following sentence has been inserted: „In case individual registry numbers are not available, the name of the flavouring substance must provide an unequivocal assignment of the configuration.

9	**1.1.1 Identity**		**Page 10, Lines 404-409**: "*Physical properties: appearance, boiling point (for liquids), melting point (for solids), refractive index (for liquids), specific gravity (for liquids), solubility in water and other solvents relevant for use of the flavouring substance in foods and in toxicity/genotoxicity tests; influence of pH on solubility; octanol-water partition coefficient (Ko/w), vapour pressure. Study reports or other sources from which these data were taken should be included in the dossier."* IOFI would appreciate clarification on the possible use of predictive values as they are accepted through other regulatory frameworks.	"Other sources" could also include predictive values; however, this might significantly increase the related uncertainty. At any rate, the need for using predictive rather than experimentally determined values would have to be justified on a case-by-case basis.
10	**1.1.1 Identity**		**Page 10, Lines 415-418:** *"Sensory properties: qualitative (e.g. odour or taste) and quantitative (e.g. odour or taste thresholds) description of the sensory properties; or provision of data substantiating the function of the flavouring substance as modifier of odour and/or taste (e.g. concentration ranges needed)."* Could EFSA clarify the significance of requesting quantitative sensory data? IOFI notes that providing quantitative sensory information for certain flavour types poses a significant challenge. In our view, qualitative attributes and quantitative intensity / frequency description of the sensory properties would likely be sufficient for substantiating the function and would reduce the significant burden that quantitative testing incurs.	On page 10, lines 415-416 of the draft guidance, the text has been changed as follows: "Sensory properties: qualitative (odour/taste) and quantitative (odour/ taste thresholds or intensity/frequency descriptions of the sensory properties);"
11	**1.1.2 Manufacturing process**		**Page 10, Lines 421-425:** *"The information on the manufacturing should particularly focus on the potential of the applied procedure to result in the presence of by-products, impurities or contaminants in the final flavouring substance. Therefore, for each type of manufacturing process a detailed description of the employed procedure to obtain the flavouring substance should be provided covering the following information requirements."* To improve clarity, IOFI suggests better defining the terms "by-product" "impurity" and "contaminant," as these would appear to either be redundant or have overlapping meaning.	Page 10, line 422: These terms may be partly overlapping. However, considering the broad array of possible production methods, a differentiation of potentially present substances other than the target flavouring substance seems appropriate. The terms have been clarified by adding examples: „by-products (e.g. substances formed in the course of chemical synthesis),

			IOFI also suggests that it would be important to specify identify/quantitation limits on by-products, impurities, and contaminants that do not have to be considered.	impurities (e.g. co-extracted substances) or contaminants (e.g. heavy metals)". Regarding the specification of identification/quantification limits, see response to comment #16
12	**1.1.2.1 Flavouring substances obtained by synthesis Enzyme - catalysed**		**Page 11, Lines 442-446:** *"Confirmation that the involved enzyme(s) has/have been assessed or is/are being assessed by EFSA in the framework of Regulation (EC) No 1332/2008 on food enzymes, the relevant EFSA question number(s) linked to the corresponding application for the food enzyme and the respective EFSA scientific opinion, if available, should be submitted."* IOFI would appreciate clarification regarding enzyme-catalyzed synthesis. Do enzymes need to be approved prior to use in flavour or can approval process occur simultaneously with the new flavour evaluation? If assessments are ongoing and concerns are raised regarding the enzymes, how does the flavour evaluation process proceed?	When a food enzyme is used in the manufacturing process of a flavouring, EFSA cannot conclude on the safety of the flavouring without having completed the assessment of the food enzyme. In case the assessment of the food enzyme is still ongoing, EFSA can request the extension of the deadline for the evaluation of the food flavouring, in line with Article 10 of Regulation (EC) No 1331/2008. At the same time the risk assessment of the enzyme in question will be prioritised by EFSA. If the assessment of the enzyme cannot be completed within a reasonable time (e.g. up to 1 year) due to the missing data in the enzyme application, EFSA could i) issue an inconclusive opinion on the flavouring or ii) in the absence of other issues leading to inconclusive/ negative opinion on the flavouring, EFSA could conclude on the safety of the flavouring (e.g. based on the data demonstrating that the enzyme is not present in flavouring) without completing the safety assessment of the enzyme under Regulation

				1332/2008[11] and then complete the opinion on the flavouring.
13	**1.1.2.1 Flavouring substances obtained by synthesis Enzyme - catalysed**		**Page 11, Line 447:** *"Demonstration of the inactivation and/or removal of the enzyme."* The Draft Guidance requests an outline of detailed enzyme involvement and assessment in the synthesis process. If the demonstration of inactivity or removal on the enzyme can be displayed, would the need for certain attributes be exempt? Further, for chemically-defined flavouring substances of high purity (>95%) that are produced in a final step that would involve chromatography, distillation or crystallization, the likelihood of carryover of the enzyme would be vanishingly low. Under these circumstances, IOFI suggests that the enzyme would not need to be assessed and the removal/inactivation of the enzyme does not need to be considered.	Please refer to answer to comment #12.
14	**1.1.2.1 Flavouring substances obtained by synthesis Microorganism - catalysed**		**Page 11, Lines 460-462***: "A list of the raw materials contributing to the medium and a compilation of the reagents used for process control is required. These should be the actual materials used; an indicative list will not be accepted."* IOFI believes this is a limiting requirement that would preclude the opportunity for improvement or alterations of production as needed. The capacity for method development would allow for flavouring substances to be improved upon in the areas of manufacture and safety.	This is also requested in the guidance document on food enzymes and does not preclude the opportunity for improvement or alterations of production as needed. In case, a future change in raw materials would result in a composition of the final flavouring substance that is not complying with the specification of the authorised material, this would trigger the need for a new application.

[11] Regulation (EC) No 1332/2008 of the European Parliament and of the Council of 16 December 2008 on food enzymes and amending Council Directive 83/417/EEC, Council Regulation (EC) No 1493/1999, Directive 2000/13/EC, Council Directive 2001/112/EC and Regulation (EC) No 258/97 (Text with EEA relevance) OJ L 354, 31.12.2008, p. 7–15.

15	**1.1.3 Compositional data (purity)**		**Page 13, Lines 553-554:** *"Purity assay value of the flavouring substance. Normally, the minimum purity should be at least 95%."* IOFI requests clarification on specific evaluations that need to occur and the lowest reporting for unknown or variable composition or biological substances, as compositional data is not always available.	See answer to comment #16.
16	**1.1.3 Compositional data (impurities)**		**Page 13, Lines 555-557:** *"Identification and quantification of chemical and biological impurities. The analysis should particularly focus on those impurities to be expected in the light of the employed manufacturing process."* IOFI requests elaboration on the ambiguity of identification and quantification for chemical and biological impurities. IOFI believes that outlining the expectation of analytical methods will be of value for the applicants and for EFSA Panels to mitigate confusion in the application review process. Without a more explicit description of identification and quantification of chemical and biological impurities, there could be confusion regarding quantification of impurities.	Considering the broad array of potential manufacturing processes and, it would virtually be impossible to come up with an exhaustive list of impurities that should be analysed and with a prescriptive set of analytical methods that should be applied. As stated in the guidance document (lines 557-558 of the draft guidance), "for the identification and quantification of the impurities state-of-the art techniques should be applied." For further clarification, the following sentence has been added in l. 560: "Limits of detection and limits of quantification generally established and accepted for these techniques should apply."

17	**1.1.3 Compositional data (impurities)**		**Page 14, Lines 561-562:** *"Unequivocal chemical identifications (names and CAS numbers) of the individual impurities should be provided."* IOFI notes that not all impurities will have CAS numbers assigned. Could EFSA clarify to what extent providing chemical names only will be considered acceptable? Further, IOFI understands from its members that for some types of impurities (e.g., sesquiterpenes) that are present at very low concentration, it will be highly unlikely that the structure can be definitively identified. Instead, it may only be possible to allocate the substance to a likely chemical class or assign a molecular weight. IOFI seeks clarification as to whether this could be regarded as sufficient for a very minor impurity.	- "If available" will be inserted before CAS numbers. - If it is only possible to allocate the substance to a likely chemical class or to only assign a molecular weight, the impurity can only be considered as "tentatively identified" (see lines 667-677 of the draft guidance).
18	**1.1.3 Compositional data (batch-to-batch variability)**		**Page 14, Lines 569-571:** *"Demonstration of batch-to-batch variability. Compositional data should be provided for at least five batches of the flavouring substance produced from different production runs. Information on how these batches were selected should be provided."* IOFI acknowledges the merit of batch-to-batch consistency, however, we would appreciate some clarification as to why the number of batches was increased from three to five. While the demonstration of batch-to-batch variability is of utmost importance, IOFI strongly encourages the reconsideration of the increase of required batches as it is not feasible to produce five batches prior to the submission of a new application, as the vast majority of flavourings are initially produced in a very small number of lab scale batches, and it would only be after the successful introduction of the flavouring on the EU market that multiple batches would be produced. Additionally, even for successfully introduced flavourings, in some cases the production may only occur on a biannual or annual basis. For flavourings with a very low flavour threshold (detectable and used at very low levels, the annual production may only be gram quantities produced by a single supplier.	Data on five batches from different runs provide a statistically sound basis to judge whether the applicant is able to produce the flavouring in a reproducible way. Therefore, compositional data from five production batches are also requested in the guidance documents on food additives, novel foods and smoke flavourings. In case, the intervals between production runs are extremely long, data on fewer batches (at least three) might be considered acceptable; however, this would have to be justified on a case-by-case basis.

19	**1.1.4 Stability**		**Page 14, Lines 574-576:** *"Demonstration of the physicochemical and chemical stability of the flavouring substance upon storage of the material of commerce under conditions reflecting the intended shelf-life,"* The Draft Guidance outlines the "assessment of the loss of the flavouring substances" and the "investigation of the effects of storage conditions." IOFI notes that there are not, to our knowledge, industry-wide approaches to measure this, and would therefore suggest that standardized methodologies should first be developed/ published prior to requiring such data.	- In order to assess the loss of a flavouring substance upon storage no specific methods other than those used to identify/quantify the flavouring substance and potential impurities/by-products are needed. - As stated in the guidance document, stability experiments may be performed under real-time conditions or under respective, accelerated conditions ("forced ageing"); for these experiments, generally accepted approaches are available.
20	**1.1.5 Reaction and Fate in Food**		**Page 14, Lines 584-585:** *"A method should be provided for the qualitative and quantitative analysis of the flavouring substance in the intended food categories."* IOFI would appreciate clarification on the potential triggers that would require such testing, or if this is required for all substances. IOFI understands the potential value of analysis for the intended food categories but holds concern that this requirement is extremely challenging, given that some flavourings are utilized in many, many food categories. Additionally, different foods within the same food category (and in some cases food subcategory) are likely to react with flavouring ingredients in drastically different ways. While IOFI recognizes that there are standard methodologies that can broadly be applicable, this requirement poses too many variables that render it inequitable. Finally, it is important to recognize that many of the flavouring substances in use by the industry are naturally occurring and thus inherently present in foods, so IOFI seeks clarification as to the value of such testing methods.	- For monitoring purposes, methods for the qualitative and quantitative analysis of the flavouring substance in the intended food categories has to be provided for all flavouring substances. - As stated in lines 595-597 of the draft guidance document, the guidance document offers the possibility to perform analyses in model systems mimicking the respective foods; justifications for the suitability of such models must be given.

21	**1.1.5 Reaction and Fate in Food**		**Page 14, Line 593-594:** "*Investigation of the nature of interactions and reactions of the flavouring substance with constituents of the foods to which the flavouring substance has been added.*" Does this requirement pertain to all flavourings? Clarification on the circumstances for these studies would be beneficial, as determining all the possible interactions that a flavouring substance may have with the multiple constituents also present in the numerous foods in which it is formulated represents an immense and unrealistic task. In addition, as noted above, the majority of flavouring compounds are naturally occurring and thus inherently present in non-flavoured food. Thus consumers are already exposed to them. Flavours are for instance added to food to compensate for the losses that occur during food processing. IOFI therefore suggests EFSA provide guidance on the scope of this requirement and to consider its applicability.	- This requirement pertains to all flavouring substances. As stated in lines 595-597 of the guidance document, experiments may be performed with the respective foods under real-time conditions or in model systems mimicking the foods; justifications for the suitability of such model systems must be given. - The term "investigation of …" has been replaced by "Information on …". As stated newly in the document: "Such information may encompass new experimental data with the flavouring substance, as well as existing literature data on structurally related substances."
22	**1.2 Flavouring Preparations** **1.2.1 Identity**		**Page 15, Lines 619-621:** *"For a flavouring preparation of which individual components are identified the complete list of identity parameters as listed in section 1.1.1 should be provided for each identified component."* IOFI's understanding of this sentence is that for complex mixtures, with this new guidance EFSA now requires that every component must now have a full identification done, including not only the chemical structure but a full description of physical and chemical properties. For some identified components, for which such data are already available, this would not be difficult. However, IOFI notes that many components that are present only at very low concentration can now be identified in flavouring preparations using analytical methods. For these components, the chemical and physical property determination would require substantially more material than would be present within the preparation. In some cases, this would then require an applicant to carry out a separate synthesis to be able to fully collect the identity parameter	- The requirements listed under the first seven indents in section 1.1.1 (up to line 403 in the draft guidance document) are sufficient.

			information. IOFI questions whether this is a realistic expectation, and requests that EFSA reconsider this and provide some clear concentration cut-off below which such additional identity parameter information would not be needed.	
23	**1.2.3 Compositional data**		**Page 15, Line 650:** *"The components of the flavouring preparation should be characterised as fully as possible."* This is related to the comment from above (1.1.3 Compositional Data). IOFI believes that it would be helpful for the Draft Guidance to more specifically indicate the level of characterization that is expected.	- The different levels of "identification" of volatile constituents, "characterisation" of the non-volatile fraction, and "information" to be provided on the unidentified fraction are outlined in detail in lines 654-706 of the draft guidance. - See also answer to comment #16.
24	**1.2.3.4 Batch to Batch variability**		Please refer to 1.1.3 for IOFI commentary regarding batch-to-batch variability for this and subsequent sections alike.	See answer to comment #18.
25	**1.2.4 Stability**		Please refer to 1.1.4 for IOFI commentary regarding stability for this and subsequent sections alike.	See answer to comment #19.
26	**1.2.5 Reaction and Fate in Food**		Please refer to 1.1.5 for IOFI commentary regarding reaction and fate in food for this and subsequent sections alike.	See answer to comment #20.
27	**1.3 Thermal Process Flavours** **1.3.1 Identity**		Please refer to 1.2.1 for IOFI commentary regarding identity for this and subsequent sections alike.	See answer to comment #21.

28	**3.3.1. Dietary exposure assessment**		**Page 25, Lines 1041- 1046**: *"Applicants should provide dietary exposure estimates of a food flavouring by means of the Food Additive Intake Model (FAIM). This model uses food consumption data from the Comprehensive Database to estimate the diet exposure based on the maximum or typical use levels …* *(this tool is) expected to overestimate the actual dietary exposure to food flavourings."* **Page 26, Lines 1068- 1073:** *"Dietary exposure results obtained with the tools should be included in the dossier submitted by applicants. EFSA may refine the exposure assessment when the estimates provided by applicants result in an insufficient margin of exposure (MOE) (see Section 4.5.1.5). Such a refined exposure assessment will consider all submitted use levels (both maximum and typical levels, EFSA ANS Panel, 2017) and aims at estimating the dietary exposure as realistically as possible based on the provided data. The refined dietary exposure assessment will be performed using the food categories in Annex II, Part D, of Regulation (EC) No 1333/2008, or FoodEx2 if the level of detail is sufficient. EFSA may use additional information, such as from the facets within FoodEx2 or from Mintel's GNPD,20 to further refine the dietary exposure assessment. EFSA will consider also any additional information (such as market share* *data) provided by applicants to refine the dietary exposure assessment; however, the Panel does not consider it mandatory to submit this information."* It is well recognized that unlike the majority of food additives that have broad applicability for functional purposes across food products, flavourings are used to impart specific flavouring profiles and are very seldomly used broadly in food categories (e.g., a blueberry yogurt would include a flavouring that imparts a blueberry note, but a peach yogurt would not include a blueberry note flavouring). Given that (1) the draft guidance acknowledges that *"[this tool is] expected to overestimate the actual dietary exposure to food flavourings"* and (2) the use of the maximum use	- The applicant could refine the exposure estimates by considering typical use levels, if applicable, as well as by using the DietEx tool. EFSA may further refine the exposure assessment during the risk assessment when the estimates provided by the applicants result in an insufficient margin of exposure (MOE). This refinement would include the use of FoodEx2 codes at the level of individual foods for all foods. Facets can also be used to further select the relevant foods containing the flavouring/flavouring substance. A probabilistic assessment of the exposure is not possible as the data required for such an assessment will not be available. For example, information on % market share would be required for such an assessment, as well as occurrence levels of the flavouring in each single brand and product variety. This type of information does not exist at the pre-market stage when the application/evaluation takes place.

			level, which for flavourings refers to an unusual use of the flavouring, this approach may exaggerate dietary exposure by up to 10000X fold. As these overestimates may also trigger additional animal toxicity testing requirements resulting in the use of >1500 animals required for that toxicity testing, additional options for refined exposure assessments (e.g., incorporation of probability of addition as included as the approach for refined exposure to flavourings in the Flavours Additives and Food Contact Material Exposure Task (FACET) program (Mistura et al., 2013), should be prioritized for inclusion in the guidance. This is also acknowledged in Ioannidou et al., 2021, which notes: *"Estimates of dietary exposure from the tools (i.e. FAIM/FoodEx2) described in this paper assume that a food ingredient or chemical hazard is present in all foods within food categories included in the exposure assessment. In the case of food additives this is a conservative assumption (Gilsenan et al., 2002). Food ingredient databases and databases such as Mintel's global new products database (GNPD) provide information on the use of food additives based on information declared on food labels (Gilsenan et al., 2002, Diouf et al., 2014, Tennant and Bruyninckx, 2018)."*	
29	**3.3.1. Dietary exposure assessment**		However, the possibility of further refinement via occurrence data provided by the Mintel GNPD as noted in the draft Guidance is not available for flavourings since they are not included on product labels. Given this and as noted above, IOFI would support the inclusion of probabilistic modelling approaches that account for the probability of addition to a specific food or food category and thus provide more realistic exposure estimations. By refining exposure with these considerations, resources and animal testing can be more efficiently allocated for those flavourings that have broad usage across food products (and resultant high intakes).	- EFSA recognises that the labelling of flavourings does not provide information on the presence of individual flavourings. However, information from Mintel GNPD can still be useful to better characterise the exposure assessment and its uncertainty because it may provide information on whether the food is flavoured with a certain type of flavouring, e.g. strawberry.

				- Regarding the inclusion of probabilistic modelling, please refer to the answer to comment 28.
30	**3.3.1. Dietary exposure assessment**		IOFI requests clarification on the "use of additional information such as from the facets within FoodEx2" to refine exposure, as we are not clear as to how the facets will be used. Additionally, it is not clear that the Mintel GNPD would contain additional information that would be helpful to EFSA in its refinement approaches. IOFI would welcome this clarity as it is critical for the applicant to determine the exposure estimate to be used in the assessment to assess viability of the application prior to submission. Additionally, the earlier that it is possible to consider a refined exposure, the less likely that unwarranted animal testing could be launched.	- Facets provide additional information that can be added to the initial selected record. For example, in the food category "yogurt", a sequential use of facets, such as "flavoured" and "strawberry" would result in a refined selection of flavoured yogurts with strawberry. More information on facets can be found on the EFSA website, e.g. EFSA Catalogue browser User Guide (EFSA, 2019); the food classification and description system FoodEx2 (revision 2) (EFSA, 2015). These two references have been added in the guidance in section 3.3.1. In addition, the two relevant webinars are available on EFSA website at the following link: https://www.efsa.europa.eu/en/events/event/180926 - Regarding the use of Mintel GNPD, please refer to the answer to comment 29.

31	**3.3.3.1. Exposure assessment from dietary sources other than as food flavouring**		**Page 28, Lines 1145-1153**: *"Applicants should provide an exposure estimate of the food flavouring for each non-dietary source … e.g., e-cigarettes … should be considered for assessment of the exposure via these sources … EFSA will perform an aggregate exposure assessment based on the intake for the oral sources on a case-by-case basis … non-oral sources will not be included in this aggregate exposure estimate"* Please clarify if non-dietary sources of flavouring (e.g., e-cigarettes) will be included in the aggregated exposure estimate. It is unclear to IOFI as to why EFSA is asking for exposure estimates for non-dietary sources (like e-cigarettes) if non-oral sources will not be included in the aggregated exposure estimate. IOFI suggests to remove this requirement.	Non-dietary oral sources of flavouring (e.g., toothpaste) could be included in the aggregated exposure estimate, whereas non-dietary, non-oral sources (e.g., e-cigarettes) will not be included. The text of the guidance in section 3.3.3.2 has been modified to clarify this issue. - EFSA asks applicants to submit exposure estimates from non-oral, non-dietary sources (e.g., e-cigarettes) for completeness of information. However, this information will not be considered in the aggregated exposure assessment, because this would require route to route extrapolation which is connected to very high scientific uncertainty.
32	**4. Safety data (ADME)**		**Lines 1559-1575:** EFSA indicates that it requires ADME data for the following reasons: *"-ADME data may demonstrate the extent of absorption from the gastro-intestinal tract. If absorption is negligible, this may reduce the need for extensive toxicity testing. Regarding criteria to decide whether absorption is negligible, the guidance on food additives should be consulted (EFSA ANS Panel, 2012). An additional option could be to compare internal exposures from the use as flavouring with the internal TTCs as suggested by Partosch et al., 2015.* *-ADME data can inform on the extent of internal exposure and, in particular, on the extent of exposure of tissues relevant for genotoxicity testing, if needed.* *-ADME data will inform about the extent of metabolism and nature of metabolites, which may be helpful in the interpretation of observations on toxicity and genotoxicity and are important for the*	The purpose of ADME is not to demonstrate that exposure is below TTC, but rather to support the interpretation of genotoxicity studies, the environmental risk assessment and the read-across, if applied, and to assist in the interpretation of the general toxicity studies. As indicated in the response to comment #5, the ADME data are also relevant to estimate internal exposure which can be used to judge the need for an EOGRTS, for instance by comparison with internal TTC.

			evaluation of environmental risk. -ADME data will inform on the extent and rate of elimination from the circulation and the body, which could lead to a request for further studies (e.g. of longer duration than a 90-day oral toxicity study. *-ADME data are supportive for read-across, in particular when it is applied to predict in vivo endpoints. This applies especially when for a data-providing, structurally related substance also ADME data are available."* • In IOFI's opinion, none of these justifications to require ADME data would provide meaningful information regarding whether the exposure to a substance is <TTC, and thus the two triggers cited in the text and shown in Appendix B are not based on the outcome from an OECD 417 study.	
33	**4. Safety data (ADME)**		• As a general comment, IOFI notes that the guidance indicates that at Tier 1 it is necessary to determine that a flavouring substance is not genotoxic and to perform a study according to OECD TG 417. IOFI proposes that if the estimated exposure to a flavour substance is less than TTC for its structural class that an OECD 417 at Tier 1 should not be required. IOFI notes that the triggers to require Tier II testing are whether the substance is not genotoxic and if the exposure < TTC. Neither of those triggers would be dependent upon the data collected in an OECD 417 study. Additionally, IOFI would suggest to refine exposure at Tier 1 to consider whether the OECD 417 might be waived for the case that a substance does not require in vivo follow-up for genotoxicity.	The suggestion to move the request for OECD TG 417 to the stage where exposure is determined to be above TTC is reasonable, provided there is no need for ADME data following genotoxicity testing. Therefore, the data requirements for ADME studies have been moved to the beginning of Tier II Scheme A (see Appendix C – Tier II, Scheme A) and the text in the guidance has been adapted to this change. A need for ADME data for the purpose of environmental risk assessment has been addressed in section 4.6 (see footnote #28 of the revised guidance).

34	**4.3 Read-Across**		**Page 30, Lines 1214-1234:** "Read-across may provide a possibility to avoid unnecessary toxicity testing in experimental animals ... ADME studies are important to support or preclude read-across ... submission should include toxicokinetic studies (OECD TG 417)" • IOFI strongly encourages reconsidering the requirement for in vivo toxicokinetic data. While utilizing in vivo studies can be helpful, it would be more beneficial to use current in vitro and in silico methods for numerous reasons. In vitro studies, and potentially in silico ADME evaluations, reduces extensive animal testing. This is consistent with the Commission-directed formation of the European Centre for the Validation of Alternative Methods (ECVAM), which helps reduce, refine or replace (3Rs) the use of animals in testing through the development, validation, and international recognition of alternative methods.	EFSA supports the use of *in vitro* and *in silico* data on ADME. For instance, it is noted that QSAR data on metabolism is usefully employed in combination with *in silico* genotoxicity predictions. EFSA considers *in vitro/in silico* data on ADME as useful supplementary information. However, such data cannot as yet replace the ADME studies in vivo.
35	**4.3 Read-Across**		• Further, as stated by EFSA in 2012, applicants should "avoid unnecessary use of animals...and (should instead conduct) alternative validated methods for other endpoints in toxicity, involving fewer or no animals" (EFSA, 2012). IOFI believes that since this was published, alternatives to animal testing have continued to be become further advanced, refined and informative.	Indeed, advances have been made in this area and EFSA encourages further development and current use to supplement the *in vivo* studies that are required according to OECD guidelines. However, at present these methods are not considered adequate to fully replace conventional testing for risk assessment, yet. See also answer to comment #7.
36	**4.3 Read-Across**		• IOFI notes that pursuing in vivo studies may require the synthesis of radiolabelled versions of the flavouring. For some flavourings, the complicated synthetic routes that have been developed are only achievable in reasonable yields by the research and development experts within those companies. And unfortunately, flavouring production facilities are not generally set up to conduct radiolabelled syntheses.	EFSA notes the utility of heavy isotopes for studies as a replacement for radioisotopes. The limited availability of a labelled flavouring substance for testing cannot be accepted as an argument to waive testing.

37	**4.3 Read-Across**		• One effective way to ensure the goals of the 3Rs are achieved in this guidance is to limit required animal testing and embrace new approach methodologies (NAMs), which encompass all methods not based on an animal study. An abundance of work in this area is already underway with significant developments toward practical application and use in a regulatory environment. NAMs data can aid all read-across approaches by building up lines of evidence that contribute to the overall weight of evidence (Mahony et al., 2020). Work is already underway at the EU-ToxRisk project and elsewhere to incorporate NAMs data for read-across based on ECHA's Read Across Assessment Framework (RAAF), (ECHA, 2015), (Escher et al., 2019; Mahony et al., 2020, Rovida et al., 2020; Rovida et al., 2021). In one example based on ECHA's RAAF, data from NAMs was used to reduce the uncertainty for a read-across assignment for a group of triazole compounds (Pestana et al., 2021).	EFSA supports the use of NAMs as supportive information to supplement the required *in vivo* studies. Actually, as outlined in the guidance document (see section 4.3), read-across is considered acceptable, provided that the read-across is properly justified, and provided that the underlying studies are of acceptable quality and be made available for evaluation. However, EFSA recognises that a full replacement of toxicity studies by *in vitro* or *in silico* methods is not yet feasible, but supports further development of these, so as to increase their reliability in prediction of toxicity. See also answer to comment #7.
38	**4.3 Read-Across**		• For these reasons noted above, IOFI encourages EFSA FAF Panel to embrace data derived from NAMs for read-across and ensure that this guidance document is sufficiently conservative to allow for NAMs to be used to fulfil data requirements that would otherwise require in vivo data.	The value of NAMs is recognised particularly in helping to justify read across in combination with structural comparisons. *In vitro* studies e.g. on cellular or molecular responses are valuable for supportive evidence but currently are not sufficiently well

				developed to replace OECD guideline studies. See also answer to comments #7 and #37.
39	**4.3 Read-Across**		**Page 30, Lines 1215-1220:** *"In the past, grouping of flavouring substances in FGEs and application of read-across of toxicity and genotoxicity data has been extensively applied. In nearly all cases, this grouping or read-across has been done on the basis of simple comparison of two-dimensional representations of the chemical structures of the candidate and supporting flavouring substances. However, it is recognized that read-across on this basis alone may not be sufficiently robust (Patlewicz et al., 2013, ECHA, 2015)."* • IOFI feels strongly that grouping approaches should be maintained for flavourings. While IOFI agrees that chemical grouping and subsequent read-across requires more than simple structural similarity (Lines 1215-1220), that is already true in practice and clearly established in legislation. In EC No. 1565/2000 (European Commission, 2000), flavourings are divided amongst 34 chemical groups. The legislation notes: "As the first step of the evaluation programme the substances of the register should receive FL-numbers according to their chemical characteristics and should be distributed in groups of structurally related compounds which are expected to show some metabolic and biological behaviour in common."	The acceptance of read across in the guidance demonstrates that the philosophy behind the grouping approach has not been abandoned. However, when a substance is allocated to one of the existing (or maybe a completely new) group(s), the risk assessment for that substance should be based on robust data, which for many of the existing groups are not available. In addition, new toxicological endpoints are now recognised to be relevant for future submissions and for these new endpoints no data are available at all in the already evaluated groups. Furthermore, even when data are available, the read-across from the source substance to the target substance should be more robust than merely the fact that they are members of the same group. Please note that read across regarding genotoxicity of new flavouring substances will not be accepted. It will also not be accepted for genotoxicity or other endpoints for flavourings that are mixtures apart from identified components of such mixtures.

40	**4.3 Read-Across**		• This statement is echoed in the original EFSA guidance document (EFSA CEF Panel, 2010) noting these chemical groups are covered in flavouring group evaluations (FGEs) and should be evaluated using a group-based approach if sufficient structural/metabolic similarity is demonstrated for the candidate flavouring substance. The ECHA RAAF cited in this proposed draft guidance closely mirrors the original language of the European Commission legislation and associated 2010 guidance document suggesting substances should grouped based on common functional group, common biotransformation processes, physico-chemical and/or biological properties (ECHA, 2015), similar to the other cited literature (Patlewicz et al., 2013) **(Lines 1219-1220)** and the OECD guidance document on the grouping of chemicals (OECD, 2014).	See answers to comments #37-#39.
41	**4.3 Read-Across**		**Lines 1230-1247, pages 30-31:** "*Whilst structural similarity is the key tenet in developing a read-across grouping, a mechanistic justification and in particular toxicokinetic similarity are critical factors in ensuring acceptance. ADME studies are important to support or preclude read-across. These studies may demonstrate (dis)similarity of absorption and elimination routes, and (dis)similarities in metabolism. Therefore the submission should include toxicokinetics studies (OECD TG 417) that address at least extent of absorption, Cmax, Tmax and T1/2 of the substance in blood or plasma, identification of tissues in which the substance or its metabolites may accumulate, identification and quantification (up to at least 90% of an oral dose) of urinary, faecal and exhaled metabolites.*" • A number of in silico tools allow accurate predictions of specific ADME parameters without the need for in vivo experimental data (Daina et al., 2017; Dong et al., 2018; Madden et al., 2020; Madden et al., 2019; Shin et al., 2017; Xiong et al., 2021; Yang et al., 2018). Since most of	EFSA supports the use of such systems to provide supportive information relating to ADME. However currently EFSA considers such predictive ADME models as insufficiently well developed to be able to replace OECD TG 417. See also answer to comment #34.

			these tools were developed for small molecule drug candidates for the pharmaceutical industry, they are expected to yield reasonable results for flavourings as well (Laroche et al., 2018). Several of these tools adhere to the ECHA guidance on QSARs and grouping of chemicals (ECHA, 2008), and are able to predict ADME parameters typically included in OECD TG 417, including bioavailability, clearance rate, volume of distribution and half-life among others. In silico metabolic profilers are also available to both identify metabolites and/or evaluate metabolic pathways (Kuseva et al., 2021; Yordanova et al., 2019; Yordanova et al., 2021). • IOFI urges support for grouping of flavourings and recommends applicants for new flavourings to be able to use both in silico and/or existing experimental ADME data (where available) in place of in vivo ADME data as part of the read-across approach.	
42	**4.3 Read-Across**		**Lines 1253-1259, page 31:** "*A case that deserves special attention is when read-across does not indicate a hazard. Such a read across tends to be more meaningful if the target substance is part of a tested negative structural domain (i.e. populated by known and well-studied 'non-toxic' substances, supported by structural, physicochemical and/or functional parameters), as opposed to when the target substance is simply not a part of positive structural domain (in other words: similarity with proven 'non-toxicants' gives a robust indication of lack of toxicity; lack of similarity with proven toxicants is no ground to waive a concern for toxicity).*" • IOFI requests clarification what specific toxicity data (Lines 1253-1259) are expected of a target substance to be part of a tested negative structural domain. Specific examples as an appendix to this guidance would be useful.	The types of toxicity data needed have been described by inserting the following text in line 1255 of the draft guidance: "for which toxicological information is available on the endpoints for which read-across is intended". Read across may be applied for one or more different endpoints. However, in the end, all the endpoints should be compliant with the data requirements as prescribed in the guidance document and should be covered, either by read-across or by newly generated toxicological data.

				For this reason, the addition of an appendix with specific examples is not considered appropriate.
43	**4.3 Read-Across**		**Page 31, Lines 1279-1280:** "*read-across will not be accepted to waive the provision of experimental genotoxicity data for new flavouring substances*" • IOFI suggests that EFSA should reconsider this approach. Structure-activity relationships for the prediction of genotoxic potential are commonplace, and these relationships are defined by many of the same principles used for read-across. For flavourings in particular, with so many that are very closely related in structure and in many cases would have shared metabolites, the lack of acceptance of read-across approaches is surprising. IOFI feels that it would be helpful and appropriate for EFSA to provide clarification / justification as to why it has concluded that read-across would not be used for the consideration of genotoxic potential.	Due to the central role of genotoxicity assessment, for substances that are intended to be added to food, experimental data are needed (EFSA Scientific Committee, 2011). In line with this guidance document, the approach for genotoxicity testing starts with two *in vitro* methods, i.e. a bacterial reverse mutation test (OECD TG 471) and an *in vitro* mammalian cell micronucleus test (OECD, 2016b)). If both were clearly negative, no animal study would be required. The uncertainty which is inherently connected to read-across can easily be avoided by performing these in vitro studies. Read-across for genotoxicity endpoints can be applied for the identified components of flavourings consisting of mixtures, if experimental data are not available.
44	**4.4 Genotoxicity** **4.4.1 Assessment of the genotoxic potential of**		**Page 31, Lines 1349-1350:** "*The in vivo Comet assay detects primary DNA damage and can be used with many target tissues*" • While it is beneficial to see the removal of the recommendation to include in vitro chromosomal aberration	Recommendations on how the exposure of target tissue could be demonstrated were given in EFSA SC guidance (EFSA Scientific Committee, 2017b) and should be followed.

	flavouring substances		studies, IOFI has concerns regarding the demonstration of toxicity in target tissues. Since many flavouring ingredients are primarily small molecules that are generally considered innocuous and of low toxic potential, it can be challenging to demonstrate toxicity in a target tissue (e.g., bone marrow), especially given the fact that these molecules can be rapidly metabolized within the liver, thereby never reaching the bone marrow in sufficient quantities that would exhibit toxicity effects. Additionally, some flavourings are very small and the analytical detection of them may not be easily achieved. IOFI wonders whether, somewhat similar to what has been published in the recent EFSA guidance related to the consideration of in vivo aneugenic potential, it might be prudent, for those flavourings for which target tissue exposure could not be definitively determined, to apply a common-sense consideration of the concentrations tested in the in vivo studies relative to actual estimated exposure.	The proposed comparison of the exposure with concentrations tested in the in vivo studies is not applicable, as gene mutations and clastogenicity are genotoxicity endpoints which are considered by EFSA to be without thresholds.
45	**4.5.1 Flavouring substances** **4.5.1.1 Initial considerations for the toxicity data requirements**		**Page 37, Lines 1496-1508:** "*From previous evaluations it has become clear that exposure levels to flavouring substances may approach those observed for food additives. Therefore, it is considered appropriate to align the toxicological data requirements for flavouring substances as much as possible with those for food additives (lines 1496-1499) [...] when the exposure to a flavouring substance under the proposed conditions of use exceeds the TTC for its structural class additional toxicity data are needed in line with the data requirements for food additives because the condition that the exposure must be below the TTC value is not met (line 1506-1508).*" • Rarely would the exposure level of a flavouring approach that typically observed for food additives given their self-limiting nature. Using the very conservative exposure technique mTAMDI, the estimated mean intake is 3 mg/person/day whereas in a review examining estimated daily intakes of food additives as submitted to the US FDA	The self-limiting nature of flavourings is *per se* not a relevant argument for risk assessment, as it does not provide information on the actual use levels and the corresponding exposure. Previous evaluations showed that for many flavouring substances use levels are in the same range as those of food additives. An additional argument is that for those flavouring substances for which use levels are available, the corresponding exposure estimates (mTAMDI values) are in most cases above the TTC. Comparison of mTAMDI exposure estimates for

			for sweeteners (Hanlon et al., 2017), the average estimated daily intake was 256 mg/person/day for sweeteners or an 85-fold difference.	flavouring substances with US-exposure estimates for sweeteners is questionable, since they are based on different methodologies. EFSA aims at a high level of protection for all substances and for all consumers. This justifies the more extensive data requirements in the current updated guidance and gives better harmonisation of the data requirements for flavourings and food additives. The text in the guidance document has been modified according to the above considerations (see section 4.5.1.1).
46	**4.5.1.1 Initial considerations for the toxicity data requirements**		**Page 31, Lines 1500-1509:** *"This concept (TTC) is based on … when exposure to a substance is below a certain threshold, no health risk to consumers is anticipated … However, when the exposure to a flavouring substance under the proposed conditions of use exceeds the TTC for its structural class, additional toxicity data are needed … because the condition that the exposure must be below the TTC value is not met."* • While internal TTC values are incredibly useful, the exposure methods cited in this guidance rely on maximum use levels and have inherent conservatisms as described in the draft guidance and EFSA publications. In addition, and as noted above, there is limited applicability of the refined exposure approach as currently described in the draft Guidance to flavourings. Due to this, we have notable doubt in the ability for an extensive number of flavourings (that we envision would be a representative sample) to	It should be noted that it is not the internal but the external TTC that drives the risk assessment in Tier I. EFSA considers that the approach to initially apply the maximum use levels is appropriate to ensure an adequate safety assessment for human exposures. In addition, as stated in the guidance document the provision of typical use levels would give EFSA the possibility to refine the exposure estimates. Thus, it is of utmost importance for industry to submit information on uses and use levels which is as detailed and accurate as possible.

			meet the expectations that they would be less than the internal TTC.	
47	**4.5.1.1 Initial considerations for the toxicity data requirements**		**Page 31, Lines 1559-1560:** *"ADME data may demonstrate the extent of absorption from the gastro-intestinal tract. If absorption is negligible, this may reduce the need for extensive toxicity testing."* • IOFI noted this within the 25 May 2022 EFSA technical hearing meeting related to the draft guidance but reiterates the importance of clarification and definition of "negligible absorption." Are there default values (e.g., percentages) that characterize "negligible?"	See answer to comment #5.
48	**4.5.1.1 Initial considerations for the toxicity data requirements**		• The most recently published food additive guidance states that, "The Panel notes that the TTC might provide a useful comparator in this assessment" when referring to possible negligible absorption from Tier 1 absorption studies (EFSA, 2012). IOFI agrees the TTC principle does incorporate ADME data and could be a useful comparator for absorption data, whether that data is derived from in silico tools or other experimental data. IOFI recommends the EFSA FAF Panel reconsider allowing the use of the TTC principle in considering whether collecting in vivo ADME data. Overall, IOFI suggests that previously obtained experimental data and predicted absorption data can serve as an adequate estimate for the extent of absorption from the GI tract without the need for *in vivo* data.	EFSA agrees to move the requirement for ADME data from Tier I to the beginning of Tier II and to ask for these data only if the exposure exceeds the TTC. See also answer to comment #33 The experience from the previous FGEs is in many cases only based on limited studies with only a few substances (mostly one) per chemical group. Sometimes that is even limited to a few in vitro studies addressing merely metabolism. Indeed, the flavouring substances that have been evaluated in the past are fairly small molecules for which absorption from the GI tract can be reasonably assumed. However, in the submissions received by EFSA after

				2010, the structures are much more complicated than just "simple molecules" and then the value of the experience from the past is not very great. As argued above (see answer to comment #41), the systems for estimating ADME characteristics based on *in silico* and *in vitro* methods are not yet robust enough for the purpose of risk assessment.
49	**4.5.1.1 Initial considerations for the toxicity data requirements**		**Page 31, Lines 1579-1581***: "When the safety evaluation of a substance will be limited to an evaluation through Tier I only … most aspects of ADME studies are of limited relevance."* • Please clarify the intention of the ADME study –is it used to avoid Tier II testing by refining exposure to higher values, to guide the design of the toxicity and potential in vivo genotoxicity studies, or purely to determine the Tier II requirements? While the scientific concepts presented in the Guidance are well-established in evaluating new pharmaceutical compounds, it is not clearly defined regarding flavouring ingredients. This is because flavor ingredients are typically small molecules broken down into innocuous metabolites, making ADME studies an incredibly difficult task to conduct and overcome. Therefore, we suggest using more practical methods to study ADME rather than in vivo, particularly in cases that can support read-across (e.g., in vitro absorption studies, metabolism studies). There are a multitude of in silico ADME property prediction tools that support this recommendation by providing the requested information from OECD TG 417. This includes predictions for absorption characteristics (human intestinal absorption, bioavailability), distribution (volume of distribution), metabolism (CYP activation), and excretion (clearance rates, half-lives). Additionally, the free in silico tool OECD	See answers to comments #32, #33, #34, #41 and #49.

			QSAR Toolbox predicts the structures of metabolites. At the same time, TIMES, which can be docked into OECD QSAR Toolbox, can both identify metabolites and simulate metabolic maps that could be compared for similarity based on common transformations, common metabolites and common reactivity pattern when used for the read-across approach (Yordanova et al., 2021).	
50	**4.5.1.1 Initial considerations for the toxicity data requirements**		• Additionally, IOFI suggests the relocation of ADME from Tier I to Tier II, and only using ADME within Tier I if in vivo genotoxicity studies are required. Additionally, several methods demonstrate target tissue exposure without the need for in vivo ADME studies are listed in the comments earlier in this section (EFSA Scientific Committee, 2017b). Given the plethora of options to demonstrate target tissue exposure, it is unclear why in vivo ADME are necessary in this respect. Therefore, IOFI recommends using in silico tools and/or existing ADME data in lieu of in vivo toxicokinetic data for applications.	See answers to comments #32, #33, #34, #41 and #49.
51	**4.5.1.2.2 Assignment to Structural Class and application of the TTC approach**		**Page 40, Lines 1630-1632:** *"Panel will use the OECD (Q)SAR Toolbox as the standard tool for the allocation … an additional evaluation according to the tool as developed by Cramer Ford and Hall"* • Please elaborate on the reasoning behind the purpose of solely relying on the OECD Toolbox as the best method to determine Cramer classification.	It is not intended to consider the OECD Toolbox as "the best method to determine Cramer classification". As already reported in the report of the WHO/EFSA workshop on TTC (EFSA, 2016), the questions as formulated by Cramer et al. are sometimes ambiguous and natural occurrence (which is a criterion in some of the questions) is not relevant for structural class determination. As a result, alternative systems have been developed, which sometimes produce

				different classifications, see also IOFI comment #53. The OECD QSAR Toolbox will be used by the FAF Panel for Cramer classification. The use of this software is not mandatory for the applicant. However, appropriate justification should be provided if the applicant uses a different approach and a reasoned comparison of outputs should be provided. A respective sentence has been inserted in the revised guidance document in section "4.5.1.2.2 Assignment to Structural Class and application of the TTC approach"
52	**4.5.1.2.2 Assignment to Structural Class and application of the TTC approach**		• IOFI would suggest considering a case-by-case expert judgment as divergences in Cramer Class determination are observed depending upon the in silico tools used. Existing tools may provide incorrect predictions (Bhatia et al., 2015).	See answer to comment #52
53	**4.5.1.2.2 Assignment to Structural Class and application of the TTC approach**		**Page 40, Lines 1638 –1642:** *"The EFSA 2019 Guidance also mentions a TTC of 0.0025 µg/kg bw per day for DNA-reactive genotoxic substances. This TTC will not be applied for the evaluation of flavouring substances but maybe applicable for the evaluation of unavoidable impurities or components of flavourings constituting mixtures (see sections 4.3.2, 4.3.3, 4.3.4 and 4.3.5)."* • IOFI wonders why EFSA accepts the so-called TTC genetox for unavoidable impurities or components in mixtures but would not accept it for flavouring substances. It is unclear to IOFI why EFSA would differentiate between flavouring substances and unavoidable impurities or mixture components since what	The reasoning for limiting the application of this TTC to unavoidable impurities has been outlined in the EFSA SC guidance document (EFSA Scientific Committee, 2011). A reference to that document has been inserted in line 1640 of the draft guidance document.

			would ultimately matter is the question of whether the intake is above or below the TTC genotox of 0.0025 ug/kg bw.	
54	**4.5.1.2.2 Assignment to Structural Class and application of the TTC approach**		**Page 40, Lines 1652-1655:** *"If in Tier I it is concluded that the exposure to the flavouring substance is above the class specific TTC and reduction of exposure to the substance by limiting uses and use levels and/or by refining the exposure assessment (see section 3.3.1) is not feasible, the safety assessment proceeds to Tier II."* • IOFI request that at this point in the guidance, EFSA include a clear statement that indicates that if the exposure is <TTC for the Cramer / Ford / Hall structural class and there is not a concern for genotoxic potential, that the safety assessment outcome would indicate no concern, as that appears to be the outcome based on the text above. Similarly, EFSA could consider also noting this, in some way, within Appendix B.	A respective sentence has been inserted in Appendix C (see explanatory text of Figure C.1).
55	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**		**Page 41, Line 1667:** *"This MOE should be sufficiently large"* • We would greatly appreciate clarification and specificity regarding what classifies as "sufficiently large" for the MOE.	The setting of assessment factors is case-by-case dependent. Explanatory text can be found in the guidance document in section "4.5.1.6 Considerations with respect to the Magnitude of the MOE".
56	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**		**Page 41, Line 1690:** "*This EOGRTS should always comprise the full arms of the parental cohorts as well as cohorts 1A, 1B, 2A, 2B, and 3"* • Considering animal welfare, it seems excessive to request the neurodevelopmental and immunotoxicological cohorts per default and in the absence of particular concerns for a substance such as coming from preliminary studies or chemical	If studies are available, they could be taken into account if they address the endpoints as covered by the EOGRTS assay and are sufficiently robust. However, EFSA anticipates that preliminary studies are unlikely to meet these requirements.

			structure. Such cohorts significantly increase the number of animals used and the overall complexity of the EOGRTS study.	Read-across would be acceptable, provided the requirements as outlined in the guidance are met. This is consistent with the data requirements for food additives. The neurodevelopmental and immunotoxicological cohorts do not significantly increase the numbers of animals needed, they only require that more animals remain in the in-life phase of the test for a longer period of time.
57	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**		**Page 41, Lines 1696-1698:** *"The toxicity studies that are to be used in the assessment should be designed…provide…lower confidence limit of the benchmark dose (BMDL)-upper confidence limit of the BMDU intervals"* • IOFI requests clarification for how this new requirement to design studies to determine BMDL would affect the ability of EFSA to use previous studies (i.e., where NOAEL values were derived) for the substance or for related substances (via read-across)?	For previous assessments in which NOAELs have been used, these remain valuable. The intention is to enhance reliability through the use of benchmark dose analysis rather than the use of NOAELs but this does not negate the use of the latter in cases where BMDL assessments are not possible. Nevertheless, EFSA may consider to estimate BMDL-BMDU intervals from older studies, when data from the studies would allow for that thus taking account of study uncertainty. EFSA may also request that study reports which are referred to in previous assessment are made available for this purpose. Obviously, NOAELs, previously used in FGEs should be based on adequately performed and adequately reported

				studies. In many old studies aspects like (developmental) neurotoxicity and immunotoxicity have not adequately been addressed, and that could result in a rejection of these NOAELs for the purpose of a safety assessment for a new submission.
58	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**		**Page 42, Lines 1709-1714:** "*Observations from the EOGRTs … could be necessary to clarify the relevance of an observed effect for human health"* • IOFI notes that EOGRT studies, unfortunately, are often quite unfeasible to place and conduct, for several reasons. Firstly, an in vivo study, such as the EOGRT study, can be complicated to conduct for flavourings due to the need to produce very substantial amounts of material—for many flavourings, the amount of material required for an EOGRT would be several times greater than the annual production volume that the entire industry would produce. Additionally, conducting this in vivo study would result in an extreme use of animals. As noted above EFSA stated in 2012 that applicants should "avoid unnecessary use of animals...and (should instead conduct) alternative validated methods for other endpoints in toxicity, involving fewer or no animals."(EFSA ANS Panel, 2012)	The EU legislation strives for a high level of protection of consumers for all substances added to food. If substances are sensorially so potent that they only need to be produced at low amounts, that also means that the use levels may be so low that the resulting exposures may be below the TTC and therefore the studies in question would not be required. Also for low production volume flavourings, read-across might be applied as explained in the guidance document.
59	**4.6 Safety for the environment**		**Page 46, Lines 1899-1900:** "The main environmental compartments of concern are surface water, sediment, soil and groundwater," • It would be beneficial and insightful if EFSA included evidence that indicates when/how a sufficient number of flavours were released into the wastewater stream that caused extreme environmental concern.	The text of the guidance has been amended as follows: "The main environmental compartments into which flavourings or their metabolites might be expected

				to enter are surface water, sediment, soil and groundwater."
60	**4.6 Safety for the environment**		**Page 46, Lines 1901-1903:** "*...EFSA does not anticipate a need to perform an environmental safety assessment on a regular basis for each new food flavouring."* **Page 46, Lines 1906-1912:** "... *indicate persistence, bioaccumulation and/or toxicity. Criteria for the identification and assessment of these three parameters can be found in Annex I Part 4 (Environmental hazards), section 4.1.2 (Classification criteria for substances) of the CLP Regulation."* • Taken together, those two lines seem to be contradictory. If an environmental assessment is considered in cases where persistence, bioaccumulation and/or toxicity for the environment is possible, and the criteria for P and B are those of the CLP Annex I Part 4, section 4.1.2. (which does not contain any definition of persistence –it only mentions rapid degradation–or bioaccumulative –it only mentions potentially bioaccumulative –or toxicity –which hazard categories are is being discussed?) which are much more inclusive than those of Annex XIII of REACH (e.g. BCF of 500 vs. 2000 in REACH), the scope will be very broad and environmental safety assessments will be required regularly. In that context, it would be useful if EFSA could clarify:	To clarify this issue the text of the guidance has been amended as follows: "An environmental risk assessment would only be required when a food flavouring is not naturally occurring, it is synthesized in quantities above 10 tonnes and it is classified according to the CLP criteria. In case the flavouring or its metabolites are identified as persistent, bioaccumulative and toxic substances (PBT substances), and very persistent and very bioaccumulative substances (vPvB substances), as per Annex XIII of the REACH Regulation (EC) No 1907/2006, they would raise a concern for the environment, irrespective of their tonnage band, as no safe concentration in the environment can be established with

				sufficient reliability for an acceptable risk to be determined in a quantitative way."
			○ what "persistence, bioaccumulation **and/or** toxicity" means: 1) P and B and T or vP and vP;or 2) P or B or T.	- This sentence has been deleted from the guidance. As mentioned in section 4.6. of the guidance, for classification criteria, please, refer to Annex I Part 4 (Environmental hazards), section 4.1.2 (Classification criteria for substances) of the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008). For PBT/vPvB criteria, please, refer to Annex XIII of the REACH Regulation (EC) No 1907/2006.
			○ if the criteria are confirmed to be those of the CLP (which has no specific definition of persistence or toxicity – categories considered should be clarified) or those of Annex XIII of REACH which are clearly identified. Lines 1912-1914 discuss PBT or vPvB criteria of Annex XIII, for consistency, using the same criteria for PBT and vPvB would be most useful. This is further needed to avoid confusion when the PBT and vPvB criteria of Annex XIII will be included in the CLP as part of the CSS actions.	- The PBT and vPvB criteria are specified in Annex XIII of the REACH Regulation (EC) No 1907/2006 and they are currently proposed as a specific category to be included in the future update of the CLP Regulation.

61	**4.6 Safety for the environment**		**Page 46, Lines 1918-1921:** "In case an environmental safety assessment is needed, it will be based on the same principles as mentioned in the EFSA guidance on the environmental risk assessment of feed additives, pharmaceuticals, and biocides and industrial chemicals." • EFSA notes that an environmental safety assessment should be made, but IOFI wonders which environmental risk assessment framework will be applied.	Considering the route in which the flavours will enter the environment (after oral application to humans), the ERA framework used for pharmaceuticals might be most relevant, but also the ones used for biocides and industrial chemicals may be considered. The text of the guidance has been modified accordingly in section 4.6.
62	**Interpretation of the Terms of Reference**	Beat Spath (Specialised Nutrition Europe (SNE)) - Belgium	243-245, 352: The definition of flavouring preparation: "material of vegetable, animal or microbiological origin, other than food", could be clarified with a few examples especially as this guidance now focusses on flavouring intended in product for infants and young children.	The different types of flavourings are already defined in Regulation (EC) No 1334/2008.
63	**Scope of the guidance**		Specialised Nutrition Europe (SNE encourages EFSA to clarify more explicitly the scope of this draft guidance. - Retroactive or not? How will this guidance apply to FGE that are undergoing re-evaluation and/ or for new proposed uses for previously assessed flavouring substances? It is our understanding that it is for new applications (under the Common Authorisation procedure Reg (EC) No 1331/2008) and also for changes in conditions of use or new methods of production of existing authorisations, but we believe that it would be beneficial to state this more prominently and explicitly in the draft guidance.	As mentioned in the abstract of the guidance, as well as under sections "Term of Reference", "Interpretation of Term of Reference" and "Scope of the guidance", this guidance only applies to applications for a new authorisation and for modifications of an existing authorisation of a food flavouring, submitted under Regulation (EC) No 1331/2008. The text was modified to make it clearer (see section "Scope of the guidance"):

				"This guidance provides information on the type and quality of the data that are required by EFSA to assess whether a new food flavouring submitted for authorisation or a proposed modification of an already authorised flavouring is safe under the proposed conditions of use."
64			- Coverage of foods intended for infants: the draft guidance states that for flavourings used in foods intended for infants for <16 weeks, the guidance from 2017 will be followed (with the extra tox studies such as EOGRT, tox testing in juvenile animals etc.,). For products intended for infants and young children in general, SNE encourages EFSA to provide more clarity on the toxicological testing requirements (whether it will follow the standard process described OR if there will be extra studies needed). This is currently not clear to us from the way it is phrased in the draft guidance.	This issue is covered by EFSA Scientific Committee Guidance, 2017a and EFSA Committee Guidance, 2019, which are already included as references in the guidance document. For further clarification the following sentence has been inserted in the guidance document in section 4.5.1.7: "Following these guidance documents, in principle no additional data would be needed if the evaluation of a substance proceeds to Tier II B. When the evaluation of a substance remains in Tier I or Tier II A, then a study in neonatal animals will be necessary."
65	**1.2.3 Compositional data**		-650 -652: For natural flavouring preparations, clarification on how the natural variation of botanicals will be considered?	As mentioned in section 1.2.3.4 of the guidance, also for flavouring preparations from botanical sources, natural variability is covered by the request that compositional data should be provided for at least five independent batches, and information

				on how these batches were selected should be provided.
66	**3.3.1 Dietary exposure assessment**		-1080-1081, 2197: How will the "proposal for use that would reduce dietary exposure by applicant" be enforced in practice. For example would it be with a maximum limit as in additives or restricted food category usage?	Such enforcement is subject to risk management and outside the remit of EFSA.
67	**4.4.2 Assessment of the genotoxic potential of flavourings consisting of mixtures**		-1386 - 1397: How will this apply to some of the genotoxic substance that are already present in Annex III of Regulation (EC) No 1334/2008. Will there be updates based on the evaluations performed to the substances already in the Annexe? Will the Annexe be expanded with new substances as when evaluations are completed?	The issue relates to risk management and falls outside the EFSA remit.
68	**4.5 Toxicity other than genotoxicity**		-1483 - 1485: Clarification required on whether ADME data is also a minimum requirement along with genotoxicity OR is it requested on a case by case basis? For example, if a substance is non-genotoxic and is below TTC then is ADME data still required?	EFSA agrees to move the data requirement for ADME studies from Tier I to the beginning of Tier II and to ask for these data only if the exposure to the substance exceeds the TTC. The text of the guidance has been amended accordingly. See also answer to comment #33
69	**4.5.1 Flavouring substances**		- 1547: Clarification on whether *in silico* simulation of ADME could be used in this part or will it be animal studies?	EFSA supports the use of *in silico* simulation to provide supportive information relating to ADME. However currently EFSA considers such predictive ADME models as insufficiently well developed to be able to replace OECD TG 417.

				See also answers to comments #7 and #37 and #41.
70			- 1617: Kindly clarify why 60kg is still used considering the EFSA default of 70kg bw/day (for additives)	The body weight of 60 kg was originally used by Munro et al., 1996 to estimate TTCs on a *per person* basis. This body weight was also used by the Scientific Committee to express the TTCs on a *per kg bw* basis. Based on these references a 60 kg body weight is mentioned in the guidance document.
71			- 1630-1633: Will there be a retrospective analysis of the FGE evaluated or FGEs under re-evaluation regarding the structural class determination using the OECD QSAR toolbox?	EFSA would perform such a retrospective analysis only when a substance that has been already evaluated in a former FGE is intended to be used as data source for read across in the course of the safety assessment of (an)other substance(s).
72			- 1639 -1642: Clarification on how the TTC for DNA reactive genotoxic substances will be used for substance present in flavouring preparations (e.g., will the limits set for estragole or safrole in Annex III be updated or revised based on this TTC or their latest BMDL10?)	The setting of limits relates to risk management issues and falls outside the EFSA remit.

73			- 1789 - 1790: Application for authorisations for use in food for infants and young children (above 16 weeks): Please kindly provide a clarification on whether "in particular EOGRTS" is only still for those substances that have relevant absorption or may have systematic effects OR a requirement for application in IYC products? Does this also include extended application to IYC for flavours already evaluated previously?	It is important to note that there are clear differences between the data requirements for flavourings intended to be added to foods for infants (below 16 weeks of age) and those intended for foods for other age groups including young children. The requirements for flavourings for foods intended for infants are outlined in the guidance document in the first two paragraphs in section 4.5.1.7 (see also answer to comment #64). On the other hand, the requirements for flavourings for foods intended for young children are described in the guidance in the last paragraph in section 4.5.1.7. For this age group as for all other population groups, an EOGRTS assay is only a requirement when the evaluation of a substance proceeds to Tier II B. Issues related to 'extended application to IYC for flavours already evaluated previously' fall in the remit of risk managers.

74	**Appendix C - Decision schemes for the toxicity testing of flavouring substances**		- 1080-1081, 2197: How will the "proposal for use that would reduce dietary exposure by applicant" be enforced in practice? For example would it be with a maximum limit as in additives or restricted food category usage?	Please refer to the answer to comment #66
75	**Appendix B - Tiered toxicity testing of flavouring substances**		- 2195: Tier I: please kindly clarify the step at which there is a need to proceed to in vivo from in vitro.	In Tier I there is no need for toxicity studies except for the investigation of genotoxic potential. It is clearly documented which *in vivo* studies should be done in case of a genotoxicity concern indicated from in vitro studies. For details, please refer to the SC guidance documents on genotoxicity and the present guidance document for flavourings. The requirements to move from Tier I to subsequent steps Tier II/Tier III which may include in vivo studies are outlined in the guidance document (see Appendix C).
76	**Abstract**	Jan Demyttenaere (EFFA)	EFFA supports and echoes the comments from the international umbrella organisation IOFI (International Organization of the Flavor Industry), as submitted previously.	Noted.

Table 3: Questions received from interested parties during the technical hearing organised by EFSA on 25 May 2022 on the draft scientific guidance on the data required for the risk assessment of flavourings to be used in or on foods.

No.	Section of the guidance	Comment	Response from EFSA
1	**Introduction**	Within the introduction 2nd paragraph, EFSA States that "The flavourings for which an evaluation and approval are required are listed in Article 9 (a) - (f) of the Regulation (EC) No 1334/2008. Although Regulation (EC) No 1334/2008 specifies those flavourings for which an evaluation and an approval prior to being placed on the market is not required according to its Article 8 (a) – (d), under certain circumstances, EFSA can also be asked to evaluate these flavourings." Can EFSA elaborate on what these "certain circumstances" may be? How would a company know whether EFSA would intend to evaluate one of these materials?	The "certain circumstances" are referring to the provisions of Regulation (EC) No 1334/2008 article 8(2) where it states: 2. Notwithstanding paragraph 1, if the Commission, a Member State or the Authority expresses doubts concerning the safety of a flavouring or food ingredient with flavouring properties referred to in paragraph 1, a risk assessment of such flavouring or food ingredient with flavouring properties shall be carried out by the Authority. Articles 4, 5 and 6 of Regulation (EC) No 1331/2008 shall then apply mutatis mutandis. Obviously, such decisions will be made in a case-by-case basis and the FBO should be aware if there are safety concerns related to their products, as it is ultimately their responsibility to launch a product in the market only if it is safe.
2		More suitable analytical techniques are still required by consumer protection and law enforcement for the detection of allergens in foods. Food allergy is an important issue in food analysis because minute amounts of the allergen can have critical consequences in sensitized persons. Another difficulty that flavour scientists must face is how to properly model and visualize the complex relationships existing between the chemical composition of foods and the flavor perception. These problems have repercussions on the reconstitution of the flavor signature of food based on the natural	Noted.

		concentrations of its key aroma and taste compounds.	
3	**1. Characterisation**	Could you further explain the exemption of extracts derived from foods? Extracts from any source can be processed to be highly concentrated (ex: standardized to 80% chemical x), and although not as pure as a flavouring substance, these extracts could have similar safety concerns. Are all extracts from food sources exempt regardless of specifications?	If the food extract results in a *flavouring substance* an evaluation and an approval are always required. In case the extract results in a less pure product, this would constitute a mixture and it would fall under the definition of a *flavouring preparation*. In this case, an evaluation and an approval are required only for *flavouring preparations* obtained from sources other than food, see section 1.2 of the draft guidance. If it is requested by the EC to perform a safety assessment of a *flavouring preparation* derived from a food source, the data requirements will follow the same principles as detailed in the draft guidance for essential oils from non-food sources, which will apply *mutatis mutandis.*
4		When food safety assessment is needed for natural aromas based on extractions from plants/fruits/microorganism?	For *flavouring substances*, a safety assessment is always required, irrespective of the source. For *flavouring preparations* extracted from plants/fruits/microorganisms, a safety assessment is only required if they originate from non-food sources.
5		How EFSA evaluate the safety of flavourings extracted from plants? All toxicological information are required or alternative solutions are possible like the analysis of each substance presented on the extract?	It would depend from the type of food flavouring that would result from the plant extraction (i.e. either a *flavouring substance* or a *flavouring preparation*). Accordingly, the data requirements will be in line with what is described in the draft guidance for the corresponding type of food flavourings.
6	**1.1.2.2 Flavouring substances obtained from material of vegetable, animal or microbiological origin**	The draft Guidance doesn't specify if exemption occur for flavouring substances isolated/extracted from natural sources for which the consumer exposure from the parent edible food consumption is significantly higher than exposure from the flavouring substance isolated/extracted from the same edible food. In such cases the Tiered safety approach shouldn't apply as the safety of consumption of the flavouring	The fact that the intake of a flavouring substance via consumption of the natural source from which the flavouring substance is obtained is higher than the intake resulting from the intended use of the isolated flavouring substance does not constitute a reason to waive the need for safety assessment. "Significant history of the safe consumption of the edible source" is not a criterion considered in the safety assessment of flavouring substances.

		substance isolated from an edible food is demonstrated by the significant history of safe consumption of the edible source. Can you please confirm this exemption?	
7	**1.1.2.1 Flavouring substances obtained by synthesis - Enzyme-catalyzed synthesis**	In Section 1.1.2.2, EFSA notes that there may be enzymes used in flavor production that are still under evaluation. Could EFSA clarify as to whether this would have the result of putting the flavor assessment on hold (pending completion of the enzyme assessment)?	See response to comment #12 in Table 2
8	**1.1.2 Manufacturing process**	A substance has been evaluated by EFSA in the past and is included in the positive list. If there are small changes in the manufacturing process, does EFSA have some examples on when a new dossier shall be submitted and when not?	The essential point is not, whether a change in the manufacturing process is "small" or not but whether such a change might have an impact on the safety of the flavouring. This could, for example, be the replacement of a catalyst or the change of a solvent which could impact on impurities and composition.
9	**1.1.3 Compositional data**	In Section 1.1.3, EFSA describes the quantification of impurities. Could EFSA clarify which impurities/at which level?	See response to comment #16 in Table 2
10	**1.1.4 Stability**	Regarding assessment of stability, EFFA and IOFI would note that it would be most informative to test stability under conditions of commerce—incorporating recommended handling/storage conditions within the trials. This could include the use of stabilizers, etc., as appropriate. Could the guidance be clarified to cover this?	The guidance document requests "demonstration of the physicochemical and chemical stability of the flavouring upon storage of the material of commerce under conditions reflecting the intended shelf-life". This could of course, also include the use of stabilizers, as appropriate. However, it should be kept in mind that if a stabilizer would necessarily be required to ensure the stability of a flavouring, the presence/use of such a stabilizer will have to become a part of the specification of the flavouring.

11	**1.2 Flavouring preparations**	Information about flavouring preparations like essential oils	An evaluation and approval are required only for *flavouring preparations* obtained from sources other than food, see section 1.2 of the draft guidance. If it is requested by the EC to perform a safety assessment of an essential oil obtained from plants which are consumed as foods, the data requirements will follow the same principles as detailed in the draft guidance for essential oils from non-food sources, which will apply *mutatis mutandis*.
12	**1.2.3.4 Batch-to-batch-variability**	We took note of the analytical requirements for flavouring materials, and specifically the request for characterization of five production batches. Can EFSA provide a rationale for why data from five batches would be necessary? Given the tight control of synthesis, could a reasonable alternative, particularly for chemically defined substances, be 2-3 batches?	See response to comment #18 in Table 2.
13		The Draft guidance states: "709 To demonstrate batch-to-batch variability, compositional data should be provided for at least 710 five independent batches of the flavouring preparation produced in different production runs." For flavourings for which commercial batches are not yet available, may pilot batches substitute provided that these adequately represent the intended manufacturing process, similar to what is suggested in the Guidance on the identity, characterisation and conditions of use of feed additives?	"Pilot batches" could be used for compositional analyses if batches of the flavouring produced at commercial scale would not yet be available. However, in such cases it would of utmost importance to provide evidence that the manufacturing process in the pilot plant is the same as the process intended in commercial production and that enlarging of the production scale will not result in compositional differences.
14	**3.3.1 Dietary exposure assessment**	EFSA's Draft Scientific Guidance on Flavourings foresees the use of the Food	The guidance deals with applications for new food flavourings as well as modification of already authorised flavourings. In these

		Additive Intake Model (FAIM) as a mandatory tool to assess the consumer intake. Is the currently accepted approach using standard portion sizes still applicable or is it completely obsolete?	cases, the approach using standard portion size is indeed obsolete.
15		EFSA refers to multiple methods for assessing exposure, and then also points out the possibility of conducting a 'refined exposure assessment' as necessary. How would this be conducted? Would it make sense to incorporate a consideration of probability of exposure within any refined exposure assessment process?	A refined exposure assessment would include the use of individual food consumption data in the EFSA Comprehensive Database at the level of individual foods (FoodEx2). Facets could be used to further select the relevant foods containing the flavouring/flavouring substance. In addition, maximum and typical use levels could both be used to refine the exposure assessment. Including a consideration of probability of exposure would mean to assess the exposure using a probabilistic approach. The data requested as part of the guidance will not allow such a detailed assessment. See also response to comment #28 in Table 2
16		The iterative exposure refinement could result in a back-and-forth between EFSA and applicants. Would it make more sense for the exposure assessment to be completed in advance of the full safety assessment?	To determine whether the exposure estimate needs to be refined, the calculated exposure should be compared with the available toxicity data. If this comparison shows that there is a possible health concern, the exposure estimate may be refined. It is therefore not possible to complete the exposure assessment in advance of the full safety assessment. Refinement regarding exposure will be performed by EFSA with the data already made available by applicants. EFSA may request other data as is the case for other parts of the risk assessment but as much as possible, all relevant information related to exposure assessment of the substance should be submitted to EFSA in the first instance. It is in the interest of the applicant to provide use /use levels that are as realistic and detailed as possible since a back-and-forth situation will only result in a delay for marketing authorisation.

17		It is difficult to compare food consumption data in the different systems (FAIM, DietEx).	Food consumption data behind FAIM and DietEx are the same. The aggregation of the FoodEx2 codes in food categories are different between FAIM and DietEx. FAIM uses food consumption data from the EFSA Comprehensive European Food Consumption Database. Consumption data are categorised according to the food categories in Annex II, Part D, of Regulation (EC) No 1333/2008. DietEx uses the same food consumption data as FAIM, but the data are categorised according to the FoodEx2 food classification system, which includes more food categories compared to Annex II, Part D, of Regulation (EC) No 1333/2008.
18		The food categories according to FAIM (and for the applications) are completely different than the 18+ food categories in the Union list of flavouring substances (Regulation (EU) 872/2012) - so how is the COM going to include new flavouring substances in the UL with the correct food categories (and correct use levels in case max levels would apply) as these are not the same categories like in the dossiers?	The food categories in FAIM follow the nomenclature as provided in Annex II, Part D, of Regulation (EC) No 1333/2008. This nomenclature is also referenced in Regulation (EU) 872/2012 and in the current Regulation (EC) 1334/2008 (see Annex I, Part A, Section 1, Column 7).
19	**3.3.2 Acute exposure assessment**	Page 27, line 1119 - EFSA may perform an acute dietary exposure assessment if needed based on the toxicity data - what information in the toxicity data would trigger this assessment?	If an acute reference dose is derived for the flavouring, an acute exposure assessment will be performed by EFSA, e.g. camphor (EFSA AFC Panel, 2008). Children exposed to camphor developed severe health effects and therefore the acute toxicity for this substance had to be addressed.
20	**3.3.3.2 Exposure assessment from non-dietary sources**	In section 3.3.3.2 'Exposure assessment from non-dietary sources' EFSA requests non-dietary exposure sources. However, if such data is not used in the final exposure assessment based on the intake for oral sources why is this requested in the first place and what is it used for?	As explained in the guidance, EFSA will perform an aggregate (i.e. considering all sources) exposure assessment based on the data provided, on a case-by-case basis depending on the data submitted by applicant. It will be performed according to agreed methodologies used by ECHA and SCCS as summarized in (EFSA, 2016).

			See also response to comment #31 in Table 2.
21	**4.3 Read-across**	Can the genotoxicity of the target substance be evaluated based on the results from genotoxicity studies on the structurally and metabolically related substances?	In the draft guidance it is reported: "Read-across will not be accepted to waive the provision of experimental genotoxicity data for new *flavouring substances.* Read-across for genotoxicity and for endpoints other than genotoxicity will not be accepted for flavourings that consist of mixtures. However, for identified individual components in such mixtures, read-across for genotoxicity and for other toxicological endpoints could be applied." See also responses to comments #39, #43 in Table 2.
22	**4.4.1 Assessment of the genotoxic potential of flavouring substances**	Question on tissues for analysis: is there a standard suite of tissues that must be used? If an Ames positive but MN vit negative is found, can only the liver be tested in a comet?	See response to comment #44 in Table 2.
23	**4.4.2 Assessment of the genotoxic potential of flavourings consisting of mixtures**	Regarding in vivo genotoxicity studies with flavouring preparation containing one or more components: What evidence of target tissue exposure (liver, bone marrow) is required in case of mixtures? Would plasma analysis of all components be required?	This is explained in section 2.3 of the "Statement on the genotoxicity assessment of chemical mixtures" (EFSA Scientific Committee, 2019) where it is noted that "In some instances it can be anticipated that negative results in the follow-up tests can support, with sufficient confidence, a lack of concern about the in vivo genotoxicity of the mixture. For example, for a mixture that is directly clastogenic in vitro, a robust assessment in vivo could be performed by applying a mammalian alkaline comet assay (OECD (2016a) Test No. 489) to several tissues, including the site of first contact, to animals in which the mixture was administered orally. For other effects, such as induction of gene mutations and/or clastogenicity in vitro following metabolic activation, the assessment of systemic genotoxic effects (e.g. in the liver or bone marrow) may be limited by the fact that target tissue exposure cannot be demonstrated, as any toxic effect elicited in the target tissue by the mixture cannot be unequivocally attributed to the (in vitro)

			genotoxic component. In this scenario, the conclusion drawn would have a higher uncertainty." In addition, it's important to consider that for mixtures, higher doses than the maximum limits mentioned in the OECD test guidelines have to be tested, in order to increase the dose of each of the individual components of the mixture. The highest dose to be applied is limited by the maximum volume that should be given to rodents (1 mL/100 g body weight except in the case of aqueous solutions where a maximum of 2 mL/100 g may be used). See Q&A on smoke flavouring guidance (the same question was addressed on pages 12-13 – Q#4)
24	**4.5.2 Flavouring that consists of mixtures**	How will the requirement of providing ADME data be handled for flavouring complexes (multi-constituent substances or UVCBs) for which it might be technically not feasible to provide such data? Will there be an option to waive such studies similar to this option in the REACH Regulation?	Similar to what is applicable for smoke flavourings, submission of ADME data will not be mandatory for flavourings that consist of many constituents (e.g. flavouring preparations, thermal process flavourings, other flavourings). However, if a flavouring consists of a single substance that would react in the food to produce the ultimate flavour (i.e. a flavour precursor), then for the parent material ADME data should be submitted unless this parent material disappears completely during food processing.
25	**4.5.1.3.1 Toxicokinetics (absorption, distribution, metabolism, excretion (ADME))**	This question is not per se on the genotoxicity but about the application of Read-Across & ADME. We understand that Read Across is NOT accepted to waive the gentox data requirements, but what about the ADME study (OECD TG 417) under Tier 1: is ADME a default requirement, or can this be omitted/waived if we can demonstrate RA with evaluated substances?	See responses to comments #33 and #34 in Table 2.
26		If ADME data are collected first, can concentrations for genotox in vivo studies be	Genotoxicity studies should be carried out according to the relevant OECD TGs as indicated in the present guidance

		based on the TK data, and no dose range finding studies required? Can data from the TK work replace data on target tissue exposure that would come directly from a genotox study?	document on flavourings. That means that also the concentrations and / or dose levels that are applied in these studies should be based on the selection criteria (e.g. cytotoxicity) as given in the OECD TGs. The results of the ADME studies can be used to demonstrate target tissue exposure. The best way to accomplish this is of course by direct measurements in the respective target tissue, but also plasma levels of parent compound and / or relevant reactive metabolites / intermediates may be acceptable for this purpose (see also EFSA Scientific Committee, 2017b). Note that following the public consultation of the draft guidance, the testing sequence in the final version of the Guidance has been changed. ADME studies are now only requested when exposure to a substance is above the TTC for its structural class or when results from genotoxicity studies require evidence of target tissue exposure for a proper interpretation.
27		Given advancements in in silico and in vitro modelling for ADME, would such alternatives be useful and lead to a significant reduction in animal usage?	See response to comment #34, #37 in Table 2.
28		In regard to ADME requirements, as a lot of flavouring materials tend to be small molecules that metabolize into innocuous and sometime endogenous molecules, the feasibility to conduct ADME studies become nearly impossible (radiolabelling is not an option, as it would contaminate the entire manufacturing process), what would EFSA recommend?	*In vivo* studies will be unavoidable to determine mass balance of absorption and elimination, which is a major aspect of the required ADME studies. Obviously, the smaller the molecules and the larger the metabolite fraction that would become endogenous the more difficult such a study will be. It could be considered to carry out *in vitro* studies and *in silico* studies to support the design of follow-up work *in vivo.* A claim that a substance is small and will be metabolised to endogenous products needs anyway underpinning by experimental data or by strong read-across. The same applies for the claim that metabolites are innocuous, which would not only depend on

			their hazard properties, but also on the amount in which they are formed. The latter can only be determined by adequate ADME data. It should be noted further that, contrary to what was applicable in the past, the reasoning that "metabolites are endogenous and innocuous" and thus reduce the need for an adequate assessment is no longer applicable / acceptable. Radiolabelling could be feasible in a small-scale laboratory facility. Alternatively, non-radioactive isotopic mass labelling may be used. See also answer to comment #36 in Table 2.
29		What is the appropriate way to conclude that absorption is negligible? Is there a numerical value? If negligible cannot be defined, how will an applicant know what studies are required? Will EFSA sign off on study plans in advance of applicants conducting studies and making submissions that may not be considered acceptable?	See response to comment #5 in Table 2.
30	**Appendix B – Tiered toxicity testing of flavouring substances**	According to Annex B - line 2195 - an Toxicokinetic study (ADME) is required already at Tier I, irrespectively if the estimated intake would to be less than the TTC of the corresponding structural class. Also in view of consistency with the revised JECFA decision tree for flavourings, could the ADME requirement not be moved as first study to Tier II?	See response to comment #33 in Table 2.

31	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**	Regarding the use of the term "negligible exposure," can EFSA provide an indication of the cut-off criteria for what would be considered "negligible exposure?"	- This guidance does not refer to 'negligible exposure' but to 'negligible absorption'. - It is not possible to provide a general % limit of what is considered 'negligible absorption', since the exposure as such is also relevant and therefore this has to be assessed on a case-by-case basis. - Some additional explanation is given in section 4.1.2 of the Guidance on food additives (EFSA ANS Panel, 2012). - A comparison with an internal TTC could be an option to justify waving of Tier II toxicity data requirements (Partosch et al., 2015). See also response to comment #5 in Table 2.
32	**4.5.1.3.2 Testing for repeated dose, reproductive and developmental toxicity**	Can you explain the background of the very extensive testing requirements what is the rationale for a 90-d study for a substances that is not resorbable?	For a substance that is non resorbable, there still can be adverse effects, e.g. resulting from interaction with microbiota and/or due to excessive water absorption in the GI tract. Such effects should also be covered in the safety assessment. Absence of absorption will need very robust evidence. Note that for flavourings that consist of many constituents, absence of absorption of all constituents will be very unlikely and virtually impossible to prove.
33	**4.6 Safety of the environment**	For the Environmental Safety Assessment, it is completely unclear what EFSA wants. The different legislations mentioned (feed, pharma, biocides, REACH) have very different information requirements and risk assessment approaches. Moreover, there are no PBT criteria in the CLP at this stage. A list of information requirements must be specified (no information requirements in CLP or Annex XIII of REACH) and a single risk assessment approach must be proposed.	In the guidance it is explained that an ERA will not be required by default for a new food flavouring. For this reason, the data requirements have been kept as general/flexible as possible, not providing any prescriptive approach to ERA. References to different legislations and guidance documents are therefore included on purpose, to give to the applicant a spectrum of references to perform an ERA. It will be up to the applicant to apply the most appropriate approach for the substance they are dealing with. Regarding the PBT criteria, it is acknowledged that currently a specific reference to PBT/vPvB criteria cannot be found in the CLP Regulation, but only in Annex XIII of the REACH Regulation

			(EC) No 1907/2006. The guidance has been modified in section 4.6. to clarify this aspect. Further, the guidance mentions on purpose other legislations to set a general risk assessment approach based on principles described thereon e.g., ERA needed when (i) the flavouring does not occur naturally; (ii) it is produced in quantities above the cut-off tonnage band in line with the requirements of REACH (currently 10 tonnes) and it is classified according to the CLP criteria for environmental endpoints; (iii) a flavouring or its metabolites are PBT or vPvB (as indicated in REACH Annex XIII) irrespective of the tonnage band of the flavouring. In addition, please note that in the guidance it is mentioned that an EFSA cross-cutting guidance document on environmental risk assessment may become available in the future reconsidering the principles and the data requirements.
34		If the applicant proposes an ERA based on one of the schemes coming from another regulatory framework, can EFSA request to redo the assessment based on another scheme?	If an ERA is needed for a new flavouring and in case the approach proposed by the applicant is considered not scientifically justified, EFSA will have the possibility to request clarification from the applicant and if appropriate to request additional testing.
35		Assuming that any of the flavoring is passed through the GI system and metabolized, what would be EFSA's recommendation on what material to assess for environmental assessment? The original flavouring material or metabolites?	ADME studies will provide information on the metabolism and excretion of the flavouring. Hence, in case any concern on the environmental safety would be foreseen according to the principles described in the current guidance, it would be up to the applicant (supported by ADME data) to decide to perform the ERA based on the flavouring and/or its metabolites that are considered of most concern.

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Abbreviations

ADME – absorption, distribution, metabolism and excretion

AFS – Panel on Food additives, Flavourings, Processing Aids and Materials in contact with Food

ANS - Panel on Food Additives and Nutrient Sources added to Food

BMDL – lower confidence limit of the benchmark dose

BMDU – upper confidence limit of the benchmark dose

CAS - Chemical Abstract Service

CEF - Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids

EC - European Commission

ECHA - European Chemicals Agency

ECVAM - European Centre for the Validation of Alternative Methods

EFFA - European Flavour Association

EOGRTS – Extended One-Generation Reproduction Toxicity

ERA – Environmental Risk Assessment

EU - European Union

FACET – Flavours Additives and Food Contact Material Exposure Task

FAF - Panel on Food Additives and Flavourings

FAIM – Food Additive Intake Model

FBO – Food Business Operator

FDA – Food and Drug Administration

FLAVIS - Flavour Information System database

GI – gastrointestinal

GNPD – global new products database GPC gel permeation chromatography

IOFI - International Organization of the Flavor Industry

JECFA - The Joint FAO/WHO Expert Committee on Food Additives

MOE – margin of exposure

MN – Micronucleus

NAMs – New Approach Methodologies

NOAEL – no-observed-adverse-effect level

OECD TG – Organisation for Economic Co-operation and Development Test Guideline

PBT – Persistent Bioaccumulative and Toxic

(Q)SAR - quantitative structure-activity relationship

RAAF - Read Across Assessment Framework

SCCS – Scientific Committee of Consumers Safety

SNE - Specialised Nutrition Europe

TTC – Threshold of Toxicological Concern

vPvB – very Persistent and very Bioaccumulative

WHO - World Health Organisation