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Outcome of the public consultation on the draft scientific guidance for the preparation of applications on smoke flavouring primary products

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 smoke flavouring primary products. 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 16th plenary meeting of the FAF Panel, open to observers, held on 21-22 September 2020. The public consultation for this document was open from 5 October until 16 November 2020. On 5 November 2020, EFSA also organised a technical hearing with interested parties with the aim to present the content of the draft guidance document and to collect preliminary comments and input on its clarity and completeness ahead of the closing date of the public consultation.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 7 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 smoke flavourings. The guidance was adopted at the FAF Panel plenary meeting on 26 January and published in the EFSA Journal.

Key words: smoke flavouring primary products, guidance, public consultation

Requestor: EFSA

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1. Introduction

1.1. Background as provided by the requestor

Smoke flavourings are a specific category of flavourings and are subject to the general Regulation (EC) No 1334/2008[1] on flavourings and certain food ingredients with flavouring properties for use in/on foods. This Regulation lays down the general requirements for safe use of flavourings, provides definitions for different types of flavourings and sets out flavouring substances for which an evaluation and approval is required.

Smoke flavourings are specifically regulated by Regulation (EC) No 2065/2003[2] of the European Parliament and of the Council on smoke flavourings used or intended for use in or on foods. This Regulation establishes a Community procedure for the safety assessment and the authorisation of smoke flavourings intended for use in or on foods on the basis of a high level of protection of human health and protection of consumers' interests, as well as to ensure fair trade practices.

Regulation (EU) No 1321/2013[3] establishing the Union list of authorised smoke flavouring primary products for use as such in or on foods and/or for the production of derived smoke flavourings, was published on 12 December 2013. This Regulation lists the 10 authorised smoke flavouring primary products for use in or on foods and their conditions of use. This list was established on the basis of the applications submitted under Article 20 of the Regulation (EC) No 2065/2003[2] and after evaluation by EFSA.

As provided for under Article 7, paragraph 4 of Regulation (EC) No 2065/2003[2], EFSA developed the existing current guidance for the submissions of applications intended to establish the list of authorised smoke flavourings in view of their evaluation under the same Regulation.

The guidance is applicable to new applications on smoke flavourings primary products and for the renewal of the existing authorisations.

The current guidance is essentially based on a set of EFSA documents mentioned below:

- Guidance on the submission of a dossier on a smoke flavouring primary product (EFSA AFC Panel, 2005)

This lays down the information required by applicants to be included in the application. It lays down requirements in terms of administrative, technical and toxicological data necessary to enable EFSA to carry out the safety assessment of a smoke flavouring primary product.

This document is supplemented by the following additional documents:

- Dietary exposure assessment methods for smoke flavouring primary products (EFSA CEF Panel, 2009)

[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 2065/2003 of the European Parliament and of the Council of 10 November 2003 on smoke flavourings used or intended for use in or on foods. OJ L 309, 26.11.2003, p. 1–8.

[3] Commission Implementing Regulation (EU) No 1321/2013 of 10 December 2013 establishing the Union list of authorised smoke flavouring primary products for use as such in or on foods and/or for the production of derived smoke flavourings. OJ L 333, 12.12.2013, p. 54–67.

Dietary exposure for smoke flavourings is assessed using specifically developed methods, the SMK-TAMDI and SMK-EPIC methods.

- Statement on the interpretation of the Margin of Safety for Smoke Flavourings Primary Products (EFSA CEF Panel, 2010)

This statement clarifies the use of the margin of safety for smoke flavouring primary products on the basis of the available toxicological data.

EFSA is asked to update the above-mentioned documents and compile them in a single comprehensive document taking into account cross-sectional guidance documents, such as:

- Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011a);
- Opinion on the clarification of some aspects related to genotoxicity assessment (EFSA Scientific Committee, 2017a);
- Statement on the genotoxicity assessment of chemical mixtures (EFSA Scientific Committee, 2019a);
- Harmonised methodologies for human and animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019b);
- Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA, Scientific Committee, 2019c).

In addition, in the preparation of the new guidance, EFSA should also consider the latest updated version of the relevant Organisation for Economic Co-operation and Development Test Guidelines (OECD TG), such as:

- OECD TG 488 (OECD, 2020) Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays;
- OECD TG 474 (OECD, 2016a) *In vivo* mammalian erythrocyte micronucleus test OECD TG 489 (OECD, 2016b) *In vivo* Mammalian Alkaline Comet Assay.

As regards the exposure assessment, EFSA should take into account that the food categories used for regulatory purposes in flavourings are the food categories mentioned in Part D of Annex II of Regulation (EC) No 1333/2008[4] on food additives. A more refined exposure assessment could also be considered, based on actual use levels and on 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 be considered, where appropriate.

Furthermore, the relevant provisions arising from the recently published transparency Regulation[5] should also be taken into account in the preparation of this updated guidance and consistency should be ensured with other sectors where similar updates will be done.

While recognizing a connection with the general guidance and requirements for flavourings which may need also to be revised, the Commission considers that it is desirable, in view of

[4] 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.

[5] Regulation (EU) 2019/1381 of the European Parliament and of the Council on the transparency and sustainability of the EU risk assessment in the food chain. OJ L 231 of 6/9/2019 p.1

the specific conditions of smoke flavourings, to consider this update of the guidance on smoke flavouring primary products separately.

1.2. Terms of Reference as provided by the requestor

The Commission requests EFSA to prepare an updated consolidated guidance for the submission of applications on smoke flavouring primary products under Regulations (EC) No 2065/2003[2] and No 1321/2013[3], taking into account the experience gained with the assessment and the regulation of the currently authorised and assessed smoke flavouring products in the EU and, notably, the numerous other relevant scientific and technical documents published by EFSA since the adoption of the current guidance related to the safety of smoke flavourings.

The guidance should be updated taking into account applications on new smoke flavourings and the renewals of the existing authorisations.

EFSA should take into account the relevant provisions of Regulation (EU) 2019/1381[5] of the European Parliament and of the Council on the transparency and sustainability of the EU risk assessment in the food chain in the preparation of this updated guidance and should ensure consistency with other sectors where similar updates will be done.

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 for the preparation of applications on smoke flavouring primary products 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 5 October 2020 to 16 November 2020. The instructions on how to submit the comments were available at the following link: https://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-guidance-preparation

During the public consultation EFSA also organised a technical hearing with interested parties, which was held on 5 November 2020 as virtual meeting (a post-meeting announcement for this event is avaialble 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 19th FAF Plenary meeting on 26 January 2021 and is published in the EFSA Journal (EFSA FAF Panel, 2021).

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://www.efsa.europa.eu/sites/default/files/consultation/consultation/Scientific-guidance-on-smoke-flavouring-primary-products_DRAFT.pdf).

Seven interested parties submitted 28 comments via the EU survey online tool and one document, including additional comments, was uploaded as attachment. 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
CleanSmoke Coalition AISBL	Private sector (e.g. industry, consultancy, etc.)	BE
EFFA (European Flavour Association) - Smoke Flavours Task Force	International organisation	BE
International Organization of the Flavor Industry (IOFI)	International organisation	US
Kompozíció Kft.	Private sector (e.g. industry, consultancy, etc.)	HU
Leveret GmbH	Private sector (e.g. industry, consultancy, etc.)	CH
Michelle Slater	Personal capacity	UK
National Institute for Public Health and the Environment (RIVM)	National authority	NL

(a): As specified by the commenter.

3. Comments received and how they were addressed

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 for the preparation of applications on smoke flavouring primary products and responses from EFSA (the line numbering corresponds to the one used in the draft guidance launched for public consultation, available here).

#	Interested party	Chapter	Comment	Response from EFSA
1	EFFA (European Flavours Association) - Smoke Flavours Task Force	Abstract	EFFA (European Flavour Association) welcomes the opportunity to comment on the EFSA Draft Scientific Guidance for the preparation of applications on Smoke Flavouring Primary Products through this public consultation. EFFA represents the European Flavour Industry; our members are Flavour Houses and National Flavour Associations and cover most of the producers as well as many users of smoke flavouring primary products. These smoke flavouring primary products are used alone or combination in thousands of different flavouring formulations which on their turn are used in a very wide variety of final food applications covering different food categories. EFFA would like to submit the following comments to the EFSA Draft Guidance document.	Noted.
2	CleanSmoke Coalition AISBL	Abstract	The CleanSmoke Coalition (CSC) concurs with the responses given by EFFA. Beyond that the CSC wishes to make some general comments on the deferment of guidelines for studies to be carried out, the ambitious timelines for their completion, potential ambiguity and variables in animal testing and the non-consideration of the conditions of the ongoing pandemic for the completion of the tasks set for the risk assessment of smoke flavourings primary products. We hope to receive communication from the EU Commission explaining a transition or deferment period due to the complexity of placing work in GLP certified contract laboratories and	Noted. However, please consider that these issues fall under the remit of risk managers. Regarding the Transparency Regulation[5], the Practical Arrangements published on

			issues associated with attrition and illnesses. Furthermore, the enactment of the Transparency Regulation presents ambiguity to study designs and timing required to sufficiently address complete application materials.	EFSA's website at: https://www.efsa.europa.eu/en/corporate/pub/tr-practical-arrangements are the reference documents that lay down the detailed arrangements for how the new rules and measures the Transparency Regulation[5] introduces will operate in practice and are aimed at helping stakeholders to better understand how the new processes and tools affect them.
3	National Institute for Public Health and the Environment (RIVM)	Summary	RIVM would like to congratulate EFSA on the work done and hopes to provide useful comments for this guidance. Further, RIVM would like to note that the RIVM-employees (Polly Boon, Wim Mennes and Joop de Knecht) that have contributed in drafting this guidance, have not been involved in drafting these comments. Line 41: 'asfor'. Please change this typo into 'as for'.	Noted. The typo was changed as suggested.

4	Kompozíció Kft.	Summary	Végezetül, de nagyon hangsúlyosan: a Bizottság figyelembe vette-e az előírások által támasztott költség/előnyök elvét? A füstaromák és „elsődleges termékek" alkalmazásakor/szabályozásánál nem az volt-e a cél, hogy a hagyományos füstölés káros hatásait ki tudja szűrni, csökkenteni tudja? Számolt-e a Bizottság azzal, hogy jelen feltételrendszer okozhatja-e ennek a célnak a visszájára fordulását az „elsődleges terméket" gyártók ellehetetlenítésével? Véleményünk szerint tudományos szempontból vizsgálva sem tűnik ez kívánatosnak. English translation submitted by the stakeholder: Lastly, and more stressfully: has the Committee considered the idea of cost/benefit when making these guidances? Was the aim not to replace and/or decrease the harmful effects of the traditional smoking process when beginning the use/legislation of „primary product"? Has the Committee considered that if the manufacturer cannot fullfill the system of criteria, then the above-mentioned original aim might be lost? In our opinion, it cannot be explained, even from scientific point of view.	Comparison with traditional smoking is out of scope of this guidance and it will not be considered in the safety assessment. See reply to comment #31 in this Table.
5	EFFA (European Flavours Association); Smoke Flavours Task Force	Summary	General Comments - There are currently 10 Smoke Flavouring Primary Products on the market which are in the EU Union list of authorised smoke flavouring primary products (Commission Implementing Regulation (EU) No 1321/2013) and which have to be re-approved before January 2024. In order to allow EFSA to assess the safety of these smoke flavouring primary products currently on the market, for the renewal of their authorisations, ideally all dossiers have to be submitted at least 18 months before the end of the current approvals, which is by mid of 2022. Given that the final Guidance of EFSA is anticipated to be published by March 2021, this would give the applicants	The timeline issue is noted. Please note that the setting of deadlines falls under the remit of risk managers. However, considerations to accommodate the timeline issue have been introduced in the final version of the guidance document.

			a little bit more than one year to conduct all the necessary genotoxicity & toxicity studies (incl. analytical experiments and exposure assessment) in order to compile a complete dossier for timely submission. As can be seen from the timeline chart (see Annex A – Figure 1) this is a very challenging timeline.	
			- In addition the applications and dossier submissions will be subject to the new Transparency Regulation (i.e. Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain and amending, amongst others the General Food Law: Regulation (EC) No 178/2002). The impact of this regulation (which applies as of 27 March 2021) is not yet fully clear but it is anticipated that the new requirements (in particular the notification of studies) will cause additional administrative burden and will have a major impact on the timings for the risk assessment and risk management steps.	Regarding the new Transparency regulation[5], please see the response provided to comment #2 in this Table.

			- Several documents and tools are referenced in this Draft Guidance which are not yet finalized or in draft form (exposure tool, aneugenicity guidance, administrative guide): we would like to note that we are currently not able to comment in a comprehensive way on these aspects but would value the opportunity to comment on these draft documents at a later stage.	The documents referenced in the guidance on smoke flavourings and not yet finalised at the time of the public consultation have their own timelines for finalisation, i.e.: (1) the Scientific Committee (SC) guidance on the assessment of aneugenicity (EFSA-Q-2019-00262), (EFSA Scientific Committee, 2020), expected to be finalised by 31 August 2021. Of note, this document underwent a public consultation which closed at the end of May 2020 (see here for further details). (2) The EFSA's administrative guidance for the preparation of applications for authorisation of smoke flavouring primary products (EFSA-Q-2020-00371), expected to be published by March 2021. This document was not released for public consultation. (3) The new 'EFSA exposure tool', intended to be made available by 1st quarter of 2021.

			- Related to the aspect of Section 4 on uncertainty, the EFSA guidance does not describe in detail how the uncertainty analysis will be utilized in developing safety conclusions. In particular some further clarification might be helpful to understand how the input from the applicant will be used both qualitatively and quantitatively to characterize uncertainty and how such will impact conclusions on the safety of the primary products.	See response provided to comment #32 in this Table.
			- Related to page 9 line 285, can EFSA specify a more precise date than "under preparation" regarding administrative guidance, i.e. when would such guidance be expected to be published?	The EFSA's administrative guidance for the preparation of applications for authorisation of smoke flavouring primary products (EFSA-Q-2020-00371) is expected to be published by March 2021.

6	CleanSmoke Coalition AISBL	Summary	The CSC wishes to point out that the complete set of guidelines only will become available in March 2021. It is from that moment only that applicants will know with certainty what is required of them in terms of studies etc. In order to meet the deadline for the submission of application of 30/6/2022 this leaves scarcely little time to satisfy the demands of the risk assessor. The Union legislator has responded swiftly to the extraordinary demands of the COVID19 pandemic. This included the postponement of legislative acts such as the Regulation on organic food and farming (Regulation (EU) 2020/1693). Given that even in 'normal' times carrying out the work is near-impossible, we hope that lenience can be demonstrated in the process of readmission of smoke products both at the stage of risk assessment and risk management. Applicants who have assessed laboratories who are competent and dually qualified in GLP-related and subject matter experts in the suggested fields i.e. EOGRT studies recognize that breeding of animals, coordinating of protocols and executing required studies will be presented with significant obstacles associated with timing. Additionally, the chronological order in which the studies are suggested to be conducted with associated decision trees detail with certainty the lack of adequate time to address EFSA's requested timeline. We humbly seek a solution to address the expiry of the existing Union List or appropriate accommodations to enable study completion.	These issues are noted. Please note that these aspects fall under the remit of risk managers. Note also the response to comment #5 in this Table.

7	International Organization of the Flavor Industry	Summary	The International Organization of the Flavor Industry (IOFI) represents the global flavor industry and assists the industry in regulatory and scientific matters. Members of IOFI are national and regional associations of the flavor industry and international flavor houses active in the sector. Through the IOFI Scientific Program, our Association and its members promote a consistent global approach for the safety assessment of flavoring ingredients based on sound science. And where appropriate, IOFI and its members carry out scientific studies to ensure the safe use of flavorings. IOFI has taken note and reviewed the EFSA draft guidance document on Smoke Flavorings Primary Products (PP). Further, IOFI has had an opportunity to review and understand the comments regarding that draft guidance that have been entered into the record by the European Flavour Association (EFFA). IOFI strongly endorses the comments made by EFFA regarding the Smoke Flavorings PP draft guidance.	Noted.

8	Kompozíció Kft.	Introduction (overall chapter)	A múlt heti (2020.11.05.) videokonferenciát követően általunk bekért laboratóriumi ajánlatok alapján a vizsgálatokhoz szükséges időtartam (min. 4-5 év) és az engedélyünk megújításához szükséges határidők betartása (max. 3 év) látszólag ellentétben áll. A Bizottság miként kívánja feloldani ezt az ellentétet, amikor a felkészülést nem lehetett megkezdeni a konkrét elvárások ismeretének hiányában? English translation submitted by the stakeholder: After last week's (2020.11.05) video conference, we asked for an offer from laboratories. They show: the period needed to create measures are longer (min. 4-5 years) than the period which we have for renewing our permission (max. 3 years). How will the Committee plan to offset this difference when we did not have enough time to prepare without concrete criteria/legislation?	The timelines issue is noted. Please note that the setting of deadlines falls under the remit of risk managers. Note also the response to comment # 5 in this Table.
9	CleanSmoke Coalition AISBL	Introduction (overall chapter)	The CSC wishes to stress the uniqueness and the complexity of smoke flavouring primary products, as they are highly complex mixtures comprising 100's of constituents. This in contrast to other flavourings that are comprised of a limited number of known compounds. It is acknowledged that such complexity can make a risk assessment complex as well, but should also lead to realistic and doable requirements with respect to the generation of data for such assessment.	The timelines issue is noted. Please note that the setting of deadlines falls under the remit of risk managers. Note also the response to comment # 5 in this Table.

			As mentioned in lines 131-135, smoke flavourings are a specific category of flavourings, complex mixtures or UVCB (Unknown or Variable composition, Complex reaction products or Biological materials). It is well acknowledged that smoke flavourings are not like flavouring substances and consist of mixtures, but compared to novel foods, smoke flavourings are already used for several decades with proven benefit for human health compared to conventionally smoked food, offering manufacturers and consumers greater alternatives and choices.	Despite some experience in the use of the authorised smoke flavourings, some safety aspects related to e.g. genotoxicity and reproductive and developmental toxicity have not been investigated according to present guidelines.
			The manufacturing process of smoke flavours involves the elimination and reduction of notable PAHs and other particulates associated with human health risks. It is understood that smoke flavourings can serve as a useful tool along with conventional smoking to provide enhanced consumer options and is safe alternative when used as intended.	Considerations on the comparison with conventionally smoked food are risk management issues. Please also note the response to comment #31 in this Table.
10	Michelle Slater	1.2 Identity of the primary product	Can they be classified as natural under Article 16 of Commission Regulation (EC) No 1334/2008?	Classification as natural is not a matter of the safety assessment but a risk management decision. Therefore, this aspect is not covered in the guidance document.
11	Leveret GmbH	1.2.3 Chemical composition	1.2.3.2 Chemical characterisation Lines 359-361 Information on the primary product should be provided via chemical sum parameters, i.e. parameters determining the content (% m/m) of major classes of components with common structural aspects (e.g. acids, carbonyls or phenols). **Comment:** It is unclear whether these structural classes should be measured as such or their percentages are calculated by summation of respective identified constituents. Single constituents could belong to several of these structural classes – how would this be considered in the summation process?	In general, these structural classes should be determined as such e.g. by colorimetric methods or titration, rather than by summing up respective identified individual constituents. This clarification has been inserted into the guidance document.

			1.2.3.3 Identification and quantification of individual components Lines 366-367 This offers applicants the opportunity and the obligation to minimize the unidentified fraction of smoke flavouring primary products. **Comment:** The Panel refers to the significant progress of analytical techniques for qualitative and quantitative analysis. However, while there is undoubtable progress on the resolution (e.g. GCxGC-MS, however, the set of molecules which might be identified using databases (e.g. NIST) has not remarkably increased for the corresponding compound classes. Newly identified compounds would automatically lead to an iterative and presumably endless re-evaluation of the potential genotoxicity of the primary products. This would make it impossible to submit the dossier until the respective deadline, considering the statement that the genotoxicity assessment should be finished before embarking on any other necessary toxicological studies, as set out in the Guidance. **Question:** Is there a recommended best practice approach up to which level unidentified peaks have to be minimised, to start with the component-based genotoxicity assessment, especially as there is no analytical cut-off mentioned within this guidance?	As mentioned in the guidance document, capillary gas chromatography coupled with mass spectrometry (for identification) and with flame ionization detection (for quantification) are considered as state-of-the-art techniques suitable for the analysis of the volatile fraction. For the non-volatile fraction, analytical approaches such as gel permeation chromatography or high performance liquid chromatography coupled with dedicated mass spectrometers are considered as suitable techniques.
			1.2.3.3.1 Identification and quantification of the volatile fraction Lines 382-385 *"The identification of a component must be considered as 'tentative', if authentic reference substances are not available and the identification is solely based on the comparison of mass spectral data of the components to those of a fragmentation mass spectral library."* **Comment and questions:** In a recent Scientific Opinion on a complex chemical mixture (EFSA Journal 2019;17(5):5675), the FAF Panel	The component-based approach requested as the first step of genotoxicity assessment requires unequivocal identifications of substances in order to be able to make predictions regarding their genotoxic potential. Therefore, the requirements for the identification of primary product

			considered components "identified" if the identification was based on comparison of the mass spectral data to those of authentic reference compounds OR commercially available MS libraries; and «tentatively identified» if the identification was based on fragmentation patterns of homologous compounds. Why is the described approach different in the present Draft Guidance? It is not specified in the text how "tentatively identified" constituents will be considered in the safety assessment. Would they need to be considered as part of the fraction of unidentified constituents as it was a case for the above-mentioned product?	components have been strengthened in the guidance on smoke flavourings. Yes, "tentatively identified" constituents will be considered as part of the fraction of unidentified constituents. In that fraction the status of tentatively identified constituents may assist to improve the assessment by taking into account the structural elements and possible similarities to identified constituents. A respective sentence has been inserted into the guidance document.
12	National Institute for Public Health and the Environment (RIVM)	1.2.3 Chemical composition	Section 1.2.3.2 Line 360-361: *"major classes of components with common structural aspects (e.g. acids, carbonyls or phenols)". A list of all classes of components to be provided would be helpful for the applicant. EFSA is requested to consider adding this."*	Based on the compositional data on smoke flavouring primary products from previous submissions, carbonyls, phenols and acids are the only reported classes of components with common structural aspects. Accordingly, the "e.g." has been deleted in the parenthesis.

13	EFFA (European Flavours Association); Smoke Flavours Task Force	1.2.3 Chemical composition	**- pg 11 lines 382-384:** For smoke flavouring primary products more than 400 different components have been reported in scientific reports. For a high number of components authentic reference substances will not be available to enable comparison of their mass spectra, so that a large part will remain tentatively identified. During the technical hearing meeting (which took place on 5 November 2020) it has been explained, that tentatively identified components are not generally accepted as part of the identified fraction. Can EFSA define a factor for which a tentatively identification would be justified? • If a chemical is determined to be "tentatively identified" can EFSA please confirm this applies to the unidentified fraction?	Yes, "tentatively identified" constituents will be considered as part of the fraction of unidentified constituents. The Panel emphases the request that as many constituents as possible should be fully identified. If constituents can only be tentatively identified, this information may be used to assist to improve the assessment of the fraction of the unidentified constituents, by taking into account the structural elements and possible similarities to identified constituents.

			- pg 12 lines 410-414: EFSA states: "Besides the concentrations of the 15 PAHs reported by Regulation (EC) No 627/2006, the concentration of benzo[c]fluorene should also be determined (JECFA, 2005)." Is EFSA suggesting that different methods not outlined in the Commission Regulation (EC) No 627/2006 for PAH quantification need to be applied or are the methods outlined in this regulation acceptable? • Can EFSA clarify the addition of a 16th PAH referenced by JECFA (but not by EC) and what is the reasoning behind?	In order to clarify the requirements, the necessity to apply the best available techniques currently available for analysis of polycyclic aromatic hydrocarbons (PAHs) has been emphasised in the text of the guidance. The Panel concluded that also benzo[c]fluorene should be included to the above priority list, considering that (i) JECFA reported in its 64th report (JECFA, 2005) that the substance may contribute to the formation of lung tumours after oral exposure to coal tar and (ii) the CONTAM Panel recommended that occurrence data for benzo[c]fluorene are needed (EFSA CONTAM Panel, 2008). Reference to CONTAM Panel opinion was added to the guidance (i.e. EFSA CONTAM Panel, 2008).

			- pg 13 lines 446-449: Can EFSA clarify how detailed and specific the chemical classes need to be defined or add the classification to the guidance? As mentioned during the technical hearing, for each chemical class the stability of 5 substances should be determined. If less (than 5) chemical classes are identified in the mixture, would this mean that less than 25 marker substances be used to determine stability in the foods?	The number of 5 constituents mentioned at the technical hearing was only exemplary. There is no fixed number of constituents which have to be assessed to demonstrate the stability of the primary product. The spectrum of selected constituents should be representative of the chemical classes identified. The assessment of the stability of the primary product may also be supported by determining the areas of unidentified peaks in the chromatograms after different intervals of storage.
14	National Institute for Public Health and the Environment (RIVM)	2.1.1 Data to be provided for new smoke flavouring primary products	Section 2.1.1 and 2.1.2 Lines 469-470: "*The food categories should be coded according to the food categories in Annex II, Part D, of Regulation (EC) No 1333/2008 and the FoodEx2 nomenclature. FoodEx2 is a standardised food 470 classification and description system developed by EFSA.*" It could be helpful for applicants if reference is made to the Guidance document describing the food categories in Part E of Annex II to Regulation (EC) No 1333/2008 on Food Additives on the website of the European Commission. https://ec.europa.eu/food/safety/food_improvement_agents/additives/eu_rules_en	The weblink to the Guidance document describing the food categories of Part E, Annex II to Regulation (EC) No 1333/2008[4], has been added as a footnote to the guidance.

			Lines 477-481 (and 505-509) "*For composite dishes with ingredients containing smoke flavouring primary products, the proposed maximum and expected typical use levels for the respective primary products should be provided per ingredient (at food name level). It may be beneficial for the exposure assessment if the quantities of the primary products-containing ingredients in the composite dishes are also specified.*" - Is it correct that no maximum and (expected) typical use levels are required for the 'composite dishes' as such? The last sentence ('It may be beneficial…') seems a more general recommendation, not only applicable for smoke flavourings. Is that correct? RIVM requests EFSA to provide an explanation.	It is correct that the applicant does not have to submit levels for composite dishes, but only for their ingredients. In order to be aligned with the Regulation, the guidance now refers to compound foods instead of composite dishes. If applicants are not able to provide information about the quantity of the ingredients containing the primary product in compound foods, EFSA will derive this information, e.g. from generic recipes.
			Lines 461-509: Sections 2.1.1 and 2.1.2 largely contain identical text. It could be considered to combine these two sections with a few lines explaining the difference in requirements between new applications and renewals.	This is noted. However, the Panel considers that merging the text would make it less clear.
15	CleanSmoke Coalition AISBL	2.1.2 Data to be provided for renewals of authorisations of smoke flavouring primary products included in Regulation	Proposed maximum use levels for smoke flavouring are calculated based on the primary product by the applicants. However, the typical usage levels are developed by the user of smoke flavourings (not publicly available as part of their recipe/IP). The proposed maximum use levels currently may overestimate final observed values, due to the complexity of analytical techniques required and varying use by customers. Add guidance on how to assess typical usage levels, considering that primary products are reprocessed into smoke flavourings and used by third parties in their recipes and processes.	EFSA has clarified this point in the guidance. Typical use levels should not be 'assessed' but may be 'provided' if available based on, for example, previous experience or information from food producers using smoke flavourings in foods, as routinely done for food additives within the re-evaluation programme. If these levels are not provided,

		(EU) No 1321/2013[3]		only maximum use levels will be considered in the exposure assessment. Providing typical use levels is not mandatory but is encouraged because their use will result in more realistic exposure estimates.
16	EFFA (European Flavours Association); Smoke Flavours Task Force	2.1.2 Data to be provided for renewals of authorisations of smoke flavouring primary products included in Regulation (EU) No 1321/2013[3]	**- pg 14 lines 496-499:** EFSA refers to the FoodEx2 nomenclature, but the problem is that smoked foods are only represented in a few food categories in FoodEx2. Given that smoked foods are not represented in the food categories, is there a way so that smoke flavourings can be more accurately represented for exposure in FoodEx2? EFFA would welcome EFSA's views or potential clarification on the following observations: The draft guidance recommends using FoodEx2 to provide use levels for more specific foods than included in Annex II Part D, yet a search of the current FoodEx2 exposure hierarchy (revision 2) indicates that the term "smoke" or "smoked" occurs in less than 10 food names, mostly for different types of smoked fish. Hence, we are of the view that dietary exposure estimates based on FoodEx2 food categories are not necessarily more accurate than those from FAIM (or even the previously recommended tools). We would highly welcome any additional guidance as to how FoodEx2 can be used to more specifically identify appropriate food categories, especially considering that the regulation will be based on Annex II Part D food categories.	This is noted, Applicants can use any food category in FoodEx2, not only those containing the terms "smoke" and/or "smoked". To help applicants with the exposure assessments, the link between FoodEx2 food categories and those mentioned in Annex II (excel file) is available at this link: https://zenodo.org/record/4461577#.YBAWc-hKiUk Please see below an example in which FoodEx2 could be used to further refine the exposure estimates. Food Additive Intake Model (FAIM) contains the main food categories from Annex II, Part D to Regulation No1333/2008[4]. FoodEx2 contains food names.

				E.g. in FAIM, you can find the category 'Ripened cheeses' while in FoodEx2 you can find each specific ripened cheese on the market (e.g. edam, gruyere, etc…). In case that a smoke flavouring is not intended to be used in all ripened cheeses, the use of the food category 01.7.2 would result in an overestimation of exposure. A refinement would be possible if the individual ripened cheese in which the smoke flavouring is intended to be used would be specified by means of the FoodEx2 classification system.
17	Leveret GmbH	2.2 Exposure assessment	Line 526 EFSA exposure tool **Comment and question:** We're interested to know more about EFSA's exposure tool. When will this be available?	The EFSA exposure tool is intended to be made available by 1st quarter of 2021.

			Lines 551-552 Additional information, such as from facets within the FoodEx2 nomenclature or form Mintel's GNPD, may be used to refine the exposure assessment. **Comment and questions:** We're pleased to note that it is the Panel's aim to estimate consumer intake to smoke flavourings as "realistically" as possible and that GNPD data may be used to refine intake assessments. Is there any best practice approach on how applicants could use the GNPD data to refine intake assessments? Would a percentage of new product launches for a specific food category containing a selected facet (e.g. smoke) over the last 5 years be helpful? How is it foreseen that facets could be used in the FoodEx2 nomenclature for smoke flavourings?	Applicants are not requested to use data from Mintel's global new products database (GNPD). Within its assessment, EFSA might search for information from this database, similar to what is already done in the re-evaluation on food additives to refine the assessment. Yes, all information that will help to refine the exposure assessment is helpful. This has been clarified in the guidance. Facets are not foreseen in the tool and they cannot therefore be used by the applicants. EFSA could use the facets to refine the assessment by differentiating between foods treated with smoke flavourings and not treated with these flavourings within one food category in the consumption data.

18	National Institute for Public Health and the Environment (RIVM)	2.2 Exposure assessment	Lines 522-530: RIVM requests EFSA to provide an explanation on the difference between the two exposure models, and on the need to submit exposure assessments with both models.	The guidance has been amended in order to make clearer the differences between the two exposure tools. In practice, the main difference is related to the level of detail of the food categories included in the assessment. The FAIM tool should be used, because only FAIM will give results expressed by food categories according to the legislation.
			Lines 538-542. Furthermore, the level of detail of foods which may contain the smoke flavouring primary product will often not be specific in these tools and consequently maximum or typical use levels will be assigned to whole food categories. Due to this, exposure estimates provided by both tools are expected to overestimate the dietary exposure to smoke flavouring primary products. RIVM would consider it helpful for exposure/risk assessors if additional information (e.g. consumption statistics, consumption/market shares) for the particular food is provided in case the two tools are not specific enough. EFSA is requested to consider adding the request for this additional information.	In the guidance a statement was added clarifying that the applicant can provide any additional information (such as market share) that may be relevant for the exposure assessment.

			Line 544. Uncertainties. RIVM requests EFSA to refer to section 4, where uncertainties are described in more detail. 'as well as possible uncertainties of the exposure estimates observed by the applicant' suggest that applicants should describe or assess the uncertainties themselves. This is contradictory with line 1034 of section 4.3 which mentions that 'Applicants do not need to describe or assess the uncertainties themselves'. Please consider rewording to be in line with section 4.3.	The second half of the sentence referring to uncertainties has been deleted from the guidance. A generic sentence about supplying information about uncertainties has been added in section 4.3.
			Line 560-561. This sentence is only clear for experienced exposure assessors. Please describe how the variability in exposure due to differences in food consumption between individuals will be taken into account.	This sentence has been deleted from the guidance document. Inter-individual variability will be explained in the opinions if necessary.
19	EFFA (European Flavours Association); Smoke Flavours Task Force	2.2 Exposure assessment	**- pg 15 line 526:** EFSA specifies that dietary exposure must be estimated using two exposure assessment tools, only one of which is available at the time the draft guidance was issued for public comment. Can EFSA provide a time estimation when the "EFSA exposure tool" which is still under development will be available?	See response to question #17 in this Table.
			- pg 15 lines 527-530: To ensure clarity in the exposure evaluation can EFSA provide the Authority's "map" between the Annex II food categories and the FoodEx2 food categories to create clarity for applicants. The draft guidance states that FAIM relies upon food categories as specified in Annex II of Regulation (EC) No 1333/2008 Part D (Annex II Part D) whereas the EFSA exposure tool relies on food categories in FoodEx2. The draft guidance also states that both exposure assessment tools use	See response to question #16 in this Table. Mapping between Annex II Part D and FoodEx2 food categories can only be provided as an example, because there are many exceptions that should be taken care of.

			consumption data from the EFSA Comprehensive European Food Consumption Database ("Comprehensive Database") (Lines 527-528). If that is the case, then we assume that EFSA would have had to "map" the Annex II Part D food categories used in FAIM to the FoodEx2 food categories. Not entirely clear however is how and when should applicants submit this info and additional clarification would be valued.	The classification of the food consumption data according to the food categories listed in Annex II Part D has been carried out by EFSA using, when necessary, the FoodEx2 facets and the original food descriptors, in addition to the Foodex2 basic codes.
			It is our understanding (see indent below) that some of Annex II Part D food categories could not be mapped to FoodEx2 and are thus excluded from FAIM. Could EFSA confirm this and provide some guidance on how to address this? See EFSA "Food Additives Intake Model (FAIM) template" – Version 2.0 – October 2017. "*Some of the food categories, restrictions and/or exceptions presented in the Regulation could not be identified in the FoodEx nomenclature and consequently are not represented in the FAIM template*." While this citation references FoodEx1 instead of FoodEx2, a comparison between Annex II Part D and FAIM indicates only ~ 60% of the Annex II Part D categories are included in FAIM.	This is correct. Some foods in the EFSA Comprehensive database are not available as proposed in the Annex II, Part D, Regulation 1333/2008[4].
			Example: The draft guidance states that proposed maximum and typical use levels should be provided for ingredients of composite dishes containing smoke flavouring primary products (Lines 505-509). While "composite dishes" is a Level 1 category in FoodEx2, there is no category specified as such in Annex II Part D. Even if Category 18 in Annex II Part D (Processed foods not covered by categories 1 to 17, excluding foods for infants and young children) is equivalent to "composite foods", Annex II Part D provides no further breakdown of this category. Additionally, Category 18 is not even included in FAIM. Further EFSA guidance as to how use levels can be provided for	Food category 18 is not present in FAIM as this category refers to a wide range of compound foods. Compound foods as reported in the EFSA Comprehensive database are linked to the food category of their main ingredient in FAIM. For example, pizza is coded as fine bakery wares (food category 07.2).

			composite dish ingredients would be very welcome to address this discrepancy.	
			Example: There is one food category in FAIM where the applicant can enter a use level for a parent food category [1.7 "Cheese and cheese products") and subcategories (1.7.1 "Unripened cheese excluding products falling in category 16," 1.7.2 "Ripened Cheese," 1.7.4 "Whey cheese," and 1.7.5 "Processed cheese"); NOTE: 1.7.3 "Edible cheese rind" and 1.7.6 "Cheese products (excluding products falling in category 16)" are not included in FAIM]. When using a fixed use level, the dietary exposure estimates for the parent food category 1.7 is lower than for subcategory 1.7.1, subcategory 1.7.2 or for the combination of all subcategories (1.7.1, 1.7.2, 1.7.4, and 1.7.5), which should not be possible. This example illustrates the need for such a mapping between Annex II Part D and FoodEx2 food categories.	Food category 1.7.3 edible cheese rind is not available in the EFSA Comprehensive database as cheese rind is always eaten together with the cheese itself. Consumption of food category 1.7.6 cheese products is also not reported in the EFSA Comprehensive database, because it is difficult to distinct between processed cheese and cheese products. Food category 1.7 in the FAIM template only contains foods that have not been classified in other food categories (food categories 1.7.1, 1.7.2, 1.7.4, 1.7.5). If a flavouring can be used in all cheeses and cheese products, all food categories should be used including 1.7.
			- pg 16 lines 541 – 559: EFSA states (line 541-542) that: "*exposure estimates provided by both tools are expected to overestimate the dietary exposure to smoke flavouring primary products*." Could EFSA consider using the average range for exposure estimates instead of the exposure estimates for high consumers (95th percentile estimated exposures across relevant	In the risk assessment of smoke flavouring, standard practice will be used. For this, high consumers will be considered

			population groups and countries, based on the proposed maximum use levels by the two exposure assessment tools). Additional justification is provided below: - EFSA's current guidance is limited to adults because the CEF Panel concluded that "…*dietary exposure to smoke flavourings in children is unlikely to be higher than that estimate for adults*." (EFSA CEF Panel, 2009). - At least for FAIM, the output includes a range of average exposure estimates (based on the same use levels), in addition to a range of 95th percentile exposure estimates, based on individual surveys from individual countries.	when assessing exposure (see chapter 6 of (WHO/IPCS, 2009), (EFSA, 2011)); people consuming high levels of foods that could contain the smoke flavourings or consumers that consume higher levels per kg body weight.
			- pg 16 lines 557 – 561: Can EFSA clarify on how the Authority will identify "relevant population groups and countries": - The Comprehensive Database includes 62 surveys from 23 countries. At least with FAIM, the output includes separate average and 95th percentile dietary exposure estimates for each survey and country. - These data are summarized as ranges of average and 95th percentile values for up to six population groups (infants, toddlers, other children, adolescents, adults, and elderly and very elderly), without any guidance as to what is "relevant." (Note: The Comprehensive Database separates elderly and very elderly into separate population groups, as well as includes lactating women and pregnant woman.)	See response to comment #18 in this Table.
			- pg 16 lines 544-545: If the applicant provides uncertainties in the exposure assessment that scientifically justify the overestimation of exposure to smoke flavourings would EFSA use this data? The draft guidance states that the applicant should include possible uncertainties in the exposure estimates even though EFSA states that the uncertainty analysis is part of the risk assessment performed by EFSA (lines 1000-1001).	Yes, as explained in Chapter 4.3. of the final version of the guidance document "*the applicant is encouraged to provide any information on potential sources of uncertainty which may be relevant for the*

			See also slide 33 from EFSA's 21 September 2020 presentation "*Applicants do not need to describe or assess uncertainties themselves*".	*risk assessment of the primary product."*
			- pg 16 lines 533-534 and 559-560: The draft guidance requires the applicant to provide separate exposure assessments based on typical use levels when EFSA later states that the risk assessment will be based on exposure estimates based on the proposed maximum use levels. Given that EFSA will use the proposed maximum use levels, it is not clear for the applicants why both exposure assessments need to be performed and further clarification on this would be helpful for the applicant to provide the most appropriate use level/exposure information.	The text has been revised to clarify for which purpose the typical use levels will be used.
20	EFFA (European Flavours Association); Smoke Flavours Task Force	3. Safety data	- **pg 22 line 819:** can EFSA provide information/clarification that supports the statement "*it has become clear that exposure levels of smoke flavouring primary products approach those observed for food additives*". Smoke Flavouring are a clear category defined amongst others according to the Flavouring Regulation (EU) No 1334/2008 (defined by Art. 3(2)(f)) which lays down the general requirements for safe use of flavourings including smoke flavourings, as reassessed in lines 132-134.	This statement is based on the exposure assessments reported in the previous scientific opinions on smoke flavouring primary products.

			- pg 22 Lines 823-824: EFSA has compared smoke flavourings with food additives in the approach taken for safety assessments; however, there are differences between these approaches and smoke flavourings are not similar to food additives. Below are examples on how smoke flavourings differ from food additives and the differences in EFSA considerations between the two guidance's: a) Smoke flavourings are identified as complex mixtures or UVCB's (substances of unknown or variable composition, complex reaction products or of biological materials); food additives are identified as single substances, simple mixtures, complex mixtures (and more). The food additive guidance does not provide specific guidance for testing of food additive complex mixtures that would align with smoke flavourings. - Section 3.3.3 (smoke flavourings): "*For primary products an individual evaluation should be performed, since they are complex mixtures for which read-across is not applicable*". For food additives (Section 4.2.1), read-across of data is suggested as a tool for understanding "relevant knowledge on the substance." No differential guidance is provided that states this is not appropriate for complex mixtures. - Section 3.2 (smoke flavourings): "*Smoke flavouring primary products are complex mixtures that may contain a substantial fraction of unidentified components. The recommended approach for the genotoxicity assessment of such type of mixtures is described by the statement of the EFSA Scientific Committee (EFSA Scientific Committee, 2019b).*" "*The genotoxic potential of the chemically identified components in a smoke flavouring primary product should be assessed individually, using all available data.*" For food additives, genotoxic potential (section 4.2.1) is assessed on a whole product level. No differential guidance is provided for complex mixtures.	a) The EFSA guidance on food additives (EFSA ANS Panel, 2012) addresses both single substances and complex mixtures. However, more specific guidance on mixtures and a statement of the genotoxicity assessment of mixtures were published later by EFSA Scientific Committee (EFSA Scientific Committee, 2019a, 2019b) and thus these have been taken into account in the current guidance on smoke flavouring primary products.

			b) The testing approach for smoke flavourings requires genotoxicity assessment/testing of each individual constituent or smoke fractions and justification to be provided for testing of the whole product. Assessment of food additives generally requires testing of the whole product. - Section 3.2 in the draft smoke flavouring guidance states "*The genotoxic potential of the chemically identified components in a smoke flavouring primary product should be assessed individually, using all available data. Genotoxicity data should be collected and evaluated based on the Scientific Committee guidance on genotoxicity (EFSA Scientific Committee, 2011a, 2017, 2020). Conclusions on genotoxicity are required for all identified components*." For food additives (section 4.1.1), no requirements are provided for the testing of individual constituents except for metabolism and toxicokinetic studies of complex mixtures where it is noted "*conventional metabolism and toxicokinetic studies may not be feasible for all components in the mixture, but should be provided for toxicologically relevant constituents. Toxicologically relevant constituents are generally considered to be the major components and those other components with known or demonstrable biological or toxicological activity, and should be determined on a case-by-case basis with a scientific justification and the rationale for their selection provided*."	b) See the response to a).
			c) The safety testing strategy for food additives has clear tiers with trigger points aimed at building an understanding of the potential mechanisms of toxicity. The smoke flavouring strategy is less clearly layered and seeks a comprehensive understanding of potential toxicity mechanisms at Tier I. - Food additives Tier 1: In vitro genotoxicity, 90-day subchronic toxicity, ADME absorption; Tier 2: In vivo genotoxicity, single dose ADME, chronic toxicity/ carcinogenicity, prenatal developmental toxicity / EOGRTS; Tier 3: Repeat dose ADME, carcinogenicity, neurotoxicity, immunotoxicity, endocrine activity (as needed)	c) It should be noted that this guidance document is not a direct "translation" of the guidance document on food additives. It rather takes into account the fact that primary products are complex mixtures with portions of unidentified constituents (with potential toxicological interactions) and this is reflected in various aspects of this guidance

			- Smoke Flavourings Tier I: In vitro genotoxicity, in vivo genotoxicity (if required), repeat dose toxicity study, and EOGRTS including neurotoxicity, immunotoxicity, endocrine activity, prenatal developmental toxicity; Tier II: chronic toxicity/ carcinogenicity, reproductive and developmental toxicity specialized studies	document. In particular it should be noted that Tier I/Tier II for smoke flavourings are not the same as Tier 1/2 for food additives. The data requirements for new smoke flavourings are clearly layered, considering that before going into Tier I testing, any genotoxicity concern should be ruled out. The considerations of absorption, distribution, metabolism and excretion (ADME), i.e. non-negligible absorption in the gastrointestinal tract, are the trigger to enter into Tier I for smoke flavourings. More extensive testing could be requested in Tier II after analysis of the results obtained from the studies carried out under Tier I. This strict tiered approach was maintained for new smoke flavourings. Considering the timeline issue, for renewals, applicants may follow a different testing approach enabling simultaneous testing. For renewals there will be no tiered testing approach (i.e. there is only one tier, since the timeline

				constraints do not allow sequential testing). Therefore, for renewal applications an alternative set of requested toxicity studies has now been included in the final version of the smoke flavouring guidance to accommodate this issue. It should be noted that the Extended One-Generation Reproduction Toxicity study (EOGRTS) which is requested in the smoke flavouring guidance Tier I, is not deviant from the EOGRTS requested in the Tier 2 for food additives. In the food additives guidance (EFSA ANS Panel, 2012) it is also clarified that an EOGRTS includes the cohorts for neurotoxicity and immunotoxicity. Endocrine disruption is also addressed, e.g. in the toxicity evaluation of the parental animals.

			d) Tier I for smoke flavourings contains all genotoxicity testing (*in vitro* and *in vivo*); all concerns for genotoxicity must be resolved before progressing to the EOGRTS or 90-day studies. This is not a requirement of food additives.	d) For applications for new smoke primary products, the requirement for genotoxicity tests to be completed prior to *in vivo* tests for toxicity other than genotoxicity is for animal welfare. This is not required for renewal applications to accommodate for the timeline constraints.
			e) Food additive testing seeks to understand how the additive is processed in the body; smoke flavouring testing starts with the assumption that the product will contain constituents that will be absorbed by the gastrointestinal tract. Thus, while food additives are subject to toxicokinetic testing and incremental toxicity testing, safety assessment of smoke flavourings require toxicity data at Tier I. - The smoke flavourings guideline (section 3.3.2) states "*Based on the information available from previous evaluations, it can be assumed that many primary products will contain constituents that will be absorbed in the gastrointestinal tract, and given the molecular structures and molecular weights of the constituents identified to date, the absorption in the gastrointestinal tract can be anticipated to be substantial. It can therefore be concluded that toxicity data are needed for the safety assessment of these primary products*". Studies to define distribution, metabolism and excretion and other basic toxicokinetic parameters are not performed for smoke flavourings. Moreover, although Tier 1 testing for food additives demonstrates whether absorption occurs, the Tier 2 tests do not include components such as immunotoxicity or endocrine activity. These are only used in Tier 3 on a case by case basis.	e) See response to c).

			f) The triggers for ascending the tiers for food additive and smoke flavouring testing are clearly defined and different. <u>Smoke Flavourings triggers for Tier I to II (Appendix E):</u> Toxicity in subchronic or cohort of EOGRTS Magnitude of Margin of Safety <u>Food additives triggers for Tier 1 to 2 (Appendix A):</u> Systemic availability Toxicity in 90-day toxicity study Positive findings in in vitro genotoxicity studies <u>Food additives triggers for Tier 2 to 3 (Appendix A):</u> Bioaccumulation Toxicity in in vivo genotoxicity Toxicity in chronic/carcinogenicity or EOGRTS study	f) The aim is that for smoke flavourings primary products the same level of confidence in toxicity data is reached as for food additives. However, since the Tiers are not identical, also the triggers are not identical. The approaches should be consistent as far as possible. However, given the impossibility to do adequate ADME studies with smoke flavourings, the differences in Tiers and Tier triggers are justified.
21	EFFA (European Flavours Association); Smoke Flavours Task Force	3.1 General considerations	- **pg 16 line 572:** indicates that "*Toxicity studies should generally be conducted in accordance with OECD TGs.*" Currently the EFSA GD does not address the "special considerations" required by OECD (2017) for complex mixtures and address artifacts introduced by high concentrations/doses that confound interpretation. Is there an intention of EFSA to also address these elements? See more details below. - OECD (2017) indicates that "*Complex mixtures require special modifications of the TGs in order to properly characterise the test chemical, appropriately metabolise the chemical, adequately expose the cells/animals, conduct an adequate test, and properly interpret the test data*." Since OECD (2017) further notes that "*Guidance for these special chemicals is not described in the TGs.*", the EFSA guidance on smoke flavouring primary products currently does not provide additional guidance, nor acknowledges, that most of the OECD TG proposed as Tier 1 or 2 testing do not have provisions specifically for complex mixtures, such as (but not limited to) the	For the testing of the unidentified components (either the isolated fraction or as part of the whole mixture) EFSA follows the Organisation for Economic Co-operation and Development (OECD) guidelines as if these substances were single compounds. By using the limit concentration for a mixture, the concentration of individual components will not reach the concentration that

			limit concentration, typically based on the single-substance MTD or the limit concentration, whichever is lower. The MTD and thus limit concentration for smoke primary product mixtures is anticipated to greatly exceed the limit concentration for single chemicals (e.g. 10 mM *in vitro* and/or 1000 mg/kg bw/day *in vivo*) and exposure levels above these limits are well known to introduce artifacts that confound interpretation. For example, *in vitro* artifacts caused by testing excessive concentrations (e.g. >10 mM) include reaction of test substances with culture medium leading to the high osmolality, high ionic strength, extremes of pH, production of reactive oxygen species, and/or secondary cytotoxicity, should be avoided (Kirkland et al., 2011). - Similarly, practical upper limits (i.e. 1000 mg/kg bw/day or 5% in feed in OECD TG 453 (OECD, 2018c)) have long been established to avoid the use of excessively high doses in animal studies. For example, a limit concentration of 5% of the test substance in the feed for dietary studies is proposed to avoid nutritional imbalances and other well-documented artifacts (and animal welfare considerations) that arise from testing higher doses. For smoke flavouring primary products, 5% in feed is equivalent to ~3700 mg/kg bw/day, which is more than 3-fold higher than the single-chemical limit dose of 1000 mg/kg bw/day (OECD TG 408 (OECD, 2018a)). How will EFSA address (1) artifacts introduced by high concentrations/doses that confound interpretation and (2) animal welfare considerations noted on page 17, lines 600-02?	would be used if tested individually. The range of concentrations or doses used in genotoxicity/toxicity tests, from a maximum tolerated dose (MTD) to a dose producing little or no toxicity, are established on the basis of the results of a preliminary range-finding study. Appropriate toxicity parameters are evaluated for each genotoxicity/toxicity assay. For example for genotoxicity tests, the solubility of the mixtures, the accuracy and the stability of the solutions and possible changes in pH and osmolality have to be checked during the test conduction, as recommended by the OECD guidelines. The highest exposure levels in a repeated dose toxicity study should be determined based on dose range finding test with a limited number of animals, on the basis of criteria given in OECD guidelines.

22	Leveret GmbH	3.1 General considerations	Line 572: **Comment and questions:** In vivo toxicity testing comprises also formulation analysis. Since smoke flavouring primary products are complex mixtures consisting of many components which are partially volatile, formulation analysis is much more challenging than it is the case for single chemical substances. Would alternative routes of administration, e.g. oral gavage, in line with considerations of respective OECD TGs, be accepted for in vivo studies with repeated dosing (e.g. according to OECD TGs 443, 488 and 453) if the administration via the diet is not feasible due to reasons that are scientifically substantiated (e.g. serious limitations of formulations analysis)?	Yes, oral gavage as alternative route of administration would be acceptable, as indicated in OECD guidelines.

			Lines 579-583: **Comment:** The Panel mentions the Guidance on harmonised methodologies for human health animal health and ecological risk assessment of combined exposure to multiple chemicals [EFSA Journal 2019;17(3):5634, 77]. To the best of our knowledge, this guidance does not foresee that mixtures containing one or more components [possibly] genotoxic in vivo cannot be tested via the whole mixture approach. **Question:** What was the reason to deviate from that approach within the Statement on the genotoxicity assessment of chemical mixtures. [EFSA Journal 2019;17(1):5519, 11 pp] and in the current draft?	Both documents were developed in parallel by EFSA SC and the genotoxicity assessment of chemical mixture was specifically described in "Statement on the genotoxicity assessment of chemical mixtures." (EFSA Scientific Committee, 2019a). In the "Guidance on harmonised methodologies for human health animal health and ecological risk assessment of combined exposure to multiple chemicals" (EFSA Scientific Committee, 2019b) genotoxicity assessment was not addressed specifically and reference was made to the "Statement on the genotoxicity assessment of chemical mixtures as mentioned above".

			Lines 595-599: **Comment:** The Panel mentions dilution effects which could prevent the detection of a potential genotoxic effect. While e.g. cytotoxicity will certainly play a role in the in vitro testing battery, this might be questionable for in vivo studies. Here we are closer to the real application and if a compound is included in non-effective concentrations it is likely that there will be no undue risk for the human population especially as there are safety factors available to calculate the potential risk. Dilution of a potential or even known genotoxic compound will – at a certain level – be associated with no biologically or toxicologically relevant, not measurable effects. **Question:** Would the Panel accept a NOAEL/BMDL10/BMDL50 from an in vivo genotoxicity study (according to OECD TG 478, 484 or 488, respectively) with the whole mixture (including presumably genotoxic compounds like 2(5H)-furanone [497-23-4]) for risk assessment, especially as the presence of other presumably genotoxic compounds in the non-identified part of the primary smoke product cannot be ruled out completely?	No, this would not be acceptable because a threshold for DNA-reactive components cannot be assumed, as explained in EFSA SC guidance on genotoxicity testing strategy (EFSA Scientific Committee, 2011a).

			Lines 600-609: In accordance with Directive 2010/63/EU15 on the protection of animals used for experimental and other scientific purposes, the unnecessary use of animals in toxicological studies should be avoided. The studies to be carried out should be those necessary to demonstrate the safety of a smoke flavouring primary product and planned in accordance with the principles of replacement, reduction and refinement of animal studies. Therefore, characterisation of individual components and an assessment of their genotoxic potential, as well as the assessment of the genotoxic potential of the unidentified constituents in a primary product should be carried out before embarking on any in vivo toxicity studies, other than to test for genotoxicity. According to the EFSA Scientific Committee (2011), clear evidence of genotoxicity in somatic cells in vivo has to be considered as an adverse effect *per se*. **Comment:** The Panel addresses the point that unnecessary animal studies should be avoided for reasons of animal welfare, and clearly state that the applicant only should embark on further toxicological studies when the concerns on genotoxicity are cleared. Depending on the results of the in vitro battery on all single substances (instead of the mixture), this might require several in vivo follow-up studies with high number of experimental animals compared to a single follow-up study of the whole mixture. In addition, at least one OECD 453 study (for substances that have been evaluated by EFSA as genotoxic in vivo, e.g. 2(5H)-furanone [497-23-4]) of the duration of two years (plus the time needed for lysis and reporting) would be required. Thus, the study report would not be available before April 2024 in case a study would start immediately after the scientific guidance is published in March 2021. **Question:** How does this reflect the need to avoid unnecessary animal testing?	If a substance turns out to be of concern for *in vivo* genotoxicity, the results of e.g. a 90-day study or an EOGRTS, cannot

			In case applicants follow the step by step approach as described in the Guidance, it appears that by the deadline of July 2022 only incomplete applications can be submitted, as the Guidance recommends embarking in toxicity studies other than those related to genotoxicity not before all genotoxicity concern is clarified. Can it be guaranteed that sufficient time will be granted to ensure that all required data can be generated to complete the assessment?	eliminate the concern for genotoxicity. Then such studies would have to be considered as unnecessary use of animals. EFSA was requested to define the data requirements for both renewals and new applications for smoke flavourings. Considering the timing issue and the tight deadlines for renewal applications, EFSA reconsidered the wording of this paragraph, to make it less prescriptive. In addition, data requirements for renewal applications have been modified to adapt to the legal deadlines of Regulation (EC) No 2065/2003[2].
23	National Institute for Public Health and the Environment (RIVM)	3.1 General considerations	Line 572. Could EFSA please explain (in a footnote) what is meant by OECD TGs? Lines 600 – 609. It might be useful to add more explicitly that before conducting any in vivo toxicity testing (other than genotoxicity testing), any concern for genotoxicity should be ruled out (as is done in lines 791-792). To RIVM it is not fully clear what the meaning in the last sentence (608-609) is in this context. EFSA is requested to provide an explanation.	The explanation has been inserted in the text. Respective guideline numbers are given where appropriate. The comment has been taken into account and the text has been modified accordingly in the final version of the guidance document.

24	Kompozíció Kft.	3.1 General considerations	Még a jelenlegi technológiai szinten sem áll rendelkezésre minden ahhoz, hogy az összetett (füst) „elsődleges termék" teljes összetevői meghatározása megtörténhessen. Az azonosítatlan részek szintézise jelenleg nem lehetséges! Mi indokolja azt, hogy az „elsődleges termék" alkotóit külön egyenként vizsgáljuk/vizsgáltassuk (különös tekintettel a genotoxicitásra), amikor az azonosítatlan részek vizsgálatához úgy is szükség van a komplett „elsődleges termék" analízisére? Ahogyan arra a jelen guidance 3.1 pontja is utal (585-593 sor). Véleményünk szerint ráadásul az egyes anyagok kölcsönhatása a komponensek egyedi és eredeti jellemzőitől teljesen eltérő anyagtulajdonságot és hatásmechanizmust eredményezhet „keverékként" (Gyakorlatunkból ismert, jó példák erre az illóolajok. Ezek a füstaromákhoz hasonlóan sokkomponensű, nem teljesen felderített összetételű illóanyag-keverékek. Az is sokszor előfordul – főleg gazdasági érdekek miatt -, hogy az illó olajokat szintetikus komponensekből összeállított keverékkel helyettesítenek/pótolnak. Ezeknek azonban a gyógyhatása rendszerint elmarad a természetes keverékekétől.) Ennek fényében, hogyan kell értelmezni a jelen guidance 3.1 pontját annak tükrében, hogy aztán külön vizsgálatokat kérne ugyanazon dokumentum 3.2 pontjának 3. bekezdésében (624-628 sor)? English translation submitted by the stakeholder: Not all of the terms are ready for the identification of all component of the „primary product", even despite the state of modern technology. Synthesis of undefinable components is not possible yet!	The Panel is aware that in some instances the identification of substances via the use of a synthesised reference compound may not be achievable. Such constituents have to be considered as "tentatively identified" and must be assigned to the fraction of unidentified constituents.

			What specifies that we have to have the component of the „primary product" measured/analysed individually if we have to have the „primary product" complete because of the undefinable parts/component. Moreover, our opinion is that, the interaction of different materials or components in a „mixture" might completely change the feature/nature of the individual, original components and/or their mode of action. (There are good examples the essential oils. They also have undefinable components, therefore – besides the economy interest – they might be replaced by synthetic mixture. However, the curative power of synthetic mixture is usually less than the organic one.). This conception appears in point 3.1 of this guidance which is not in accordance with rows 624-628 (in point 3.2 of this guidance). Could you advise then which one should be applied?	In the view of the Panel the text in chapter 3.1 is not inconsistent with the text in lines 624-628 of the draft guidance. In chapter 3.1, the general concept comprising the application of a whole mixture approach for toxicity testing, other than genotoxicity, and the combination of component-based approach and a whole mixture approach for the genotoxicity testing is outlined. The background of this component-based approach as the first step of genotoxicity testing is then described in further details in section 3.2 of the guidance.

			A Bizottság figyelembe vette-e az EU lex 1381/2019 (22) pontjában megfogalmazott irányelvet, ami szerint csökkenteni kell az állatkísérletekkel igazolható számításokat? Nem gondolja-e, hogy a rengeteg költséget és állati életet (több ezer patkány) felemésztő komponensenkénti vizsgálatok, valamint a több generációs állatkísérletek helyett, akár a biztonsági tényező 300-ról magasabb szintre emelésével – az egyszer, a komplett anyagon elvégzett, 30 napos patkánykísérletek megtartásával – hasonló biztonság érhető el? English translation submitted by the stakeholder: Has the Committee taken into consideration the directive of EU LEX 1381/2019 (22) which suggests decreasing the number of such calculations which need animal experiences? Would the Committee consider increasing the safety coefficient/margin of safety (from 300 to a higher level) – while keeping 30 days rats experiences – instead of taking a lot of measure of the components and the animal experience on multiple generation which require the unnecessary killing of more than thousand rats, not to mention the cost of these actions.	The Panel is aware that from a societal point of view animal welfare is an important issue to be considered in requesting animal toxicity studies. This is one of the reasons why a tiered approach was applied in the guidance. Reducing animal testing, including numbers of animals and duration of treatment reduces also the validity of the study outcome. Trying to compensate this by increasing the minimum required margin of safety (MOS) would not be appropriate for the assessment of regulated products.

25	EFFA (European Flavours Association); Smoke Flavours Task Force	3.2 Genotoxicity	**- pg 18 lines 627-628 and Appendix C**: "*Conclusions on genotoxicity are required for all identified components*." Some clarifications on the way EFSA will conclude on genotoxicity would be helpful especially since the genotoxicity "conclusions" for each compound will have a major impact on the genotoxicity assessment of the mixture. - In particular we wonder if the EFSA response to genotoxicity (for each component) will be a "yes" [genotoxicity concern] *versus* "no" [no genotoxicity concern] or whether a dose-response approach will be taken into consideration?	See response to comment #22, i.e. "No, this would not be acceptable because a threshold for DNA-reactive components cannot be assumed, as explained in EFSA SC guidance on genotoxicity testing strategy (EFSA Scientific Committee, 2011a)."

			- A potential option/solution for this problem could be providing discrete guidance for genotoxicity conclusion options and their impact on the assessment. In other words, EFSA may want to consider standard phrases for defined scenarios, such as described by WHO (2017). For example, when a compound "*has been tested for genotoxicity in an adequate range of in vitro and in vivo assays"* and "no evidence of genotoxicity is found", it is acceptable to conclude that the compound *"is unlikely to be genotoxic*". We would further suggest that these standard phrases/scenarios include an option for "inadequate" to allow a conclusion on genotoxicity, such as described by WHO (2017)	EFSA considers the phrasing used in its opinions to express the conclusions on genotoxicity as appropriate. If the genotoxicity data available are inadequate, then more data would be required.
			- In addition to genotoxicity data, best practices for genotoxicity evaluations include a weight of evidence evaluation based on all available evidence, particularly if chronic bioassays are available for individual constituents, then mode of action, potency, biological and human relevance should also be considered. This is consistent with EFSA guidance on weight of evidence and biological relevance (EFSA, 2017b). Further, the degree of confidence of each conclusion depends on data availability, such as described in reliability frameworks for empirical and *in silico* genotoxicity data (Hasselgren et al., 2019; Myatt et al., 2018). Conclusions with low reliability should be distinct from those with higher reliability. Based on our reading of the EFSA Guidance document, we somehow miss an acknowledgement and a consistent application of the EFSA guidance on weight of evidence, reliability and biological relevance (EFSA, 2017b). Could EFSA clarify how the WoE approach is also being applied in this GD?	EFSA evaluates the reliability of genotoxicity studies and the relevance of the results related to specific genetic endpoints following the criteria reported in OECD test guidelines.

			- pg 22 Lines 791-792: The Draft GD states: "*Applicants are reminded that before conducting any* in vivo *toxicity testing, any concern for genotoxicity should be ruled out*", from which we would understand that toxicity testing should not occur until after genotoxicity testing is conducted. In view of the limited time frame (in order to meet the submission time lines), testing in succession, rather than concurrently, may not be feasible. In addition, combining certain studies (assessing genotoxic and toxic endpoint in combined studies) may contribute significantly to reduction of animal use and thus contribute to animal welfare. We would like to find a common understanding that studies performed concurrently, rather than in succession would be acceptable by EFSA.	Same response as provided for comment #22, i.e.: "EFSA was requested to define the data requirements for both renewals and new applications for smoke flavourings. Taking into account the timing issue and the tight deadlines for renewal applications, EFSA reconsidered the wording of this paragraph, to make it less prescriptive. In addition, data requirements for renewal applications have been modified to accommodate the legal deadlines of Regulation (EC) No 2065/2003[2].

			- pg 17 lines 598-9: EFSA states "…*genotoxicity of individual components may not be detected in a whole mixture testing approach, e.g. as a result of dilution*". According to line 673: "*the Scientific Committee recommends evaluating the genotoxic potential of the unidentified fraction of the mixture*." But the GD does not provide clear guidance as to how to isolate the unidentified fraction prior to genotoxicity testing: this is a very challenging step and additional guidance would be highly appreciated.	As pointed out in the guidance on smoke flavourings, the Panel is aware of the technical difficulty of isolation of the "unidentified fraction", particularly because unidentified constituents may be volatile as well as non-volatile. This is one of the reasons why the applicant should try to minimise the fraction of unidentified constituents as much as possible. In the end the testing of the unidentified fraction may be covered by the testing of the whole mixture.
			- pg 17 lines 608-609: "According to the EFSA Scientific Committee (2011), clear evidence of genotoxicity in somatic cells i*n vivo* has to be considered as an adverse effect per se." We would argue that genotoxicity in somatic cells *in vivo* is a hazard endpoint, or a key event in a mode of action, which requires additional context from studies for the risk assessment. We would like to ask if EFSA would consider to provide additional context as outlined below: We would suggest that for the interpretation of *in vivo* genotoxicity assays the following elements be considered: biological relevance, including reproducibility and biological significance.	EFSA evaluates the reliability of genotoxicity studies and the relevance of the results related to specific genetic endpoints following the criteria reported in OECD guidelines. *In vivo* genotoxicity of a test item via a relevant route of administration is a reason to express a safety concern.

			- pg 20 lines 723-725: Could EFSA clarify when the combined Comet/micronucleus assay is relevant to follow up a positive *in vitro* micronucleus and how EFSA will interpret if only the comet assay is positive - The Comet is an alternative to the rodent transgenic assay, not the micronucleus assay (Kirkland et al., 2019). Thus, we suggest that it be clarified that EFSA Scientific Committee (2011a) recommends this combined assay only if the *in vitro* micronucleus positive response is seen exclusively (or predominantly) in the presence of rat liver S9, for the purposes of examining the involvement of liver-specific clastogenic metabolites. In this situation, EFSA Scientific Committee (2011a) notes "*that a single rodent study combining micronucleus analysis (in bone marrow or blood) and a Comet assay in the liver should be considered. If an adequately conducted combined* in vivo *micronucleus test/Comet assay (with evidence for significant exposure of the target tissues from ADME study or from changes in the percentage of polychromatic erythrocytes in the blood) is negative, it will normally be possible to conclude that the test substance or its metabolites are not clastogenic* in vivo." - Relatedly, a combined Comet/micronucleus assay, to follow up a positive *in vitro* micronucleus assay, may lead to situations where the *in vivo* micronucleus assay in blood or bone marrow may be negative while the Comet assay in the liver is positive. How would EFSA interpret these findings, if only the Comet assay is positive?	In such a case, a positive effect in the Comet assay in liver indicates a clastogenic mode of action of the compound and would not be inconsistent with a positive *in vitro* micronucleus (MN) assay. A negative result in the *in vivo* MN test may be due to limited exposure of target tissue. Then, a positive response in *in vivo* Comet would be a concern. Another possible scenario is represented by a compound positive in vitro with MN test without metabolic activation. In this case the Comet assay in duodenum (i.e. the site of first contact) is recommended as follow-up.

26	Leveret GmbH	3.2 Genotoxicity	Lines 666-670 If a primary product contains one or more components that are evaluated to be genotoxic in vivo via a relevant route of administration (i.e. after oral exposure), then the primary product raises concern for genotoxicity and the risk to human health related to this identified hazard needs to be taken into account in the risk assessment (step A.2 of the evaluation scheme reported in Appendix C). **Comment:** The compound 2(5H)-furanone [CAS No. 497-23-4; Fl.-No. 10.066] is expected to be present in low amounts in all primary products. In their opinion on the FGE 217 [EFSA Journal 2019;17(1):5568] EFSA came to the conclusion that this compound is genotoxic in vivo. However, EFSA's conclusion might be seen in the scientific community as overly conservative and leaves no room for weight of evidence [see pp. 18-19 of Gooderham et al., 2020, CRITICAL REVIEWS IN TOXICOLOGY 2020, VOL. 50, NO. 1, 1–27]. I remember we discussed this last year and that time you low success rates challenging the EFSA opinion. **Questions:** 1.Taking into account the diverse interpretation and discussion of the data for 2(5H)-furanone in the scientific community, could EFSA confirm and potentially explain, why this compound is considered an in vivo genotoxic compound by EFSA?	1. The evaluation of the compound 2(5H)-furanone and the interpretation of the genotoxicity results are explained in details in the EFSA opinion published in 2019 (EFSA FAF Panel, 2019) The EFSA's experts followed the criteria reported in the OECD TGs for the evaluation of the reliability of the studies and for the interpretation of the results.

			2. Does the Panel see other opportunities for risk assessment besides the TTC concept, assuming, that the mentioned threshold will be exceeded based on exposure data from the existing dossiers? 3. Should one or more components be identified that have already been considered by EFSA as in vivo genotoxic substances (e.g. 2(5H)-furanone), would newly generated data be considered to improve the weight of evidence based re-evaluation of the genotoxicity endpoint?	2. No, we don't see other opportunities besides besides Threshold of Toxicological Concern (TTC) concept. 3. Yes, such additional data may be considered. In case of inconsistent data, most weight would be assigned to the data that are most reliable and have the most statistical power.
27	EFFA (European Flavours Association); Smoke Flavours Task Force	3.3 Toxicity other than genotoxicity	The guidance describes use of many GLP, guidelines tests – most of which have dose range-finding preliminary assays which are based on selecting a dose with an effect. This generally conflicts with the concept suggested in the guidance that safety is based on tests which are negative. Can EFSA provide additional information regarding dose selection as it related to exposure in the flavour product should be provided, particularly when testing constituents vs. the mixture.	Guidance for dose selection is given in the respective OECD test guidelines. There it is expressed that at the highest dose tested some toxicity should occur. For the study of toxicity other than genotoxicity the whole mixture approach is followed, which considers the mixture rather than individual components as the material that is studied.

			- pg 23-24 Lines 823- 883: Is there a specific reason why Tier I testing does not include a 90-day toxicity study as well as a screening Reproductive and Developmental study (OECD TG 422) prior to determining the need to move onto an Extended One Generation Reproductive Toxicity Study (EOGRT) which is overwhelmingly animal intensive? This clarification is not provided in previously cited guidance.	The Panel advocates the need for an EOGRTS because the proposed alternative, i.e. the combined 28-day toxicity study plus reproductive and developmental screening study (OECD TG 422 (OECD, 2016c)) is not appropriate for toxicological risk assessment of regulated products. In addition, the proposed approach (90-day toxicity study plus OECD TG 422 provides only very limited information regarding immunotoxicity. An OECD TG 422 is recommended to guide the design of the EOGRTS required in the submission of new applications. A full 90-day oral toxicity study is implicit in the design of the EOGRTS. For renewal applications, however, given the time constraints for the re-evaluation of already authorised primary products, the FAF Panel decided that for renewal applications alternative information could be submitted, albeit that consequential to this some uncertainty will be introduced.

				The Panel still considers the EOGRTS as preferred option for renewals. However, for renewal applications, an alternative option for the applicant is to perform a new repeated dose 90-day study, in line with OECD TG 408 (OECD, 2018a), including additional parameters for the assessment of immunotoxicity plus an additional OECD TG 414 (OECD, 2018b) prenatal developmental toxicity study in rats. This alternative has the advantage of accommodating the timelines issues and to allow the identification of potential neurotoxic, endocrine, immunological (OECD TG 408), with additional immunotox parameters) and developmental (OECD TG 414) effects. The downside of this option is that it provides only limited information on potential effects on reproductive functions. In addition, in case in the 90-day study some indication of reproductive effects will be observed which may warrant further in-depth investigation,

				there will be insufficient time to request and obtain further data. The latter will also apply, in case the new 90-day study would raise a concern for carcinogenicity. If uncertainty remains in these respects due to lack of information, this may need to be highlighted in the conclusions of the EFSA's opinions.
			- "*In agreement with this approach, Tier I of the safety assessment of smoke flavouring primary products, subchronic oral toxicity data are needed. Based on already available knowledge on primary products as presented in previous Opinions, it can be assumed that at least part of any orally administered primary product will be absorbed and systemically available. As a result of this anticipated absorption of constituents of a smoke flavouring primary product, data on developmental and reproductive toxicity will also be needed and are included as a requirement in Tier I.*" - It would be useful if this was further explained/justified especially since Tier II testing goes directly to a Combined Chronic Toxicity and Carcinogenicity Study (OECD TG 453).	It should be noted that for new applications, the Tier I includes assessment of subchronic toxicity as part of EOGRTS and the outcome does not directly trigger a Combined Chronic Toxicity and Carcinogenicity Study (OECD TG 453 (OECD, 2018c)), but it is subject to assessment to decide on the need for follow-up in Tier II. The text of the guidance has been modified in order to clarify that sub-chronic assessment is part of Tier I.

			- pg 23 Lines 832- 843: Is there a reason why Tier I testing for renewals is not composed of an OECD 421 TG in which additional endpoints to cover endocrine or measures of reproductive and developmental endpoints can be included to determine if an EOGRT TG is necessary? Testing in the EOGRT study seems to be extreme. This protocol, with all the separate cohort uses ~1500 animals. A recommendation we would like to propose is, e.g. to only require EOGRTS when there are specific concerns from earlier studies. Also for the EOGRTS additional cohorts (neurodevelopmental/immunotox), the Food Additives guidance only requires those if there are special concerns. So we might suggest that for smoke flavouring PP's a similar approach be used. - "*It is recognised that all the data needed at Tier I can be obtained from an Extended One Generation Reproductive Toxicity study (EOGRT), according to OECD TG 443 (OECD, 2018a). In the EOGRT study, testing should be in both male and female animals covering a defined pre-mating period (minimum of two weeks) and a two-week mating period, with parental males being treated until at least the weaning of the F1, for a minimum of 10 weeks, and parental females during pregnancy and lactation until weaning of the F1.* *Dosing of the F1 offspring should begin at weaning and continue until scheduled necropsy in adulthood. The EOGRT study will provide information evaluating specific life stages not covered by the other toxicity studies: on fertility and reproductive function, and on short- to long-term developmental effects from exposure during pregnancy, lactation and pre-pubertal phases, as well as effects on juveniles and adult offspring. In addition, an EOGRT study will provide information on immunotoxicity and neurotoxicity.*"	The Panel considers that OECD TG 421 (OECD, 2016d) and OECD TG 422 (OECD, 2016c) are not full reproduction developmental toxicity studies, but only limited screening tests. OECD TG 421 or OECD TG 422 in combination with a 90-day oral toxicity study cannot replace the EOGRTS. The number of animals necessary for the assessment of sub-chronic toxicity, neurotoxicity and immunotoxicity are already included in those foreseen in the EOGRTS design. The cohorts for neurotoxicity and immunotoxicity are by default elements of the EOGRTS requested in Tier 2 of the guidance document for food additives (EFSA ANS Panel, 2012). However, as already clarified above, due to time constraints, for the evaluation of renewal applications, also an alternative data package may be submitted. For further details please refer to the final version of the guidance document.

			- So, a potential suggestion could be to consider a 90-day study and/or an EOGRT study as Tier II depending on the results of Tier I, OECD 422 only. Then based on these results the decision for a two-year study may be predicted from a 90-day study. Considering the product is not genotoxic, histology from a 90-day study along with selected other biomarkers should be able to predict potential cancer responses.	See the reply directly above. The only alternative that would provide the same level of information is a combination of OECD TG 408 (OECD, 2018a), OECD TG 415 (OECD, 2019) and OECD TG 414 (OECD, 2018b). This however would require an even larger number of animals, and this is not requested, rather discouraged, by the FAF Panel.
			- pg 23 Lines 850 – 858: According to the EFSA GD: "*For new applications it is recommended to perform a dose range-finding study, e.g. according to OECD TG 422*." We wonder if there are pragmatic ways to avoid a full EOGRT study if not absolutely warranted. - Considering an EOGRT study uses up to 1500 animals, perhaps additional endpoints can be added to OECD 422 to determine if there is a need to move directly into an EOGRTS study?	For new applications, the Panel recommended to use the OECD TG 422 (OECD, 2016c) study as a dose-range finding study for the mandatory subsequent OECD TG 443 (OECD, 2018d) study. However, the applicant may perform an OECD TG 422 or OECD TG 421 (OECD, 2016d) if they consider it necessary. Nevertheless, the OECD TG 443 study remains the mandatory testing in Tier I for new applications and the preferred option for testing of renewal applications. As mentioned above, OECD TG 421 and 422 studies are too limited to be the basis for risk assessment on regulated products.

			- pg 23 Lines 860-866: For renewal of applications, when a 90-day study has been conducted previously, there is no requirement for OECD 422 to be conducted. However, considering an EOGRT is mandated, the only way to select dose levels for sensitive subpopulations would be to conduct OECD 422 or OECD 421. Would it be acceptable within the OECD guidance to use an OECD 408 as a DRF for an OECD 443? Upon consultation of some contract labs we received the response that they would not recommend performing the OECD 443 without first doing an OECD 421 or 422. We wonder if EFSA could agree with such recommendation. - Based on the need to conduct OECD 422 or 421, would it be more efficient, especially since more specific endpoints have now been added to this guideline, to use this information to determine if an EOGRT is needed?	In Tier I the OECD 422 (OECD, 2016c) study is only recommended as a basis to design the EOGRTS and cannot be used to waive the need for such study, which is mandatory anyway.
			- pg 24 Lines 873-897: The decision to move onto to Tier II (Appendix F) is based on the findings in a subacute toxicity (4 weeks in male rats) and reproductive and developmental screening study (OECD 422) along with the results of an EOGRT. Guidance for the maximum MOS is based on what has been used for a 90-day or 13-week subchronic study in male and female rats, also from histological changes that would be indicative of potential pre-carcinogenic lesions or limiting exposure based on food categories. Is a 4-week subacute exposure long enough to observe potential pre-carcinogenic lesions to predict potential carcinogenic activity? Based on these studies, other modes of action of carcinogens typically produce low incidence tumors in rodents that generally may be difficult to predict from a 4-week exposure. Perhaps there are examples in which OECD 422 has been used to set the dose levels for a chronic toxicology study. - EOGRT now reported that the OECD 422 study along with the EOGRT study results could be discussed to demonstrate strategy used for the decision making. For example, if the OECD 422 screening study comes up clean, could EFSA clarify and confirm if it is necessary to run an EOGRT?	The sub-chronic assessment from the EOGRTS involves a 13-weeks exposure (not a 4-weeks exposure) which should be sufficient to indicate such changes. The decision on the need for carcinogenicity tests indeed would need to take into consideration relevant changes seen in the sub-chronic toxicity that might be important in non-genotoxic modes of action. Respective clarifications have been included in the final version of the guidance document.

			- pg 24 Lines 879-902: Can EFSA provide some examples on their case-by-case decision making? Since it states in the guidance that a general strategy has not been developed for a sufficient MOS? Especially since the required toxicity testing uses a large number of animals in just Tier I alone. - It is stated "*However, no general strategy has been developed yet to give a precise cut-off value here and a case-by-case assessment will be needed to decide on the need for a follow-up in Tier II. Nevertheless, similar to what has been described above for repeated dose toxicity, the applicant may try to mitigate the need for testing in Tier II by limiting the number of food categories for use of the smoke flavouring primary product and/or the maximum use levels applied.*"	Case-by-case decisions will *per se* always require individual and case-specific considerations. In such cases the overall database will also have to be taken into account and therefore the Panel did not consider it useful to include such hypothetical scenarios in the guidance document.
			- pg 25 912-917 & p. 38-39 (Appendix F): Can EFSA clarify regarding the wording in the figure in Appendix F what type of specialized studies may be requested and under what conditions? For example, the GD notes that if there is toxicity in the EOGRTS or the MOS is of a certain magnitude, specialized studies, labelled under 'Reproductive and Developmental Toxicity' may be warranted on a case-by-case. A more specific example of this scenario would be useful to anticipate testing challenges and how, and with what information decisions will be made. - "*Apart from data specifically required in this guidance document, there may be additional toxicity studies that could be supportive for the safety assessment. For instance, toxicity studies that are not required for evaluation of the primary products, but which may have been conducted for other purposes (e.g. acute toxicity (see Section 3.3.1), irritation and sensitisation studies). If such studies are available, they should be submitted as they may provide useful background information.*"	To get an idea about the specialised studies that could be requested as follow-up from the EOGRTS, the guidance on food additives (EFSA ANS Panel, 2012) could be consulted where such studies have been mentioned under Tier 3. The quoted text in italics is not related to the issue raised on the text in lines 912-917 of pages 38-39, which could result in request for additional studies. The text in italics addresses submission of available information. The heading of

				section 3.3.4 has been changed in the final version of the guidance document.
			pg 23 Line 847: Can EFSA provide clarification and some rationale for conducting benchmark dose modelling on "all parameters"? - EFSA benchmark dose guidance (EFSA Scientific Committee, 2017) does not specify that BMD modelling be conducted on all endpoints examined in a study. A standardized OECD TG 408 90-day study has over a hundred parameters, most of which will be unaffected by treatment. For example, it would be helpful if EFSA could clarify the scientific integrity and biological or toxicological relevance of BMD or dose-response analyses for parameters that are not statistically altered by treatment in at least one, and preferably multiple treatment levels. A statistically significant finding indicates a likely relationship to treatment but may not automatically constitute a biologically adverse effect or a toxicologically significant effect (EFSA Scientific Committee, 2011b). Further, "*in the interpretation of statistical analyses it should always be kept in mind that the definition of biological relevance of any change found should be of primary importance in the assessment rather than the specific level of statistical significance*" (EFSA Scientific Committee, 2011b).	The Panel would like to clarify that the text in lines 847-849 does not request the applicant to perform the lower confidence limit of the benchmark dose (BMDL) modelling on all parameters nor will EFSA do this. However, the intention of the text was to enable BMDL modelling on any parameter if required and to ensure that the data are submitted in a format which can be directly used by the assessors. The respective text in the guidance has been modified accordingly.

			- pg 23 Line 844-849: Can EFSA clarify which default benchmark response (BMR) level will be used for continuous responses, particularly if not accompanied by other related effects, such as histopathology? - Could EFSA clarify which default benchmark response (BMR) level(s) will be used for continuous responses, when there is not a justifiable biological basis for a BMR, as this is not clear in EFSA Scientific Committee (2017c). For example, for the evaluation of food additives and contaminants, including residues in food, WHO considers that, when evaluating slight changes in serum liver enzymes, a change greater than 50% is a starting point to consider adverse (WHO, 2015, 2017). Would EFSA require a BMR of 5%, 10%, 1 control standard deviation, or other BMR, for a continuous endpoint, particularly if not accompanied by other related effects, such as histopathology? Relatedly, could EFSA clarify the BMR for organ weight changes not accompanied by histopathology. For example, a 15% coefficient of variation (CoV) has been reported for kidney or liver weight changes relative to body weight in control rats from 90-day studies and could provide a rough estimate for the threshold of adversity for this response (WHO, 2017). These CoV thresholds are higher for other tissues such as the heart (20%) and spleen (25%) and lower for brain (10%) and testes (10%).	Currently default values of 5% or 10% have been mentioned in the EFSA guidance on dose response (EFSA Scientific Committee, 2017c). However, it is recognised that these default values may not reflect the effect sizes that are actually biologically relevant. Indeed, other approaches, taking e.g. background variability into account, have been developed, but this is a field in dose response modelling which is still evolving and no standard approach suitable to be incorporated into this guidance document is available yet. Biological considerations to determine a benchmark response (BMR) are given more weight than statistical considerations, which is not different from the classical approach in toxicology.

			- pg 24 Lines 882 – 910: EFSA determines a MOS of 300 or higher to be sufficient for safety for smoke flavourings. However, in the MOS (EFSA CEF Panel, 2010) guidance it states that the MOS for smoke flavourings should be evaluated on a case-by-case basis based on the available information. Can EFSA clarify how they have updated the MOS based on the new guidance since the old MOS guidance relies on outdated required toxicity information (e.g., Smoke flavouring primary product authorizations only including 3 *in vitro* assays and a 90-day study)?	The MOS of 300 was mentioned in this statement (EFSA CEF, 2010) as a cut off value. In the statement the Panel took into account "that, normally, an extra uncertainty factor of 3-fold in addition to the default uncertainty factor of 100, should be sufficient to cover the limited duration and statistical power of the pivotal study." Although now more information is asked for on toxicity and characteristics of smoke flavouring primary products, the reference point for the assessment may still be derived from a sub-chronic toxicity study. In that case the MOS of 300 is still applicable.

			- pg 24 Lines 882 – 910: If EFSA is comparing smoke flavouring primary products to food additives, could EFSA elaborate on a reasoning or clarification why an ADI is not developed? Since, as stated in the EFSA ((EFSA CEF Panel, 2010) MOS guidance, the justification to moving to a MOS approach for safety is based on the lack of repro, carcinogenicity and acute toxicity testing data. EFSA had determined in the new guidance that acute data is not required and if the mixture is found to be not genotoxic, why would a carcinogenicity study be warranted? On the other hand we have noted that JECFA develops ADI's using sub-acute studies (13 weeks) (http://www.fao.org/3/a-at894e.pdf).	In order to meet the Terms of Reference, i.e. to demonstrate the safe use of primary products under the intended conditions of use, the Panel did not see the necessity of deriving an acceptable daily intake (ADI) for the purpose of the present evaluation on smoke flavouring primary products.
			- pg 24 Lines 882 – 910: Since the guidance is being updated would EFSA consider taking into account the use of newer risk assessment methods including the use of a human equivalent dose for the NOAEL v. using the exposure concentrations in animals?	Considering that primary products are complex mixtures with a (substantial) portion of unidentified constituents, the Panel does not consider it feasible to require determination of internal exposure concentrations of primary products in animals. Converting a no-observed-adverse-effect level (NOAEL) or BMDL into a human equivalent dose would either require a standard conversion factor or a kinetic model. The latter is hardly feasible for these complex mixtures, and a standard conversion factor is to some

				extent included in the requirement of the magnitude of the MOS.
			- pg 24 Lines 873 – 910: Can EFSA clarify and provide quantitative examples of a need for further testing in Tier II for chronic toxicity/carcinogenicity, if the genotoxicity weight of evidence suggests low or no concern? - We would welcome some clarification and some examples of what is meant by "*A need for further testing in Tier II for chronic toxicity/carcinogenicity may also emerge from histological changes that could be indicative of pre-carcinogenic changes*", independently and in relation to when the genotoxicity weight of evidence is negative and suggests low genotoxicity/carcinogenicity concern. For example, cytotoxicity/regenerative hyperplasia is a lesion that is well documented in shorter-term assays to be predictive of cancer in longer term assays by non-DNA reactive mechanisms. Further, these effects are often high-dose effects that have unclear relevance to human exposures and the conditions of use. To achieve the MTD and thus comply with OECD TG 408, the top concentration in 90-day studies with smoke primary products are anticipated to significantly exceed 1000 mg/kg bw/day, the long-established practical limit dose, for animal welfare considerations, for single chemicals. Having such high-doses serve as the justification for a Tier II for chronic/carcinogenicity study, particularly if the weight of evidence suggests low genotoxic potential, is inconsistent with page 17, lines 600-02 which states "*In accordance with Directive 2010/63/EU on the protection of animals used for experimental and other scientific purposes, the unnecessary use of animals in toxicological studies should be avoided*."	Extensive and quantitative examples cannot be given. The considerations given in the comment are acknowledged. Observations indicative of potential of pre-carcinogenic changes may require a cut-off MOS higher than 300. However, if e.g. hyperplasia is only observed at extremely high dose levels, Tier II testing would not be required.

			- Can EFSA clarify the particulars of the risk assessment that will be conducted by the EFSA Panel? How points of departure will be determined and how adversity will be determined when selecting endpoints to develop PODs/NOAELs (i.e., will this be based on conclusions from the lab report)?	For smoke flavouring primary products this will not be different from the evaluation of toxicity data of other substances. The study reports will be thoroughly considered and the conclusions of the study authors will certainly be weighed. Expert knowledge within EFSA may lead to conclusions that deviate from those of the test lab. Points of departure will then be developed for the most sensitive endpoints for toxicity, with use of statistical methods, that also account for uncertainty in the study data due to biological and experimental variability.
28	National Institute for Public Health and the Environment (RIVM)	3.3 Toxicity other than genotoxicity	Line 791-792: could EFSA please replace 'any *in vivo* toxicity testing' by 'any *in vivo* toxicity testing (other than genotoxicity)'?	Please refer to the response to comment #23.
29	Leveret GmbH	3.3.3 Testing for repeated dose, reproductive and developmental toxicity	Line 835 In the EOGRT study, testing should be in both male and female animals covering a defined pre-mating period (minimum of two weeks) and a two-week mating period, with parental males being treated until at least the weaning of the F1, for a minimum of 10 weeks. **Comment:** Could the Panel provide more detailed guidance for cases where the minimum of a two week pre-mating period is not sufficient.	Only in very rare cases a pre-mating exposure period of up to 10 weeks would yield information that is not provided following a pre-mating exposure period of 2 weeks. Therefore, there is no requirement in the guidance for the (re)evaluation

			Alternatively, the "ECHA approach" could be followed, requesting a pre-mating period of 10 weeks. Data requirements for renewal applications at Tier I	of smoke flavouring primary products to extend the pre-mating exposure period of the parental generation up to 10 weeks. The default is that the pre-mating may be as short as two weeks. However, exposure of the parental males should at least be up to 10 weeks post mating and for the parental females exposure should last up to at least the weaning of the F1.
			Lines 867-868 *"and this study should further comprise the cohorts 1A, 1B, 2A, 2B and 3 as prescribed by OECD TG 443."* **Comment:** Not all cohorts should be tested per se other than required in the current draft Guidance. For selection of the EOGRT's cohorts triggers should be specified considering the findings observed in the existing studies (OECD TG 408, 422). Cohorts 2a, 2b and 3 should be only required if there is a concern regarding neuro- and immunotoxicity. A similar approach as introduced by ECHA could be followed (ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a., 2017). The unconditional requirement to perform all EOGRT cohorts is a clear violation of the EU animal protection Directive 2010/63/EU.	No triggers will be specified for the inclusion of cohorts 2a, 2b and 3, since no information on these aspects of toxicity is obtained with a sufficient level of reliability from the already available studies or from an OECD TG 422 (OECD, 2016c) screening test. When a EOGRTS assay is performed, be it for new applications or for renewal applications, these cohorts should be included. The inclusion of these cohorts does not increase the total number of animals in the test. EFSA considers that the request for the EOGRTS is not in conflict

				with the legislation (i.e. Directive 2010/63/EU[6]), since it would rule out the need for an OECD TG 414 (OECD, 2018b) and a (at least one generation) breeding study. It would also rule out the need for a separate OECD TG 408 (OECD, 2018a), and inclusion of all cohorts would provide more information on toxicity than the three separate studies mentioned here. Thus, if the same level of information as gained from a EOGRTS were to be provided from separate studies, a much higher number of animals would be involved.
30	National Institute for Public Health and the Environment (RIVM)	3.3.3 Testing for repeated dose, reproductive and developmental toxicity	Line 844-847. RIVM asks EFSA to consider adding that this is already covered when studies are performed according to OECD guidelines.	Too often studies are performed with dose levels that do not result in toxicity, despite the requirements in the OECD guidelines. Also it does not harm to reiterate that estimation of reliable and useful benchmark dose (BMD) confidence intervals should be feasible. Information on this in the OECD guidelines is fairly limited and some more

[6] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. OJ L 276, 20.10.2010, p. 33–79.

				information can be found in the EFSA SC opinion on dose response modelling (EFSA Scientific Committee, 2017c).
			Line 882. In the previous EFSA guidance that is referred to (EFSA CEF Panel, 2010), the NOAEL is used as reference point. RIVM asks EFSA to consider adding information on the BMDL as reference point (e.g. is the required MOS the same in that case).	As clearly mentioned in the final version of the guidance document, see section 3.3.3, "*An MOS of less than 300 (irrespective of whether it is based on an NOAEL or on a BMDL) would indicate that a combined chronic oral toxicity/carcinogenicity study, Test No. 453 (OECD, 2018b) would be required in Tier II testing.*"
31	CleanSmoke Coalition AISBL	3.4 Safety for the environment	It is understood that the risk assessment of smoke flavouring primary products will not include in its scope the environmental product footprint of primary products of these products and neither consider their status as best available techniques in emission control confirmed by the Union legislator. These, it is said, will be considered at the risk management stage of readmission process (Article 9(1) of Regulation (EC) No 2065/2003: "other legitimate factors relevant to the matter under consideration").	The Product Environmental Footprint of smoke flavouring primary products and their status in terms of Best Available Technique are out of the scope of this guidance and will not be considered in the safety assessment. In line with Article 9(1) of Regulation (EC) No 2065/2003[2], these aspects will be considered at the risk management level. Accordingly, comparisons between smoke flavouring primary products and conventional methods of smoking and their impact on human health and the impact of

				their production processes on the environment are not relevant in the context of the assessment of smoke flavouring primary products.
32	CleanSmoke Coalition AISBL	4.1 Introduction to uncertainty analysis	- **pg 27-28:** The guidance does not describe how the uncertainty analysis will be utilized in developing safety conclusions; will EFSA please clarify how the input from the sponsor will be used both qualitatively and quantitatively to characterize uncertainty and how this interpretation might impact conclusions?	The principle underlying the assessment of uncertainty analysis as performed by EFSA is described in chapter 4 of the guidance document. For clarification of these aspects additional descriptions have been included in the final version of the document.
			- For example, will safety be based on central tendency, lower, or upper bounds?	The assessment is carried out based on the framework of margin of safety using lower bounds on estimates of the reference point and uncertainty factors. Hence, this is a conservative approach for uncertainty analysis.

			- **pg 27-28:** Will the EFSA panel please describe the process for determining and evaluating non-standard uncertainties for smoke flavourings, specifically considering what is already known about the variables?	When assessing the uncertainties in the way described in chapter 4 of the guidance document, EFSA will consider the criteria in Appendix G and also any other relevant issues raised by the submitted data.
			- Will EFSA provide specific examples of non-standard areas of uncertainty to help the applicants better understand our highest levels of application submissions?	Anything that goes outside the criteria in Appendix G is a potential non-standard uncertainty. The applicant can contribute to reducing uncertainties by providing comprehensive information on all aspects of the safety assessment as laid down in this guidance document and doing every effort to fulfill these requirements using state-of-the-art approaches.
			- **pg 27-28:** Will the EFSA panel please be more specific in characterizing how the 2018 Uncertainty Analysis guidance will be applied for these Smoke Flavour applications?	Chapter 4 of the guidance has been updated to provide more details on this aspect. Please refer to the final version of the guidance document.

			- For example, which variables from Table 1 Appendix G might applicants reference if it is anticipated that aspects such as non-variable quantities vs variable quantities, quantification of uncertainty with probability distributions, bounds are used in the logic models and determination of distributions by the experts panels?	There are no specific requirements for applicants on how to report uncertainty, other than those requested to perform the safety assessment according to high quality standards.
			- **pg 27:** Could EFSA please clarify the how we might utilize Table 1 Appendix G; the narrative describes it both as the list of standard uncertainties (line 1024) and list of criteria for determining non-standard uncertainties (lines 1030-1031)?	Table 1 in Appendix G is only provided for information outlining key elements of the procedure employed by EFSA to treat uncertainties in the safety assessment.
			- **pg 27-28:** In a scenario where compounding uncertainties will be accommodated; can you describe how compounding conservatism will be utilized in the quantitative calculations?	The Panel has already made judgements about the degree of compounding, i.e. accumulated, conservatism when developing the standard procedure and made any adjustments needed to keep the overall level of conservatism appropriate. In order to keep the level of conservatism in the case of non-standard uncertainties, these will be assessed separately and may then be combined using calculation methods that ensure the level of conservatism is not inappropriately compounded.

33	National Institute for Public Health and the Environment (RIVM)	Appendix C – Genotoxicity assessment of primary products	Should question A4 be placed before the 'Safety concern for genotoxicity'? If so, EFSA is requested to change this.	The box has been changed accordingly.
34	National Institute for Public Health and the Environment (RIVM)	Appendix E – Tiered toxicity testing of primary products	RIVM asks EFSA to consider adding the value of the MOS that triggers the need for additional testing.	A specific numerical value for MOS cannot be given. The required MOS depends on the nature of the reference point and on the type of toxicity data considered. A cross-reference to the main text has been added in the final version of Appendix E.
35	National Institute for Public Health and the Environment (RIVM)	Appendix F – Decision scheme for Tier II toxicity testing	The 'Y' after 'Calculate MoS subchr' should be moved to the field 'MoSsubchr sufficient?'. RIVM asks EFSA to change this.	Thanks for noting this. The Y and the arrow were misplaced. The figure has been modified accordingly.
			RIVM considers that it might be more clear if the field 'Initial or lowered exposure estimate' in the upper right corner of the scheme is deleted. EFSA is asked to consider deleting this field.	The box cannot be deleted, but the scheme has been modified to make it more transparent. Note that the schemes have been modified to differentiate between new applications and renewal applications.
			Lines 1224 – 1226 It is stated that in case the MOS is not sufficient, the MOS could be lowered by refining the exposure estimates (to be done by EFSA during the risk assessment) and/by reducing the uses (to be done by the applicant). Is it correct that the applicant cannot provide refined exposure assessments? Also, RIVM asks what will be the procedure in case	The recalculation will be done by EFSA, since it would require application of advanced exposure assessment models. When these become publicly

			the applicant has to lower the use levels. Will the opinion be finalized and will a revised opinion be drafted after revised use levels are submitted? Or is the applicant requested to submit these level before finalizing the opinion? RIVM requests EFSA to provide an explanation.	available, an applicant may also do these calculations during the preparation of their application and before submitting it for evaluation, but EFSA will check them anyway during risk assessment. If during the evaluation of a primary product, EFSA concludes that the MOS is too low, the applicant will be requested to lower the exposure to the primary product. If for new applications reduction of exposure is not possible, additional toxicity testing as outlined in Tier II will be requested. Once this is clarified, an opinion can be finalised by EFSA. For renewal applications, EFSA can only conclude on the data submitted in Tier I. If time permits, EFSA may request to lower the exposure if the MOS is not high enough. Requesting additional studies according to Tier II will not be applicable for renewal applications under the current timeline restrictions.

Table 3: Questions received from interested parties during the technical hearing organised by EFSA on 5 November 2020 on the draft scientific guidance for the preparation of applications on smoke flavouring primary products

#	Subject/Chapter	Comment	Response from EFSA
1	Regulatory and procedural aspects	Question to EFSA in relation to public consultation & submission of comments. The draft Guidance refers to other guidances (i.e., exposure tools, food consumption data, administrative data etc.,) that are currently not available. Given that the GD is incomplete (e.g. in relation to the exposure assessment part), will this result in a second comment period? Will all written comments be addressed? Will the (to be published) 'EFSA exposure' tool also be subject to public consultation?	See response to comment #5 in Table 2.
2		Question to European Commission: How does the pending transparency legislation impact the process for submission and what has been described to date? Will it be required that the applicant meet with EFSA about all protocols and how will this timing impact the smoke flavourings deadlines? Can you describe the process as an audit or mentorship?	The new Art 32c(1) of the General Food Law[7], as amended by the Transparency Regulation[5], will only kick in if the potential applicant on 27 March 2021 still intends to carry out studies to support a future application for renewal. In particular, if in March 2021 the potential applicant still needs to carry out additional studies (i.e. have not yet been commissioned), then it will have to notify under Art. 32c(1) these additional studies, including information on how the various studies are to be carried out to ensure compliance with regulatory requirements. It is anyway possible, in parallel/or soon after, to proceed with the commissioning of the same studies (Art. 32b) – so the two provisions would apply simultaneously, even pending the pre-submission advice of Art. 32c(1) by EFSA.

[7] 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.

			After the notification of the intended studies for renewal under Art. 32c(1), EFSA will launch a public consultation for three calendar weeks. Based on the comments received which are relevant for the risk assessment of the intended renewal application, EFSA will provide advice to the potential applicant on the content of the intended renewal application, as well as on the proposed design of the studies, within 30 working days after the closure of the consultation. The advice will in general be provided in wring, meetings being only exceptional. The advice of Art. 32c(1) is a service to the applicant but it is also non-committal neither for EFSA, nor for the applicant. And precisely because it is not committal, it cannot delay the process of submission, which has to comply with the prescribed deadline. On the contrary, the non-compliance with the new Art. 32b of the GFL as of 27 March 2021 has potential procedural consequences on the application. If the applicant does not comply post 27 March 2021, with the notification requirement of any study commissioned after that day and there is no valid justification for this, the applicant may lose its window of submitting a renewal application on time; in this case, non-compliance on the part of the applicant would be a reason within its control and no extension can be granted.

3		At what stage of the submission the applicant can ask EFSA for pre submission advise according to Regulation (EU) No 2019/1381?	General pre-submission advice under new Article 32a of the General Food Law, as amended by the Transparency Regulation[5], can be requested at any time. EFSA Practical Arrangements on pre-submission phase and public consultations recommends to Practical Arrangements submitting the request at least six months before the envisaged submission date of the application.
4		More general question on the timelines, especially for EC on the end of expiration (Jan 2024). The entire world is currently impacted by the covid-19 pandemic; contract laboratories for GLP testing, animal availability and discussions with any regulatory authority have become strained. What considerations are being made to address timelines and transitions?	See response to comment #5 in Table 2.
5		It's assumed EFSA will rely upon NOAEL values established by the lab study director to determine MoS. Without feedback from EFSA, if there are disagreements between the EFSA Panel and the Study Director on the NOAEL, the higher tier studies may not be performed by the applicant, and given the currently proposed, unrealistic timing for submission and evaluation (see Annex A – Figure 1), this would practically guarantee that submissions would not make it through an evaluation in sufficient time without a proper transition period.	See response to comment #5 in Table 2.
6		What would it take for the European Commission to modify the deadlines? A decision by the SCoPAFF with EC and Member States support?	See response to comment #6 in Table 2.

7		Have you done an estimated time frame for accomplishing the steps to approval as described in the guidance document by actually going through the whole process as has been described? Also, have you done a cost analysis to determine the estimated cost for the entire process? Has an analysis been done on the time frame required to finish the whole process as described in the guidance and has an analysis been done on what the estimated cost would be for a finished submittal?	See response to comment #6 in Table 2.
8		Smoke Flavourings have been treated inconsistently and incompletely as food additives. Can you clarify what the process is for classifying UVCB's like smoke flavourings which possess decades of commercial history of consumption, centuries of human health use? And in other words: why are the regulatory requirements for these flavourings now being assessed similarly to novel food additives?	As mentioned in the guidance document *"from previous evaluations it has become clear that exposure levels of smoke flavouring primary products approach those observed for food additives. Consequently, toxicity data are needed in line with the data requirements for food additives."* It should be noted that this guidance document is not a direct "translation" of the guidance document on food additives. It rather takes into account the fact that primary products are complex mixtures with portions of unidentified constituents (with potential toxicological interactions) and this is reflected in various aspects of this guidance document.
9		Why EFSA is referring to Food Additives when Smoke Flavours are regulated by 1334/2008 Flavour legislation and not 1333/2008? What are the similarities and differences behind the risk assessment rationale for dossiers submitted for the one or the other?	See response to comment #8 in Table 2.

10		As a follow-up to the question about testing of constituents, EFSA suggested that hundreds of tests won't be required. However, testing for even 50 constituents would be a very significant obstacle for a GLP laboratory to conduct (particularly the in vitro MN). Pragmatically, this could take one lab up to one year. Additionally, the GLP lab testing is finite in capacity and it can be exceedingly difficult to find availability. This may well make it impossible to make a 'valid' submission by the anticipated deadline. Does EFSA have suggestions to placing studies at GLP qualified labs to fulfill the guidance?	See response to comment #6 in Table 2.
11	Chapter 1. Characterisation of smoke flavouring primary products	For smoke flavouring primary products more than 400 different compounds have been reported in scientific reports. For a number of compounds authentic reference materials will not be available, so that a part will be tentatively identified. Could you confirm that the tentatively identified components belong to the identified fraction?	See response to comments #11 and #13 in Table 2.
12		In a recent Scientific Opinion on a complex chemical mixture (EFSA Journal 2019;17(5):5675), the FAF Panel considered components "identified" if the identification was based on comparison of the mass spectral data to those of authentic reference compounds OR commercially available MS libraries; and «tentatively identified» if the identification was based on fragmentation patterns of homologous compounds. Why	See response to comments #11 in Table 2.

		is the described approach different in the present Draft Guidance?	
13		It is not specified in the text how "tentatively identified" constituents will be considered in the safety assessment. Would they need to be considered as part of the fraction of unidentified constituents?	See response to comments #11 and #13 in Table 2.
14		Is there a recommended best practice approach up to which level unidentified peaks have to be minimized, to start with the component-based genotoxicity assessment, especially as there is no analytical cut-off mentioned within this guidance?	See response to comments #11 in Table 2.
15		Question to EFSA on the stability testing: Since the focus of the dossier is the smoke flavouring primary product, section 1.4 which requires documenting the stability and fate in food is unclear since it is the derived smoke flavouring that is used in foods. Why do we need to do this and how will this information guide continued, safe use of Smoke Flavourings? We would propose stability of the smoke flavouring primary product ex application of significant value as fate in food(s) category (application, rate) is not feasible to design and interpret. Can you clarify / explain the reasoning behind the "minimum of 25 substances" for the stability testing?	See response to comments #13 in Table 2.
16		The Guidance mentions that "Information on the primary product should be provided via chemical sum parameters, i.e. parameters determining the content (% m/m) of major classes of components with common structural aspects (e.g. acids, carbonyls or phenols)." It is unclear whether these structural classes should be measured as such or their percentages are calculated by	See response to comments #11 in Table 2.

		summation of respective identified constituents. Single constituents could belong to several of these structural classes – how would this be considered in the summation process?	
17		The Panel refers to the significant progress of analytical techniques for qualitative and quantitative analysis. However, while there is undoubtable progress on the resolution (e.g. GCxGC-MS, however, the set of molecules which might be identified using databases (e.g. NIST) has not remarkably increased for the corresponding compound classes. Newly identified compounds would automatically lead to an iterative and presumably endless re-evaluation of the potential genotoxicity of the primary products. This would make it impossible to submit the dossier until the respective deadline, considering the statement that the genotoxicity assessment should be finished before embarking on any other necessary toxicological studies, as set out in the Guidance. Could you please comment on this?	See response to comments #11 in Table 2.
18		There are multiple approaches that can be used to determine the batch-to-batch variability of smoke. If we can demonstrate using GC-MS overlays that constituents have low variability between lots, is it necessary to identify the individual constituents for each batch?	As indicated in the draft guidance (Section 1.2.3.6. Batch-to-batch variability), "*the variability should be judged based on the relative standard deviations of the data determined on individual components in the different batches. The similarity of the different batches should be tested using appropriate statistical methods*". Unidentified peaks in the gas chromatography (GC) chromatograms can be also used to follow the batch-to-batch variability. Statistical tools other than the standard deviation can be applied to demonstrate similarities or dissimilarities in terms of variability in the tested

			batches. Sole provision of GC chromatogram overlays is not sufficient to properly judge the batch-to-batch variability of a primary product smoke flavouring. It should be noted that quantification should always be performed via GC- flame ionisation detector (FID) analysis.
20	Chapter 2. Proposed uses and exposure assessment	Proposed maximum use levels for smoke flavouring are calculated based on the primary product by the applicants. However, the typical usage levels are developed by users of smoke flavourings. How to assess typical usage levels, considering that primary products are reprocessed into smoke flavourings and used by third parties in their recipes and processes?	See response to comment #15 in Table 2.
21		What is the rationale behind considering typical use levels in the refined exposure assessments when it's the maximum use levels that represent the determining factor for the risk assessment	See response to comment #15 in Table 2.
22		It is stated that: the more detailed the information is on foods in which the primary product is or may be used, the less conservative the exposure estimate will be. Statement: For estimating the exposure to primary products, special food categories that are more detailed than FoodEx2 nomenclature are necessary. Question: Can the applicant for renewal of authorization enter more detailed special food categories that are outside of FoodEx2 (i.e. filled pasta)?	See response to comment #16 in Table 2.
23		FoodEx2 was noted as being exhaustive and sufficient today. However, there is little and poor data for smoke flavour in this database particularly. What is the process	See response to comment #16 in Table 2.

		for updating the database so that it can be most useful in this SF PP situation?	
24		Question on exposure & food categories: a. Why is EFSA then recommending the FoodEx2 database when there are only 3 limited categories that represent smoked foods with data? b. Why is it believed FoodEx2 is more representative of exposure than other models? Would there be an opportunity to consider more relevant information?	See response to comment #16 in Table 2.
25		How is it foreseen that facets could be used in the FoodEx2 nomenclature for smoke flavourings.	See response to comment #16 in Table 2.
26		The draft guidance says that Mintel GNPD data may be used to refine intake assessments. Is there any best practice approach on how applicants could use the GNPD data to refine intake assessments? Would a percentage of new product launches for a specific food category containing a selected facet (e.g. smoke) over the last 5 years be helpful?	See response to comment #17 in Table 2.
27		In response to the comment on FoodEx2 - can an applicant submit smoke flavourings specific food consumption data. The guidance states that member states can that's why I asked.	As written above, EFSA would welcome all kind of information (see response to comment #17 in Table 2). This cannot be mandatory requested by EFSA.
28	Chapter 3. Safety Data – 3.2 Genotoxicity	The Panel mentions the Guidance on harmonised methodologies for human health animal health and ecological risk assessment of combined exposure to multiple chemicals [EFSA Journal 2019;17(3):5634, 77]. To the best of our knowledge, this guidance does not foresee that mixtures containing one or more	See response to comment #22 in Table 2.

		components [possibly] genotoxic in vivo cannot be tested via the whole mixture approach. What was the reason to deviate from that approach within the Statement on the genotoxicity assessment of chemical mixtures [EFSA Journal 2019;17(1):5519, 11 pp] and in the current draft?	
29		In the guidance it is stated that individual constituents have to be tested for genotoxicity this would be equivalent to testing potentially hundreds of chemicals if no data exist already and this is likely the case - please explain the rationale when the genotox guidance suggests unless mechanism is understood whole mixture testing would be preferred	The guidance indicates that the genotoxic potential of the chemically identified components should be assessed using all available data including published or unpublished studies. If no or only inadequate experimental data are available, structure-activity relationship (SAR) analysis may be applied using more than one quantitative structure-activity relationship ((Q)SAR) model for each genotoxicity endpoint. The combination of different (Q)SAR models increases the overall sensitivity. When the *in silico* analysis gives indications of potential genotoxicity, appropriate experimental testing should be conducted.
30		If we have already conducted genotox tests on the whole complex mixture, do we need to go further into the genotoxicity assessment of individual components? The question is in the case of renewal dossier as we have already conducted genotoxicity studies in the original dossier. So, do we have in that dedicated case to go on the individual component.	Yes, the genotoxicity assessment of individual components is needed also for renewal dossiers. It is suggested to start with the assessment of individual components in order to exclude the presence of genotoxic substances in the mixture. This analysis is needed because genotoxicity assays are not so sensitive to detect small percentage of genotoxic substances in a mixture due to dilution effect. As indicated in the draft guidance several approaches can be used to collect data on genotoxicity (including literature search and in silico analysis).

			In addition, it should be noted that the genotoxicity tests previously performed with the whole mixture of already authorised primary products may be inadequate or insufficient according to the current standards.
31		Rationale for "constituent approach" versus "whole mixture approach" The question is: Would EFSA not accept an application if in vivo toxicity testing was run concurrently with genetic toxicology evaluation? If whole mixture approach (WMA) in vitro AND in vivo genotoxicity data is of no safety concern, what value does additional constituent genetic toxicology testing provide for safety?	See responses to comments #20 d) and # 22 in Table 2. To perform in parallel genotoxicity and toxicity studies is not a criterion for not accepting an application. See response to comment # 22 in Table 2. Compared to the whole mixture approach, the genotoxicity testing of the identified components allows to assess potential genotoxic effects, which may not be detected in the testing of the whole mixture due to dilution of the components. For example it has been shown that the Ames test allows the identification of certain genotoxic substances only if their concentration is above about 5% in a mixture (Kenyon et al., 2007). This was demonstrated considering tests results from substances with different potency. As recommended in the draft guidance, all identified components need to be evaluated for genotoxicity. Possible approaches are described in the guidance (e.g. literature search, in silico analysis).
32		EFSA indicates that it will 'closely consider' in silico information. Can EFSA more explicitly describe criteria/expectations? Section 3.2.1 and Appendix D provides some insight, but "closely consider" implies other factors may be important.	The *in silico* analysis will be checked considering the principles outlined by ECHA (2008, 2012, 2016) and in the OECD guidance documents (OECD, 2007) mentioned in the draft guidance on smoke flavourings. If some important criteria are

			not met additional information may be required to the applicant. 'Closely' has been deleted in the final version of the guidance document.
33		Previous in vitro data on individual flavourings has often given results where the OECD guidance for a 'clear' positive are not met, such as there is statistical significance but the increases are within the laboratories robust historical control data. Can EFSA indicate what it would consider to be positive, triggering in vivo follow up?	When evaluating the *in vitro* data EFSA will take into account the three evaluation criteria included in the OECD test guidelines. If all 3 criteria are met, the result is positive. If none of the 3 criteria are met, the result is negative. If only 1 or 2 criteria are met, result is equivocal and further clarification may be necessary.
34		The compound 2(5H)-furanone [Fl.-No. 10.066] is expected to be present in low amounts in all primary products. In their opinion on the FGE 217, EFSA came to the conclusion that this compound is genotoxic in vivo. However, EFSA's conclusion might be seen in the scientific community as overly conservative and leaves no room for weight of evidence. I remember we discussed this last year and that time you low success rates challenging the EFSA opinion. Taking into account the diverse interpretation and discussion of the data for 2(5H)-furanone in the scientific community, could EFSA confirm and potentially explain, why this compound is considered an in vivo genotoxic compound by EFSA? Does the Panel see other opportunities for risk assessment besides the TTC concept, assuming, that the mentioned threshold will be exceeded based on exposure data from the existing dossiers? Should one or more components be identified that have already been considered by EFSA as in vivo genotoxic substances (e.g. 2(5H)-furanone), would newly generated data be	See response to comment #26 in Table 2.

		considered to improve the weight of evidence based re-evaluation of the genotoxicity endpoint?	
35		Can you clarify what evidence of target tissue exposure will be accepted in in vivo studies, given that it would be exceedingly difficult to demonstrate exposure of unidentified substances in that fraction (plasma or otherwise)?	In case of testing mixtures it is very difficult to assess systemic exposure through plasma analysis. In the Scientific Opinion "Clarification of some aspects related to genotoxicity assessment", (EFSA Scientific Committee, 2017a) the adequacy to demonstrate target tissue exposure in *in vivo* studies, particularly in the mammalian erythrocyte micronucleus test, is described. Different lines of evidence for systemic exposure are described, which can be considered in a weight of evidence approach.
36		A recent draft EFSA Guidance on aneugenicity assessment proposed that there are non-OECD guideline studies that could be used to assess in vivo aneugenic potential (e.g., liver MN). Can EFSA confirm their willingness to accept such studies for smoke flavorings primary product should in vivo aneugenic potential require assessment?	In the draft guidance on aneugenicity, possibilities to investigate micronucleus tissues other than bone marrow are described. In particular, references to international recommendations on the in vivo micronucleus assay in liver are included. It should be noted that the micronucleus assay in liver is recommended as follow-up study of positive findings in vitro in the presence of metabolic activation. If the substance is positive in vitro only in the absence of metabolic activation possible effects at the first site of contact should be investigated and an in vivo micronucleus assay targeted at the first site of contact may be considered.
37		It has been indicated that if a substituent that tested positive for genotoxicity is present, EFSA may consider the application of the TTC for that substituent (0.15	It is acknowledged that for aneugenic substances a threshold may be identified. In order to clarify the possible testing and how to derive a threshold

		µg/person/day). What if the substance is a recognized aneugen? Could an alternative threshold be established, given that there is general consensus that aneugenicity is a thresholded effect?	for aneugenic substances, the EFSA Scientific Committee is working on a guidance document which has already been released for public consultation (EFSA Scientific Committee, 2020).
38		-What happens when you arrive to the annotated red box (see Appendix C)? - Can EFSA provide clarity on what happens when a mixture has a known genotoxic component via the oral route (Appendix C) and that constituent is determined as a safety concern for genotoxicity? - If you review the graphic, before doing anything based on last submission results, applicants are already at the red box without clear next steps.	If it is demonstrated that a component in the mixture is genotoxic in vivo, this will raise a concern for genotoxicity. However, if the exposure of the component is below the TTC value of 0.0025 µg/kg bw per day, it can be concluded that there is a low probability of adverse health effects. Subsequently the potential genotoxicity of the unidentified fraction has to be investigated. Finally, it is in the remit of risk managers to decide about the use of the product.
39		The Panel mentions dilution effects which could prevent the detection of a potential genotoxic effect. While e.g. cytotoxicity will certainly play a role in the in vitro testing battery, this might be questionable for in vivo studies. Here we are closer to the real application and if a compound is included in non-effective concentrations it is likely that there will be no undue risk for the human population especially as there are safety factors available to calculate the potential risk. Dilution of a potential or even known genotoxic compound will – at a certain level – be associated with no biologically or toxicologically relevant, not measurable effects. Would the Panel accept a NOAEL/BMDL10/BMDL50 from an in vivo genotoxicity study (according to OECD TG 478, 484 or 488, respectively) with the whole mixture (including presumably genotoxic compounds like 2(5H)-furanone [497-23-4]) for risk assessment, especially as the	See response to comment #22 in Table 2.

		presence of other presumably genotoxic compounds non-identified part of the primary smoke product cannot be ruled out completely?	
40		Please note, the previously EFSA reviewed and published data clearly show we have positive genotoxicants. Are you stating to stop testing?	It is not in the remit of EFSA to advise applicants whether to continue testing or not. EFSA can only give guidance on the requirements for the safety assessment of primary products.
41	Chapter 3 Safety Data – 3.3 Toxicity other than genotoxicity	Testing in the EOGRT study appears to have excessive animal use (approximately 1500 animals). Why is a repro screening assay or a 90-day with additional repro endpoints not required prior to the EOGRT? Realizing that excessive animal testing should be limited, would a screening assay to determine if large animal studies would even be warranted be a potential consideration? this in order to avoid unnecessary testing & unnecessary use / killing of animals.	See response to comment #27 in Table 2.
42		The Panel addresses the point that unnecessary animal studies should be avoided for reasons of animal welfare, and clearly state that the applicant only should embark on further toxicological studies when the concerns on genotoxicity are cleared. Depending on the results of the in vitro battery on all single substances (instead of the mixture), this might require several in vivo follow-up studies with high number of experimental animals compared to a single follow-up study of the whole mixture. In addition, at least one OECD 453 study (for substances that have been evaluated by EFSA as genotoxic in vivo, e.g. 2(5H)-furanone [497-23-4]) of the duration of two years (plus the time needed for analysis and reporting) would be required. Thus, the study report	See responses to comments #6, #27 and #29 in Table 2.

		would not be available before April 2024. How does this reflect the need to avoid unnecessary animal testing? In case applicants follow the step by step approach as described in the Guidance, it appears that by the deadline of June 2022, only incomplete applications can be submitted, as the Guidance recommends embarking in toxicity studies other than those related to genotoxicity not before all genotoxicity concern is clarified. Can it be guaranteed that sufficient time will be granted to ensure that all required data can be generated to complete the assessment?	
43		The Guidance mentioned in Line 835: In the EOGRT study, testing should be in both male and female animals covering a defined pre-mating period (minimum of two weeks) and a two-week mating period, with parental males being treated until at least the weaning of the F1, for a minimum of 10 weeks. Could the Panel provide more detailed guidance for cases where the minimum of a two week pre-mating period is not sufficient? Could, alternatively, the "ECHA approach" be followed, requesting a pre-mating period of 10 weeks?	See response to comment #29 in Table 2.
44		Question to Lines 867-868 of the Guidance "…and this study should further comprise the cohorts 1A, 1B, 2A, 2B and 3 as prescribed by OECD TG 443." Not all cohorts should be tested per se other than required in the current draft Guidance. For selection of the EOGRT's cohorts triggers should be specified considering the findings observed in the existing studies (OECD TG 408, 422). Cohorts 2a, 2b and 3 should be only required if there is a concern regarding neuro- and immunotoxicity. A similar approach as introduced by ECHA could be followed (ECHA Guidance on Information	See response to comment #29 in Table 2.

		Requirements and Chemical Safety Assessment Chapter R.7a., 2017). The unconditional requirement to perform all EOGRT cohorts appears to be in conflict with the EU animal protection Directive 2010/63/EU.	
45		Follow-up question on animals: see the document sent by EFFA on number of animals used for assays (Annex A – Table 4): is the EU-Commission not considering ways to reduce the number of animals? the current data requirements will result in a huge killing of animals.	See response to comment #29 in Table 2.
46		In vivo toxicity testing comprises also formulation analysis. Since smoke flavouring primary products are complex mixtures consisting of many components which are partially volatile, formulation analysis is much more challenging than it is the case for single chemical substances. Would alternative routes of administration, e.g. oral gavage, in line with considerations of respective OECD TGs, be accepted for in vivo studies with repeated dosing (e.g. according to OECD TGs 443, 488 and 453) if the administration via the diet is not feasible due to reasons that are scientifically substantiated (e.g. serious limitations of formulations analysis)?	See response to comment #22 in Table 2.
47		The smoke flavorings PP clearly indicates that genotoxicity must be assessed before other toxicology. Several genotoxicity studies can now be incorporated into in vivo repeat-dose tox studies (e.g., comet assays). Would it something EFSA can consider combining in vivo toxicity and genotoxicity, to save both animals and time?	See response to comment #22 in Table 2.

48	Chapter 3 Safety data - 3.4 Safety for the environment	The CleanSmoke Coalition worked together with different NGOs and the JRC to finally establish in 2019 purified smoke generated from smoke flavourings as Best Available Technique in emission control (BAT). It could be demonstrated that the use of purified smoke has the potential to reduce emission and consumption of resources during food processing. By replacing conventionally smoking methods, purified smoke and smoke flavourings reduce the occurrence of undesired substances in smoked foods which raise concern. How will these benefits of smoke flavourings be considered in the risk assessment?	See response to comment #31 in Table 2.
49		It is clear that conventional smoke is not under the scope of this work. Nevertheless in the calculation for food categories contribute we could consider that every time we use primary smokes we are substituting Conventional smoke reducing exposure to the same typical common chemicals.	This aspect falls under the remit of risk managers and is not considered in the risk assessment of smoke flavouring primary products.
50	Chapter 4 Uncertainty	It is not clear how the uncertainty analysis will impact the overall safety conclusions. Can EFSA please elaborate on this process?	See response to comment #32 of Table 2.

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Abbreviations

ADI – acceptable daily intake

ADME - absorption, distribution, metabolism and excretion

BMD - benchmark dose

BMDL - lower confidence limit of the benchmark dose

BMR - benchmark response

EOGRTS - Extended One-Generation Reproduction Toxicity study

FAIM - Food Additive Intake Model

FID - flame ionisation detector

GC - gas chromatography

GLP - good laboratory practices

MN - micronucleus

MOS - margin of safety

MTD - maximum tolerated dose

NOAEL - no-observed-adverse-effect level

OECD - Organisation for Economic Co-operation and Development

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

PAHs - polycyclic aromatic hydrocarbons

(Q)SAR - quantitative structure-activity relationship

SAR - structure-activity relationship

TTC - Threshold of Toxicological Concern

Annex A – EFFA (European Flavour Association) - Smoke Flavours Task Force – Upload submission

The following information was submitted by EFFA and uploaded as attachment, as their additional contribution to the public consultation:

Figure 1: Gantt chart depicts the order and time associated with the conduct of scientific and good laboratory practices (GLP)-regulated studies in support of the DRAFT Smoke Flavour Guidance requirements for application submissions. The chart represents the continuous flow of work and does not take into account selection of GLP-accredited laboratories capable and most qualified to conduct in vivo and in vitro studies to substantiate safety conclusions. Additionally, not noted in the Gantt chart is the uncertainty associated with pending legislative transparency initiatives (March 2021). The expiry for currently approved Smoke Flavours SF 001-010 is January 2024 with a request for dossier submissions to occur 18 months prior to the deadline.

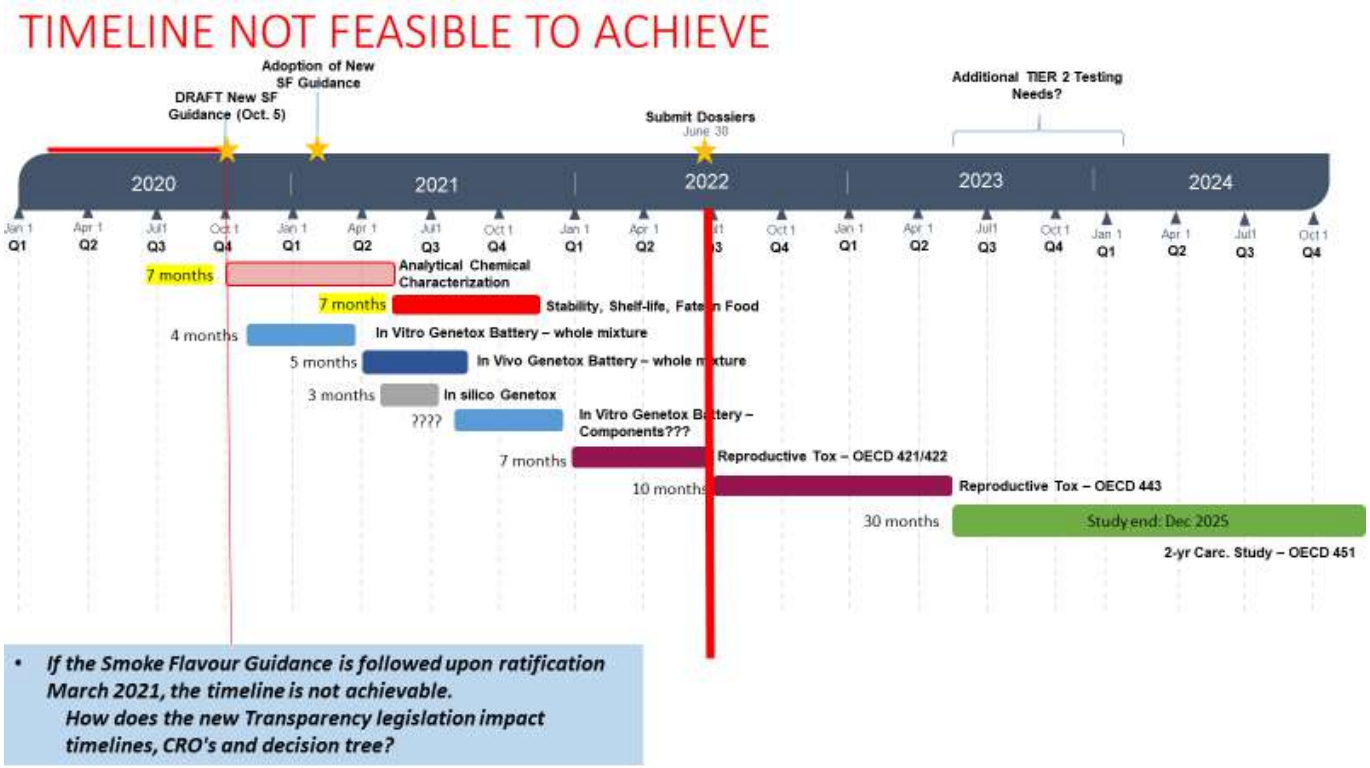

Table 4: The table summarizes the type and study-type associated with DRAFT Smoke Flavour Guidance. The costs and total animal numbers are estimates and can vary significantly based upon study starts authorizations, animal availability, protocol variances, good laboratory practices (GLP)-qualified laboratory selection(s). Approximate numbers of animals utilized, will vary by dose groups and other factors. It should further be mentioned that the genotox in vivo studies may be needed / conducted on several of the constituents which will further increase the entire study duration and number of sacrificed animals.

Assay Summary; *in vivo* GLP-Prescribed Studies per Smoke Flavour Application Submission

Assay	Description	Cost Estimate	Study Duration (range)	# of Animals (range)
OECD 474 & 489	In vivo genetox Combined Comet and MN Assay	$ 53,400 (one sex, one tissue for comet assay) $ 80,910 (two sexes, one tissue for comet assay)	17 weeks from acclimatization to draft report	40 animals per sex
OECD 421/422	Repro Screening Assay	$ 169,510 (OECD 421) $ 216,610 (OECD 422) Analytical support not included in the price	21 weeks from acclimation to draft report	F0-generation: 80 animals in main study plus 11 spare animals F1-generation: appr. 480 pups (12 pups/litter)
OECD 443	Extended One Generation Repro Assay	$ 1,127,880 – oral diet $ 1,310,090 – oral gavage Analytical support not included in the price	52 Weeks from acclimation to draft report	F0-generation: 200 animals F1-generation: appr. 1200 pups (12 pups/litter)
OECD 451	2-yr Chronic Carcinogenicity Assay	$ ~1,200,000 – oral diet	132 weeks from acclimatization to draft report	400