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Scientific Opinion on Flavouring Group Evaluation 69, Revision 1 (FGE.69Rev1): consideration of aromatic substituted secondary alcohols, ketones and related esters evaluated by JECFA (57th meeting), structurally related to aromatic ketones from chemical group 21 evaluated by EFSA in FGE.16Rev2

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Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 35 flavouring substances attributed to the Flavouring Group Evaluation 69 (FGE.69), using the Procedure as outlined in the Commission Regulation (EC) No 1565/2000. Thirty-two substances have already been considered in FGE.69 [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.080, 07.004, 07.013, 07.022, 07.023, 07.025, 07.026, 07.028, 07.029, 07.032, 07.038, 07.040, 07.042, 07.070, 07.079, 07.086, 07.087, 09.144, 09.178, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501]. The remaining three substances [FL-no: 02.066, 07.024 and 07.027] have been cleared with respect to genotoxicity in FGE.215Rev1 and are considered in this revision FGE.69Rev1. The substances were evaluated through a stepwise approach, namely the Procedure, that integrates information on the structure–activity relationships, intake from current uses, Threshold of Toxicological Concern (TTC) and available data on metabolism and toxicity. The Panel considered that for 33 flavouring substances evaluated through the Procedure the specifications are adequate and the Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' when based on the MSDI approach. For two flavouring substances [FL-no: 07.038 and 07.042], there is insufficient information on their chemical identity to reach a final conclusion. For six substances [FL-no: 02.066, 07.013, 07.024, 07.028, 07.032 and 07.086], there is no concern when the exposure was estimated based on the 'modified Theoretical Added Maximum Daily Intake' (mTAMDI) approach. For 28 substances, use levels are needed to calculate the mTAMDI estimates in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly. For one substance [FL-no: 07.027], more reliable data on uses and use levels are required in order to finalise the safety evaluation.

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1. Introduction

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of two aromatic substituted ketones [FL-no: 07.024, 07.027] and one secondary alcohol [FL-no: 02.066] evaluated by the JECFA (57th meeting). They are precursors of α,β -unsaturated carbonyl substances and have been evaluated with respect to genotoxicity in FGE.215Rev1. According to the Mandate and Terms of Reference of this FGE, when for a flavouring substance the concern for genotoxicity is ruled out, the European Food Safety Authority (EFSA) proceeds to the full evaluation of these flavouring substances, taking into account the requirements of the Commission Regulation (EC) No 1565/2000¹ and of Regulation (EU) No 1334/2008². The mandate for FGE.215Rev1 is cited below.

1.1. Background and Terms of Reference as provided by the requestor

1.1.1. Background to Mandate from FGE.215Rev1 (M-2015-0066)

The use of flavourings is regulated under Regulation (EC) No 1334/2008¹ of the European Parliament and Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of Article 9(a) of this Regulation, an evaluation and approval are required for flavouring substances.

The Union list of flavourings and source materials was established by Commission Implementing Regulation (EC) No 872/2012³. The list contains flavouring substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000.

On 26 March 2014, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA CEF Panel) adopted an opinion on Flavouring Group Evaluation 215 (FGE.215): Consideration of genotoxic potential for FGE.215 α,β -unsaturated aldehydes, straight chain, α,β -unsaturated cinnamyl ketones, subgroup 3.2, FGE.19.

The Panel concluded that for (4-phenylbut-3-en-2-one [FL-no: 07.024] and 1-(4-methoxyphenyl) pent-1-en-3-one [FL-no: 07.030]) of subgroup 3.2 of FGE.19 the concern with respect to genotoxicity could not be ruled out and subsequently additional data are requested.

On 5 November 2014 the applicant submitted additional studies on the representative substances [FL-no: 07.024] and [FL-no: 07.030] in response to this EFSA evaluation (Ares (2015) 786221).

1.1.2. Terms of Reference of Mandate from FGE.215Rev1 (M-2015-0066)

The European Commission requests the European Food Safety Authority (EFSA) to evaluate the new information and, depending on the outcome, proceed to the full evaluation on the flavouring substance in accordance with Commission Regulation (EC) No 1565/2000¹.

1.2. Interpretation of the Terms of Reference

Flavouring substances [FL-no: 02.066, 07.024, 07.027] were first allocated to FGE.215Rev1 for evaluation with respect to genotoxicity. Based on new genotoxicity data submitted, the Panel concluded that these three flavouring substances do not give rise to concern with respect to genotoxicity and can accordingly be evaluated through the Procedure in the present revision of FGE.69 (FGE.69Rev1), in accordance with Commission Regulation (EC) No 1565/2000.

In addition, since the publication of FGE.69, data on EU production volumes and data on stereoisomerism and/or compositional information of 12 substances [FL-no: 02.065, 07.038, 07.042, 07.070, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501] have been provided by industry. Therefore, their safety evaluation through the Procedure can also be finalised in the current revision.

The methodology for the evaluation of these substances is clarified in Appendix A.

¹ Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96. OJ L 180, 19.7.2000, p. 8–16.

² 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.

³ Commission implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1–161.

1.3. History of the evaluation of the substances in FGE.69

The JECFA has evaluated at its 57th meeting (JECFA, 2002a,b) a group of 38 aromatic substituted secondary alcohols, ketones and related esters. Five of these are α , β -unsaturated ketones or precursors for such [FL-no: 02.066, 07.024, 07.027, 07.030 and 07.049] and were included by the CEF Panel (EFSA, 2008) in FGE.19 subgroup 3.2 together with other α , β -unsaturated substances for evaluating their potential genotoxicity in a separate opinion (FGE.215).

Therefore, in FGE.69 (EFSA AFC Panel, 2008a), 33 JECFA-evaluated substances were considered. These substances were considered structurally related to four aromatic ketones from chemical group 21 evaluated in the Flavouring Group Evaluation 16 (FGE.16) (EFSA AFC Panel, 2006).

The AFC Panel agreed with the application of the Procedure as performed by JECFA for all 33 substances considered in FGE.69. Thirty-two substances were evaluated through the A-side of the Procedure. For 12 of these [FL-no: 02.065, 07.038, 07.042, 07.070, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501], the AFC Panel had reservations, i.e. no EU production volumes available, preventing them from being evaluated using the Procedure, and/or missing information on specifications and/or missing information on stereoisomerism. For the remaining 20 substances [FL-no: 02.033, 02.034, 02.036, 02.064, 02.080, 07.028, 07.004, 07.013, 07.022, 07.023, 07.025, 07.026, 07.029, 07.032, 07.040, 07.079, 07.086, 07.087, 09.144 and 09.178], the AFC Panel agreed with the JECFA conclusion 'no safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach. For one substance, 4-acetyl-6-t-butyl-1,1-dimethylindane [FL-no: 07.133] evaluated through the B-side of the Procedure, a no observed adverse effect level (NOAEL) could not be established. Therefore, the AFC Panel concluded that for [FL-no: 07.133], additional data should be made available (EFSA AFC Panel, 2008a). However, after the publication of FGE.69, the substance [FL-no:07.133] was no longer supported by industry for use as flavouring substances in Europe and it was not included in the union list.²

For all 33 substances evaluated through the Procedure use levels are needed to calculate the mTAMDI in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

EU production volumes and/or data on stereoisomerism have been provided for four flavouring substances [FL-no: 07.070, 09.189, 09.200 and 09.501] and were evaluated in FGE.96 (EFSA CEF Panel, 2011). FGE.96 is a transversal opinion on 88 flavouring substances considered by EFSA for which EU production volumes/anticipated production volumes have been submitted by industry upon request by DG SANCO (Documentation provided to EFSA nr.3).

Five flavouring substances [FL-no: 02.066, 07.024, 07.027, 07.030 and 07.049] were evaluated in FGE.215 with respect to their potential genotoxicity. Based on positive results observed in *in vitro* studies for the two representative substances, 4-phenylbut-3-en-2-one [FL-no: 07.024] and 1-(4-methoxyphenyl)pent-1-en-3-one [FL-no: 07.030], the CEF Panel could not rule out the genotoxicity concern in FGE.215 (EFSA CEF Panel, 2014) and requested a combined *in vivo* micronucleus and Comet assays in liver and duodenum.

The present revision of FGE.69, FGE.69Rev1, includes the safety evaluation of three candidate substances: phenylbut-3-en-2-ol [FL-no: 02.066], phenylbut-3-en-2-one [FL-no: 07.024] and methyl-4-phenylbut-3-en-2-one [FL-no: 07.027] evaluated by JECFA in its 57th meeting (JECFA, 2002a) and cleared with respect to genotoxicity in FGE.215Rev1 (EFSA FAF Panel, 2019) following the assessment of additional genotoxicity data. With respect to flavouring substances [FL-no: 07.030 and 07.049], the Panel concluded in FGE.215Rev1 that the representative substance [FL-no: 07.030] is aneugenic *in vitro* (EFSA FAF Panel, 2019). For such substances, there is currently no agreed follow-up strategy to finalise their safety assessment. The Panel is aware that the EFSA Scientific Committee is going to address this issue and a statement clarifying the assessment of *in vitro* aneugenic substances is under preparation. Therefore, for the time being, the representative substance 1-(4-methoxyphenyl)pent-1-en-3-one [FL-no: 07.030] and the structurally related substance 1-(4-methoxyphenyl)-4-methylpent-1-en-3-one [FL-no: 07.049] cannot be evaluated through the Procedure and will not be considered in this revision of FGE.69 (FGE.69Rev1).

Together with the 32 substances that were already considered in FGE.69, the current revision comprises 35 substances. The 32 flavouring substances for which the evaluation was finalised in FGE.69 will not be further discussed. Nevertheless, for the sake of completeness, the information on the specifications, evaluation status and intake are maintained in the respective tables in this FGE. For more details on the previously evaluated flavouring substances, the former version of this FGE (FGE.69) should be consulted.

EU production volumes and/or data on stereoisomerism have been provided for 12 flavouring substances [FL-no: 02.065, 07.038, 07.042, 07.070, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501], considered in the previous revision (FGE.69). This is taken into account in this revision FGE.69Rev1.

FGE	Adopted by EFSA	Link	No of substances
FGE.69	31 January 2008	https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2008.869	33
FGE.69Rev1	22 September 2020	https://www.efsa.europa.eu/en/efsajournal/pub/6265	35

2. Data and methodologies

2.1. Data

The present opinion is based on the data presented in Table 1.

Table 1: Data considered in the current revision of FGE.69 (FGE.69Rev1)

FL-no	Chemical name	Data provided for the current revision 1 of FGE.69	Appendix (Table nr) and relevant section of the opinion	Documentation provided to EFSA nr:
02.066	Phenylbut-3-en-2-ol	Specifications EU poundage data Use levels	Appendix B (Table B.1)	Documentation provided to EFSA nr. 1 and 2
07.024	Phenylbut-3-en-2-one	Specifications EU poundage data Use levels	Appendix B (Table B.1)	Documentation provided to EFSA nr. 1 and 2
07.027	Methyl-4-phenylbut-3-en-2-one	Specifications EU poundage data Use levels	Appendix B (Table B.1) Appendix C (Tables C.1 and C.4)	Documentation provided to EFSA nr. 1 and 2
02.065	4-Methyl-1-phenylpentan-2-ol	Specifications	Appendix B (Table B.1)	Documentation provided to EFSA nr. 3
07.038	4-Methoxyacetophenone	Specifications	Appendix B (Table B.1)	
07.042	4-Isopropylacetophenone	Specifications	Appendix B (Table B.1)	
07.070 ⁴	3-Benzylheptan-4-one	Specifications EU poundage data	Appendix B (Table B.1) Appendix C (Table C.4)	
09.179	1-Phenethyl formate	Specifications	Appendix B (Table B.1)	
09.189 ³	1-Phenylpropyl butyrate	Specifications EU poundage data	Appendix B (Table B.1) Appendix C (Table C.4)	
09.200 ³	1-Methyl-3-phenylpropyl acetate	EU poundage data	Appendix C (Table C.4)	
09.231	1-Phenethyl butyrate	Specifications	Appendix B (Table B.1)	
09.249	1-Methyl-2-phenethyl butyrate	Specifications	Appendix B (Table B.1)	
09.476	Ethyl 3-phenyl-3-oxopropionate	Specifications	Appendix B (Table B.1)	
09.486	1-Phenethyl isobutyrate	Specifications	Appendix B (Table B.1)	
09.501 ³	Ethyl 2-acetyl-3-phenylpropionate	Specifications EU poundage data	Appendix B (Table B.1) Appendix C (Table C.4)	

⁴ The evaluation of flavouring substances [FL-no: 07.070, 09.189, 09.200, 09.501] was finalised in FGE.96(EFSA CEF Panel, 2011) and was concluded at step A3 of the Procedure as of no safety concern at the estimated levels of intake as flavouring substance, based on the MSDI approach.

FL-no	Chemical name	Data provided for the current revision 1 of FGE.69	Appendix (Table nr) and relevant section of the opinion	Documentation provided to EFSA nr:
07.013	Methyl 2-naphthyl ketone	Use levels	Appendix C (Table C.4)	Documentation provided to EFSA nr. 4
07.028	Benzoin	Use levels	Appendix C (Table C.4)	
07.032	Benzophenone	Use levels	Appendix C (Table C.4)	
07.086	1,3-Diphenylpropan-2-one	Use levels	Appendix C (Table C.4)	

In addition, the following data have been used in FGE.69Rev1:

- JECFA specifications for the three candidate substances [FL-no: 02.066, 07.024 and 07.027] (JECFA, 2002a);
- Genotoxicity data evaluated in FGE.215 (EFSA CEF Panel, 2014) and FGE.215Rev1 (EFSA FAF Panel, 2019);
- 57th JECFA report (JECFA, 2002a);
- JECFA safety evaluation of certain food additives and contaminants. WHO Food Additives Series: 48 (JECFA, 2002b).
- EFSA Scientific Opinion on FGE.69 (EFSA AFC Panel, 2008a);
- EFSA Scientific Opinion on FGE.16, (EFSA AFC Panel, 2006) FGE.16Rev1 (EFSA AFC Panel, 2008b) and FGE.16Rev2 (EFSA CEF Panel, 2009).

2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee. The assessment strategy applied for the evaluation programme of flavouring substances, as laid down in Commission Regulation (EC) No 1565/2000, is based on the Opinion on a Programme for the Evaluation of Flavouring substances of the Scientific Committee on Food (SCF, 1999).

2.2.1. Procedure for the safety evaluation of flavouring substances

The approach for safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000, named the 'Procedure', is described in Appendix A.

2.2.2. Approach used for the calculation of exposure

The approach used for calculation of the intake of the flavouring substances is described in Appendix A (point 'a' *Intake*) and in Appendix C (Section C2 'mTAMDI calculation').

3. Assessment

3.1. Specifications

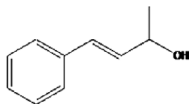
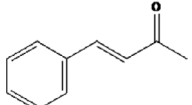
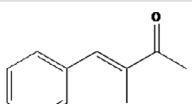
JECFA status

The JECFA specifications are available for all the 35 flavouring substances [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.066, 02.080, 07.004, 07.013, 07.022, 07.023, 07.024, 07.025, 07.026, 07.027, 07.028, 07.029, 07.032, 07.038, 07.040, 07.042, 07.070, 07.079, 07.086, 07.087, 09.144, 09.178, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501] considered in the present opinion (FGE.69Rev1) (JECFA, 2002a,b).

EFSA considerations

Table 2 shows the chemical structures of the candidate substances considered in this revision of FGE.69 (FGE.69Rev1).

Table 2: Flavouring substances under evaluation in FGE.69Rev1

FL-no	Chemical name	Structural formula	Structural class*
02.066	Phenylbut-3-en-2-ol		Class II
07.024	Phenylbut-3-en-2-one		Class I
07.027	Methyl-4-phenylbut-3-en-2-one		Class I

FGE: Flavouring Group Evaluation; FL-no: FLAVIS number.

*: Determined with OECD Toolbox (version 4.4.1 available online <https://qsartoolbox.org/>). Considering the structural similarity between [FL-no: 02.066 and 07.024], and in agreement with Toxtree (Toxtree version 3.1.0 available at <http://toxtree.sourceforge.net/>) classification, the Panel decided to allocate [FL-no: 02.066] also to Cramer Class I.

The three newly included flavouring substances [FL-no: 02.066, 07.024 and 07.027] can exist as geometrical stereoisomers due to the presence of a double bond. Adequate information related to the composition of the stereoisomeric mixtures has been submitted by industry for all three flavouring substances [FL-no: 02.066, 07.024 and 07.027] (Documentation provided to EFSA nr. 1). The three stereoisomeric mixtures have the following composition: (*Z*)- isomer ranging from 30 up to 60% and (*E*)- isomer ranging from 40% up to 70%. Industry also informed that flavouring substance [FL-no: 02.066] is a racemate (Documentation provided to EFSA nr. 1).

Following the publication of FGE.69 (EFSA AFC Panel, 2008a), in which data gaps for specifications for certain substances were identified, industry provided the missing information (Documentation provided to EFSA nr. 3).

Industry informed that the materials of commerce of [FL-no: 02.065, 07.070, 09.179, 09.189, 09.231, 09.249, 09.486 and 09.501] are racemates. With respect to the four flavouring substances [FL-no: 7.038, 07.042, 09.179, 09.476], for which the Panel in FGE.69 requested information on the composition, industry informed that materials of commerce for [FL-no: 07.038 and 07.042] are mainly the para-isomer with ortho and meta isomers as minor components. The Panel noted that only the percentage of the overall sum of positional isomers has been provided for these two substances, but no quantitative information of each positional isomer is available. The Panel considered the information on the composition of the mixture of positional isomers of flavouring substances [FL-no: 07.038 and 07.042] as insufficient.

Industry provided data indicating that [FL-no: 09.179] is a racemic mixture of the ester (92–93%) and alpha-methylbenzyl alcohol (5–6%); total sum 98%. The Panel noted that alpha-methylbenzyl alcohol [FL-no: 02.064] is an authorised flavouring substance evaluated in FGE.69. [FL-no: 09.476] is a mixture of ethyl 3-phenyl-3-oxopropionate (88%), 3-oxo-3-phenylpropionic acid (7–8%) and ethyl benzoate. The Panel noted that 3-oxo-3-phenylpropionic acid is the corresponding acid formed upon hydrolysis of [FL-no: 09.476] and that ethyl benzoate [FL-no: 09.726] is an authorised flavouring substance evaluated in FGE.54 (EFSA AFC Panel, 2008c).

The Panel also noted that the purity requirements for flavouring substances [FL-no:09.179, 09.476,] should be updated, as outlined in Table B.1 – Appendix B (see 'EFSA comments' column), in accordance with the latest specifications data provided by industry (Documentation provided to EFSA nr.3).

The most recent specifications data for all 35 substances in FGE.69Rev1 are summarised in Table B.1 – Appendix B. The information on specifications is complete for 33 flavouring substances in this FGE. The information on the composition of the mixture of positional isomers of the material of commerce is insufficient for [FL-no: 07.038 and 07.042].

3.2. Estimation of intake

JECFA status

For 31 flavouring substances [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.066, 02.080, 07.004, 07.013, 07.022, 07.023, 07.024, 07.025, 07.026, 07.027, 07.028, 07.029, 07.032, 07.038,

07.040, 07.042, 07.079, 07.086, 07.087, 09.144, 09.178, 09.179, 09.231, 09.249, 09.476 and 09.486], evaluated through the JECFA Procedure, intake data are available for the EU (JECFA, 2002a,b). For four substance [FL-no: 07.070, 09.189, 02.200 and 09.501], a production figure is only available for the US, and thus, the MSDI value for the EU cannot be calculated for these substances.

EFSA considerations

Updated EU production figures for the three newly allocated flavouring substances [FL-no: 02.066, 07.024, 07.027] have been submitted (Documentation provided to EFSA nr. 1).

Additionally, for four flavouring substances [FL-no: 07.070, 09.189, 09.200 and 09.501] considered in the previous version of this FGE (FGE.69), EU production volumes have been provided (Documentation provided to EFSA nr. 3), and therefore, the EU MSDI value can be calculated. These four flavouring substances were considered and evaluated in FGE.96 (EFSA CEF Panel, 2011), where it was concluded that these were not of safety concern based on MSDI approach. The MSDI values range from 0.012 to 170 $\mu\text{g}/\text{capita}$ per day (Table C.4 – Appendix C).

Normal and maximum use levels for flavouring substances [FL-no: 07.013, 07.028, 07.032, 07.086] are available (Documentation provided to EFSA nr. 4). The mTAMDI intake estimates calculated from these data for flavouring substances [FL-no: 07.013, 07.028, 07.032, 07.086] are below the toxicological threshold of concern (TTC) for structural class III. For the three newly allocated flavouring substances [FL-no: 02.066, 07.024, 07.027], normal and maximum use levels have been submitted (Documentation provided to EFSA nr. 2). The mTAMDI intake estimates calculated for [FL-no: 02.066] and [FL-no: 07.024] are below TTC values for their structural class I, while for [FL-no: 07.027] is above TTC value for its structural class I. Therefore, for [FL-no: 07.027], more detailed data on uses and uses levels should be provided in order to refine the exposure assessment and to finalise its safety evaluation.

No normal and maximum use levels have been provided for 28 flavouring substances [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.080, 07.004, 07.022, 07.023, 07.025, 07.026, 07.029, 07.038, 07.040, 07.042, 07.070, 07.079, 07.087, 09.144, 09.178, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501], previously considered in FGE.69.

The MSDI values for the 35 flavouring substances and the mTAMDI intake estimates for [FL-no: 02.066, 07.013, 07.024, 07.027, 07.028, 07.032, 07.086] are shown in Table C.4 – Appendix C.

3.3. Biological and toxicological data

3.3.1. ADME data

According to JECFA (57th meeting), the three candidate flavouring substances [FL-no: 02.066, 07.024 and 07.027] are rapidly absorbed through the gastrointestinal tract. The flavouring substance 4-phenyl-3-buten-2-one [FL-no: 07.024] may be reduced to flavouring substance 4-phenyl-3-buten-2-ol [FL-no: 02.066]. The resulting alcohols are then either conjugated with glucuronic acid and excreted in the urine, or are further oxidised and excreted as glycine conjugates. The ketone may also be conjugated with glutathione (GSH).

Toxicokinetics data of 4-phenyl-3-buten-2-one [FL-no: 07.024] proved that [FL-no: 07.024] is subjected to complete first-pass metabolism in rats and mice after oral administration and is rapidly eliminated (with a half-life of 20 min in rats and 10 min in mice) after intravenous administration (JECFA, 2002a). The glycine conjugate of phenylacetic acid, phenaceturic acid (65%), was the major urinary metabolite collected 48 h after administration of [FL-no: 07.024] as single dose (200 mg/kg body weight (bw)) to rats by oral gavage (JECFA, 2002b).

Therefore, JECFA concluded that the aromatic substituted secondary alcohol and the two aromatic substituted ketones [FL-no: 02.066, 07.024 and 07.027] can be anticipated to be metabolised to innocuous substances and therefore can be evaluated along the A-side of the Procedure (see Appendix A).

EFSA considerations

In accordance with JECFA, the Panel agrees that the three candidate substances [FL-no: 02.066, 07.024, 07.027] are rapidly absorbed from the gut. The flavouring substances [FL-no: 07.024, 07.027] can be expected to be reduced to the corresponding alcohols. The flavouring substances [FL-no: 07.024] and [FL-no: 02.066] are readily interconvertible. The resulting alcohols are then conjugated with glucuronic acid and excreted in urine.

Toxicokinetic data for (4-phenyl-3-buten-2-one [FL-no: 07.024]) indicate that orally administered phenyl alkyl ketones undergo essentially complete first-pass metabolism prior to systemic distribution (Sauer et al., 1997a,b). The CEF Panel in FGE.16Rev2 (EFSA CEF Panel, 2009) concluded that aryl ketones are rapidly absorbed from the gut, metabolised in the liver and further excreted mainly in the urine within 24 h.

Overall, the FAF Panel concurs with the JECFA view that the three candidate substances [FL-no: 02.066, 07.024, 07.027] in FGE.69Rev1 can be evaluated along the A-side. This is in line with the approach followed for structurally similar substances in FGE.16Rev2 (EFSA CEF Panel, 2009).

3.3.2. Genotoxicity data

This revision involves the inclusion of three flavouring substances [FL-no: 02.066, 07.024, 07.027], for which a concern for genotoxicity (EFSA, 2008) had been identified based on the presence of a structural alert (i.e. α,β -unsaturated carbonyl substance or precursor for that), preventing their evaluation through the Procedure (see also Appendix A). Therefore, these substances needed further attention in FGE.215 and its revision 1 (FGE.215Rev1), where their genotoxic potential has been assessed and ruled out (EFSA CEF Panel, 2014; EFSA FAF Panel, 2019). Therefore, the safety evaluation through the Procedure can be performed for these flavouring substances.

3.3.3. Toxicological data

In the JECFA evaluations at its 57th meeting (JECFA, 2002b), two acute toxicity studies on the candidate substance 4-phenyl-3-buten-2-one [FL-no: 07.024] were considered. An oral median lethal dose (LD50) of 5.0 and 5.2 mL/Kg bw for rats have been reported (study by Levenstein & Wolven, 1972 and Trubek Labs, 1964 as cited in JECFA, 2002b).

No subacute, subchronic/chronic toxicity and carcinogenicity studies are available on the three newly included candidate substances. When available, subacute, subchronic/chronic toxicity and carcinogenicity studies for previously evaluated flavouring substances in FGE.69 are summarised in FGE.16Rev2 (EFSA CEF Panel, 2009).

3.4. Application of the procedure

Application of the Procedure by JECFA (2002a,b)

JECFA allocated the three candidate flavouring substances [FL-no: 02.066, 07.024, 07.027], currently under evaluation in FGE.69Rev1, to structural class I according to the decision tree approach presented by Cramer et al. (1978).

JECFA considered that these three flavouring substances can be anticipated to be metabolised to innocuous products (step 2). The intakes, based on MSDI approach, for all substances are below the threshold of concern for structural class I (1,800 $\mu\text{g}/\text{person}$ per day) (step A3). Therefore, JECFA concluded that these three substances would pose no safety concern at their estimated level of use, based on the MSDI approach.

The JECFA safety evaluations of the three flavouring substances are summarised in Table D.1 – Appendix D.

EFSA considerations

The FAF Panel agrees with JECFA with respect to the allocation of three candidate flavouring substances [FL-no: 02.066, 07.024, 07.027] to Cramer class I.

The Panel agrees with the way of the application of the Procedure has been performed by JECFA for flavouring substances [FL-no: 02.066, 07.024, 07.027].

The MSDI exposure estimates for the three candidate flavouring substances [FL-no: 02.066, 07.024, 07.027] are below the threshold of concern for structural class I (i.e. 1,800 $\mu\text{g}/\text{person}$ per day) (see Table C.4 – Appendix C). Therefore, the FAF Panel concludes, at step A3 of the Procedure scheme, that the candidate flavouring substances do not raise a safety concern when used as flavouring substances at the estimated levels of intake, based on the MSDI approach.

For all three candidate flavouring substances, use levels are available and mTAMDI values have been calculated (see Table C.4 – Appendix C). For two substances, [FL- no: 07.024] and [FL- no: 02.066], the mTAMDI intake estimates are below the TTC for their structural class (I). For one substance, [FL-no: 07.027], the mTAMDI intake estimate is above the TTC for its structural class (I).

Therefore, for this flavouring substance, more detailed data on uses and use levels should be provided in order to refine the exposure assessment and to finalise its safety evaluation.

For four flavouring substances [FL-no: 07.013, 07.028, 07.032, and 07.086], already considered in FGE.69, uses and use levels data were submitted after publication of FGE.69 (EFSA AFC Panel, 2008a) and mTAMDI values have been calculated (see Table C.4 – Appendix C). The mTAMDI intake estimates are below the TTC for their structural class (III).

4. Discussion

This revision of FGE.69 comprises in total 35 flavouring substances, 32 of which have already been considered in FGE.69. The remaining three substances [FL-no: 02.066, 07.024, 07.027] have been included in this revision, following an extensive evaluation in FGE.215Rev1 of their genotoxic potential due to the presence of a structural alert for genotoxicity (i.e. α,β -unsaturated carbonyl or precursors for that).

Based on considerations of structural class, metabolism data and absence of genotoxic potential *in vivo* and the MSDI exposure estimates, the FAF Panel concludes that the flavouring substances considered in this revision of FGE.69 (FGE.69Rev1) do not raise a safety concern at step A3 of the Procedure, when based on MSDI approach.

For seven substances, including the three newly included flavouring substances in FGE.69Rev1 and four substances from the previous revision FGE.69 [FL-no: 07.013, 07.028, 07.032, and 07.086], normal and maximum use levels have been provided. For six substances [FL-no: 02.066, 07.013, 07.024, 07.028, 07.032 and 07.086], the mTAMDI intake estimates are below the TTC for their structural classes. For one substance [FL-no: 07.027], the mTAMDI intake estimate is above the threshold of concern for its structural class (I). Therefore, for this substance, more detailed data on uses and use levels should be provided in order to refine the exposure assessment and to finalise its safety evaluation.

For the remaining 28 substances previously considered in FGE.69 [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.080, 07.004, 07.022, 07.023, 07.025, 07.026, 07.029, 07.038, 07.040, 07.042, 07.070, 07.079, 07.087, 09.144, 09.178, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501], no normal or maximum use levels have been provided. For these 28 substances, normal and maximum use levels are needed to calculate the mTAMDI estimates in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly.

To determine whether the conclusions for the 35 JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications, including complete purity criteria and identity, are available for 33 flavouring substances. For two substances [FL-no: 07.038 and 07.042], the information on the composition of the mixture of positional isomers is insufficient.

5. Conclusions

The Panel considered that for 33 flavouring substances evaluated through the Procedure the specifications are adequate and the Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' when based on the MSDI approach. For two flavouring substances [FL-no: 07.038 and 07.042], there is insufficient information on their chemical identity (the composition of the mixture of positional isomers is lacking) to reach a final conclusion.

For six substances [FL-no: 02.066, 07.013, 07.024, 07.028, 07.032 and 07.086], there is no concern when the exposure was estimated based on the mTAMDI approach.

For 28 substances, use levels are needed to calculate the mTAMDI estimates in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly. For one substance [FL-no: 07.027], more reliable data on uses and use levels are required in order to finalise the safety evaluation.

6. Recommendation

The Panel recommends the European Commission to consider:

- to request normal and maximum use levels for [FL-no: 02.033, 02.034, 02.036, 02.064, 02.065, 02.080, 07.004, 07.022, 07.023, 07.025, 07.026, 07.029, 07.038, 07.040, 07.042,

07.070, 07.079, 07.087, 09.144, 09.178, 09.179, 09.189, 09.200, 09.231, 09.249, 09.476, 09.486 and 09.501].

- to request more detailed data on uses and use levels for the flavouring substance [FL-no: 07.027] in order to refine the exposure assessment and to finalise its safety evaluation.
- to request information on the composition of the mixture of positional isomers of flavouring substances [FL-no: 07.038 and 07.042].
- to update the purity requirements in the Union List for flavouring substances [FL-no: 09.179 and 09.476], in accordance with the latest specifications for the materials of commerce provided by industry (see Table B.1 – Appendix B).

7. Documentation provided to EFSA

- 1) EFFA (European Flavour Association), 2020a. EFFA submission of additional information on stereoisomerism.
- 2) EFFA (European Flavour Association), 2020b. EFFA submission of additional information on Use levels and mTAMDI.
- 3) EFFA (European Flavour Association), 2010a. EFFA Letter to EFSA, clarification of specifications and isomerism.
- 4) EFFA (European Flavour Association), 2007. EFFA Letter to EFSA, use levels of flavouring substances class III.
- 5) EFFA (European Flavour Association), 2002. Letter from EFFA to Dr. Joern Gry, Danish Veterinary and Food Administration. Dated 31 October 2002. Re.: Second group of questions. FLAVIS/8.26.

References

- Cramer GM, Ford RA and Hall RL, 1978. Estimation of toxic hazard – a decision tree approach. *Food and Cosmetics Toxicology*, 16, 255–276.
- EFSA (European Food Safety Authority), 2008. Minutes of the 26th Plenary meeting of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food, Held in Parma on 27 - 29 November 2007. Available online: <https://www.efsa.europa.eu/sites/default/files/event/afc071127-m.pdf> [Accessed: 7 January 2008].
- EFSA AFC Panel (EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food), 2006. Opinion of the Scientific Panel AFC related to Flavouring Group Evaluation 16: Aromatic ketones from chemical group 21. *EFSA Journal* 2006;4(8):330, 45 pp. <https://doi.org/10.2903/j.efsa.2006.330>
- EFSA AFC Panel (EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food), 2008a. Scientific Opinion on Flavouring Group Evaluation 69, (FGE.69) Aromatic substituted secondary alcohols, ketones and related esters evaluated by JECFA (57th meeting) structurally related to aromatic ketones from chemical group 21 evaluated by EFSA in FGE.16 (2006). *EFSA Journal* 2008;6(11):869, 35 pp. <https://doi.org/10.2903/j.efsa.2008.869>
- EFSA AFC Panel (EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food), 2008b. Scientific Opinion on a request from Commission on FGE.16Rev1: Aromatic ketones from chemical group 21. *EFSA Journal* 2008;6(10):810, 45 pp. <https://doi.org/10.2903/j.efsa.2008.810>
- EFSA AFC Panel (EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food), 2008c. Scientific Opinion on a request from Commission on Flavouring Group Evaluation 54 (FGE.54): consideration of benzyl derivatives evaluated by JECFA (57th meeting) structurally related to benzyl alcohols, benzaldehydes, a related acetal, benzoic acids and related esters evaluated by EFSA in FGE.20 (2005). *EFSA Journal* 2008;6(10):835, 73 pp. <https://doi.org/10.2903/j.efsa.2008.835>
- EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2009. Scientific Opinion on Flavouring Group Evaluation 16 Rev2. *EFSA Journal* 2009;12(7):1022, 49 pp. <https://doi.org/10.2903/j.efsa.2009.1022>
- EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2011. Scientific Opinion on Flavouring Group Evaluation 96 (FGE.96): consideration of 88 flavouring substances considered by EFSA for which EU production volumes/anticipated production volumes have been submitted on request by DG SANCO. Addendum to FGE. 51, 52, 53, 54, 56, 58, 61, 62, 63, 64, 68, 69, 70, 71, 73, 76, 77, 79, 80, 83, 84, 85 and 87. *EFSA Journal* 2011;9(12):1924, 60 pp. <https://doi.org/10.2903/j.efsa.2011.1924>
- EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2014. Scientific Opinion on Flavouring Group Evaluation 215 (FGE.215): seven α , β -Unsaturated Cinnamyl Ketones from subgroup 3.2 of FGE.19. *EFSA Journal* 2014;12(4):3623, 23 pp. <https://doi.org/10.2903/j.efsa.2014.3623>
- EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), 2019. Scientific Opinion on Flavouring Group Evaluation 215 Revision 1 (FGE.215Rev1): seven α , β -unsaturated cinnamyl ketones from subgroup 3.2 of FGE.19. *EFSA Journal* 2019;17(11):5875, 34 pp. <https://doi.org/10.2903/j.efsa.2019.5875>

- EFSA Scientific Committee, 2009. Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: general Principles. EFSA Journal 2009;7(7):1051, 22 pp. <https://doi.org/10.2903/j.efsa.2009.1051>
- EFSA Scientific Committee, 2019. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. EFSA Journal 2019;17(6):5708, 17 pp. <https://doi.org/10.2903/j.efsa.2019.5708>
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1995. Evaluation of certain food additives and contaminants. Forty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO. Technical Report Series, no. 859. Geneva.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1996. Toxicological evaluation of certain food additives. The forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives and contaminants.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1997. Evaluation of certain food additives and contaminants. Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 6-1 February 1996. WHO Technical Report Series, no. 868. Geneva.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1999. Evaluation of certain food additives and contaminants. Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. Rome, 17-26 June 1997. WHO Technical Report Series, no. 884. Geneva.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2002a. Evaluation of certain food additives and contaminants. fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, no. 909, 2001, Rome, Italy.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2002b. Safety evaluation of certain food additives. Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO food additives series: 48, 2001, Rome, Italy.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2016. Evaluation of certain food additives, eighty second report of the Joint FAO/WHO Expert Committee on Food Additives, WHO technical report series; no. 1000, 2016, Geneva, Switzerland.
- Levenstein I and Wolven AM, 1972. Acute toxicity studies in rats and in rabbits. Unpublished report to RIFM. cited in JECFA, 2002b.
- Sauer JM, Smith R, Bao J, Kuester R, Mayersohn M and Sipes IG, 1997a. Absorption, disposition, and metabolism of t-methyl styryl ketone in female B6C3F1 mice. Drug Metabolism and Disposition, 25, 1184–1190.
- Sauer JM, Smith R, Bao J, Kattnig MJ, Kuester R, McClure TD, Mayersohn M and Sipes IG, 1997b. Oral and topical absorption, disposition kinetics, and the metabolic fate of t-methyl styryl ketone in the male fischer 344 rat. Drug Metabolism and Disposition, 25, 732–739.
- SCF (Scientific Committee on Food), 1995. First annual report on chemically defined flavouring substances. May 1995, 2nd draft prepared by the SCF Working Group on Flavouring Substances (Submitted by the SCF Secretariat, 17 May 1995). CS/FLAV/FL/140-Rev2. Annex 6 to Document III/5611/95, European Commission, Directorate-General III, Industry.
- SCF (Scientific Committee on Food), 1999. Opinion on a programme for the evaluation of flavouring substances (expressed on 2 December 1999). SCF/CS/FLAV/TASK/11 Final 6/12/1999. Annex I the minutes of the 119th Plenary meeting. European Commission, Health & Consumer Protection Directorate-General.
- Trubek Laboratories, Inc., 1964. Acute oral LD50 of 4-phenyl-3-buten-2-one in rats and sensitization test of 4-phenyl-3-buten-2-one in guinea pigs. Unpublished report. cited in JECFA, 2002b.

Abbreviations

ADME	Absorption, Distribution, Metabolism, Elimination
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
BW	Body Weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFFA	European Flavour Association
FAF	Panel on food Additives and Flavourings
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavour and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
ID	Identity
IR	Infrared Spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD ₅₀	Median lethal dose

MS	Mass Spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NMR	Nuclear Magnetic Resonance
No	Number
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
SCF	Scientific Committee on Food
TTC	Threshold of Toxicological Concern
UL	Union List
WHO	World Health Organization

Appendix A – Procedure of the safety evaluation

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000, named the 'Procedure', is shown in schematic form in Figure A.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995, 1996, 1997, 1999), hereafter named the 'JECFA Procedure'.⁵

The Procedure is a stepwise approach that integrates information on intake from current uses, structure–activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II and III) for which toxicological thresholds of concern (TTCs) (human exposure thresholds) have been specified. Exposures below these TTCs are not considered to present a safety concern.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The TTCs for these structural classes of 1,800, 540 or 90 µg/person per day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996).

In step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- Can the flavourings be predicted to be metabolised to innocuous products⁶ (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous⁷ (step A4)?
- Does a NOAEL exist on the flavourings or on structurally related substances (steps A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure. The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

⁵ The FAF Panel is aware that a Revised Procedure for the Safety Evaluation of Flavouring agents has been agreed by JECFA (JECFA, 2016). Also, the EFSA Scientific Committee has recently developed a modified procedure for evaluation of substances based on the TTC approach (EFSA Scientific Committee, 2019). However, these developments have no impact on the present evaluation, which should follow the requirements as set out in Commission Regulation (EC) No 1565/2000.

⁶ *Innocuous products*: products that are known or readily predicted to be harmless to humans at the estimated intake of the flavouring agent (JECFA, 1997).

⁷ *Endogenous substances*: intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997).

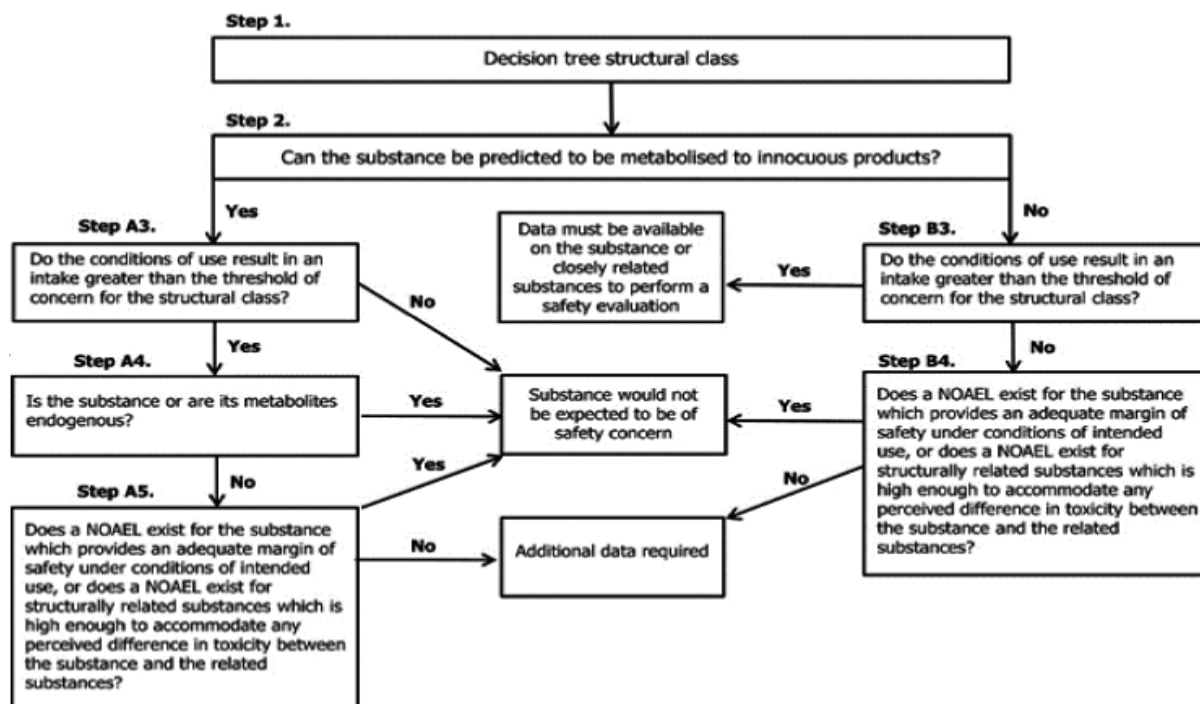


Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances

For the flavouring substances considered in this Flavouring Group Evaluation (FGE), the EFSA Panel on Food Additives and Flavourings (FAF) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The considerations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance:

a) *Intake*

In its evaluation, the Panel as a default uses the 'maximised survey-derived daily intake' (MSDI)⁸ approach to estimate the per capita intakes of the flavouring substances in Europe.

In its evaluation, JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by JECFA only on the basis of these figures. For substances in the Union List³ of flavouring substances for which this is the case, the Panel will need European Union (EU) production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use levels reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach. It is noted that JECFA, at its 65th meeting, considered 'how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods' (JECFA, 2006).

In the absence of more accurate information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an

⁸ EU MSDI: Amount added to food as flavour in (kg/year) × 10⁹ / (0.1 × population in Europe (= 375 × 10⁶) × 0.6 × 365) = µg/capita per day.

estimate of the daily intakes per person using a modified Theoretical Added Maximum Daily Intake (mTAMDI) approach based on the normal use levels reported by Industry (see Appendix C.2).

As information on use levels for the flavouring substances has not been requested by JECFA or has not otherwise been provided to the Panel, it is not possible to estimate the daily intakes using the mTAMDI approach for many of the substances evaluated by JECFA. The Panel will need information on use levels in order to finalise the evaluation.

b) Threshold of 1.5 microgram/person per day (step B5) used by JECFA

JECFA uses the threshold of concern of 1.5 µg/person per day as part of the evaluation procedure:

'The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 µg/person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents, used at the 46th meeting, should be amended to include the last step on the right-hand side of the original procedure ('Do the conditions of use result in an intake greater than 1.5 µg per day?')' (JECFA, 1999).

In line with the opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 µg per person per day.

c) Genotoxicity

As reflected in the opinion of SCF (1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *in vitro*, will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

d) Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of JECFA, since the Panel requests information on e.g. isomerism.

e) Structural Relationship

In the consideration of the JECFA evaluated substances, the Panel will examine the structural relationship and metabolism features of the substances within the flavouring group and compare this with the corresponding FGE.

Appendix B – Specifications

Table B.1: Summary table on specifications data for flavouring substances in FGE.69Rev1, for chemical structures see Appendix D

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
02.033 822 2884 82 93-54-9	1-Phenylpropan-1-ol	(b)	Liquid C ₉ H ₁₂ O 136.19	Insoluble Miscible	219 IR 97% (racemate)	1.517–1.522 0.993–1.000	
02.034 825 2953 83 705-73-7	1-Phenylpentan-2-ol	(b)	Liquid C ₁₁ H ₁₆ O 164.25	Insoluble Miscible	247 IR 96% (racemate)	1.508–1.513 0.957–0.964	
02.036 815 2879 85 2344-70-9	4-Phenylbutan-2-ol	(b)	Liquid C ₁₀ H ₁₄ O 150.22	Insoluble Miscible	229 IR 97% (racemate)	1.514–1.518 0.977–0.983	
02.064 799 2685 2030 98-85-1	1-Phenylethan-1-ol	(b)	Liquid C ₈ H ₁₀ O 122.17	Insoluble Miscible	204 19–20 IR 99% (racemate)	1.524–1.529 1.009–1.014	
02.065 827 2208 2031 7779-78-4	4-Methyl-1-phenylpentan-2-ol	(b)	Liquid C ₁₂ H ₁₈ O 178.28	Insoluble Miscible	250 IR 96% (racemate)	1.500–1.510 0.940–0.949	(Documentation provided to EFSA nr. 3)

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
02.066 819 2880 2032 17488-65-2	Phenylbut-3-en-2-ol	(b)	Liquid C ₁₀ H ₁₂ O 148.21	Insoluble Miscible	140 (16 hPa) IR 96% (30–60%(Z)- isomer and 40–70%(E)- isomer), racemate	1.558–1.567 1.006–1.012	Stereoisomeric mixture: 30–60% (Z)- isomer and 40–70% (E)- isomer. (Documentation provided to EFSA nr. 1).
02.080 805 3139 10197 536-50-5	1-(p-Tolyl)ethan-1-ol	(b)	Liquid C ₁₀ H ₁₂ O 136.19	Miscible Miscible	218–219 IR 96% (racemate)	1.520–1.524 0.980–0.990	
07.004 806 2009 138 98-86-26	Acetophenone	(b)	Liquid C ₈ H ₈ O 120.15	Very slightly soluble Miscible above 20°	202 IR 98%	1.530–1.535 1.022–1.028	
07.013 811 2723 147 93-08-3	Methyl 2-naphthyl ketone	(b)	Solid C ₁₂ H ₁₀ O 170.21	Insoluble Soluble	300 53 IR 97%	n.a. n.a.	
07.022 807 2677 156 122-00-9	4-Methylacetophenone	(b)	Liquid C ₉ H ₁₀ O 134.18	Insoluble Very soluble	226 22–24 IR 95%	1.530–1.536 0.999–1.010	
07.023 809 2387 157 89-74-7	2,4-Dimethylacetophenone	(b)	Liquid C ₁₀ H ₁₂ O 148.21	Insoluble Miscible	228 IR 96%	1.532–1.536 0.993–0.999	

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
07.024 820 2881 158 122-57-6	Phenylbut-3-en-2-one	(b)	Solid C ₁₀ H ₁₀ O 146.19	Insoluble Very soluble	260 39–42 IR 97% (30-60%(Z)- isomer and 40–70%(E)- isomer)	n.a. n.a.	Stereoisomeric mixture: 30-60%(Z)- isomer and 40-70% (E)- isomer. (Documentation provided to EFSA nr. 1)
07.025 828 2740 159 5349-62-2	4-Methyl-1-phenylpentan-2-one	(b)	Liquid C ₁₂ H ₁₆ O 176.26	Insoluble Miscible	251 NMR 96%	1.500–1.510 0.940–0.949	
07.026 817 3074 160 777-79-0	4-(p-Tolyl)butan-2-one	(b)	Liquid C ₁₁ H ₁₄ O ₂ 162.23	Insoluble Miscible	85 (9 hPa) IR 97% (racemate)	1.503–1.508 0.981–0.988	
07.027 821 2734 161 1901-26-4	3-Methyl-4-phenylbut-3-en-2-one	(b)	Solid C ₁₁ H ₁₂ O 160.22	Insoluble Very soluble	124–125 (13 hPa) 38–40 NMR 97% (30–60%(Z)- isomer and 40–70%(E)- isomer)	n.a. n.a.	Stereoisomeric mixture: 30–60%(Z)- isomer and 40–70% (E)- isomer (Documentation provided to EFSA nr. 1)
07.028 836 2132 162 119-53-9	Benzoin	(b)	Solid C ₁₄ H ₁₂ O ₂ 212.25	Insoluble Slightly soluble	194 (16 hPa) 137 IR 98% (racemate)	n.a n.a	
07.029 818 2672 163 104-20-1	4-(4-Methoxyphenyl)butan-2-one	(b)	Liquid C ₁₁ H ₁₄ O ₂ 178.23	Insoluble Miscible	277 IR 96%	1.515–1.525 1.041–1.050	

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
07.032 831 2134 166 119-61-9	Benzophenone	(b)	Solid C ₁₃ H ₁₀ O 182.22	Insoluble Very soluble	305 48 IR 98%	n.a. n.a.	
07.038 810 2005 570 100-06-1	4-Methoxyacetophenone	(b)	Solid C ₉ H ₁₀ O ₂ 150.18	Insoluble Very soluble	153 (34 hPa) 36–38 IR 97% as sum of para (predominant), ortho and meta isomers (minor constituents)	n.a. n.a.	Occurs mainly as the para-isomer. Other minor constituents are the other two positional isomers: ortho and meta (sum of all isomers: 97% purity). (Documentation provided to EFSA nr. 3) Composition of the mixture of positional isomers to be specified
07.040 824 3469 599 93-55-0	1-Phenylpropan-1-one	(b)	Liquid C ₉ H ₁₀ O 134.18	Insoluble Miscible	218 21 IR 98%	1.521–1.531 1.004–1.014	

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
07.042 808 2927 651 645-13-6	4-Isopropylacetophenone	(b)	Liquid C ₁₁ H ₁₄ O 162.23	Insoluble Miscible	252 IR 98% as sum of para (predominant), ortho and meta isomers (minor constituents)	1.520–1.527 0.967–0.975	Occurs mainly as the para-isomer (4-isopropyl form). Other minor constituents are the other two positional isomers: ortho and meta (sum of all isomers: 98% purity) (Documentation provided to EFSA nr. 3) Composition of the mixture of positional isomers to be specified
07.070 830 2146 2140 7492-37-7	3-Benzylheptan-4-one	(b)	Liquid C ₁₄ H ₂₀ O 204.31	Insoluble Miscible	158–160 (13 hPa) IR 99% (racemate)	1.490–1.495 0.931–0.937	(Documentation provided to EFSA nr. 3)
07.079 833 3226 2275 579-07-7	1-Phenylpropan-1,2-dione	(b)	Liquid C ₉ H ₈ O ₂ 148.16	Insoluble Miscible	103–105 (18 hPa) IR 97%	1.526–1.536 1.096–1.116	
07.086 832 2397 11839 102-04-5	1,3-Diphenylpropan-2-one	(b)	Solid C ₁₅ H ₁₄ O 210.28	Insoluble Very soluble	330 32–37 IR 97%	n.a. n.a.	

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
07.087 813 2674 11836 122-84-9	4-Methoxyphenylacetone	(b)	Liquid C ₁₀ H ₁₂ O ₂ 164.21	Insoluble Miscible	260 IR 97%	1.520–1.530 1.067–1.073	
07.133 812 3653 13171-00-1	4-Acetyl-6-t-butyl-1,1-dimethylindane	(b)	Solid C ₁₇ H ₂₄ O 244.38	Insoluble Soluble	68–70 IR 97%	n.a. n.a.	No longer supported by industry Was not included in the UL
09.144 802 2689 425 120-45-6	1-Phenethyl propionate	(b)	Liquid C ₁₁ H ₁₄ O ₂ 178.23	Insoluble Miscible	91–92 (7 hPa) IR 98% (racemate)	1.487–1.494 1.002–1.009	
09.178 801 2684 573 93-92-5	1-Phenethyl acetate	(b)	Liquid C ₁₀ H ₁₂ O ₂ 164.20	Insoluble Miscible	214 IR 98% (racemate)	1.492–1.504 1.020–1.035	
09.179 800 2688 574 7775-38-4	1-Phenethyl formate	(b)	Liquid C ₉ H ₁₀ O ₂ 150.18	Insoluble Miscible	198 IR Ester (92–93%) SC: alpha-methylbenzyl alcohol (5–6%) (racemate)	1.502–1.508 1.042–1.050	(Documentation provided to EFSA nr. 3) The purity requirements should be updated in the UL, as in accordance with the specifications provided
09.189 823 2424 628 10031-86-4	1-Phenylpropyl butyrate	(b)	Liquid C ₁₃ H ₁₈ O ₂ 206.28	Insoluble Miscible	282 IR 97% (racemate)	1.486–1.491 0.986–0.992	(Documentation provided to EFSA nr. 3)

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
09.200 816 2882 671 10415-88-0	1-Methyl-3-phenylpropyl acetate	(b)	Liquid C ₁₂ H ₁₆ O ₂ 192.26	Insoluble Miscible	72–74 (0.7 hPa) IR 98% (racemate)	1.498–1.505 0.975–0.980	(Documentation provided to EFSA nr. 3)
09.231 803 2686 2083 3460-44-4	1-Phenethyl butyrate	(b)	Liquid C ₁₂ H ₁₆ O ₂ 192.26	Insoluble Miscible	93–94 (4 hPa) IR 98% (racemate)	1.484–1.490 0.977–0.997	(Documentation provided to EFSA nr. 3)
09.249 814 3197 2276 68922-11-2	1-Methyl-2-phenethyl butyrate	(b)	Liquid C ₁₃ H ₁₈ O ₂ 206.29	Insoluble Miscible	138–140 (13 hPa) NMR 99% (racemate)	1.480–1.487 0.975–0.985	(Documentation provided to EFSA nr. 3)
09.476 834 2423 627 94-02-0	Ethyl 3-phenyl-3-oxopropionate	At least 88%; secondary component 7-9% ethyl benzoate	Liquid C ₁₁ H ₁₂ O ₃ 192.21	Insoluble Miscible	147 (14 hPa) IR Ethyl 3-phenyl-3-oxopropionate (88%) SC: 3-oxo-3-phenylpropionic acid (7–8%) and ethyl benzoate	1.524–1.533 1.107–1.120	(Documentation provided to EFSA nr. 3) The purity requirements should be updated in the UL in accordance with the specifications provided
09.486 804 2687 2088 7775-39-5	1-Phenethyl isobutyrate	(b)	Liquid C ₁₂ H ₁₆ O ₂ 192.26	Insoluble Miscible	219 IR 98% (racemate)	1.480–1.486 0.977–0.983	(Documentation provided to EFSA nr. 3)

Information included in the EU Union List Regulation No (EU) 1334/2008 as amended			Most recent available specifications data ^(a)				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	Chemical name	Purity of the named compound	Phys. form Mol. formula Mol. weight	Solubility ^(c) Solubility in ethanol ^(d)	Boiling point, °C ^(e) Melting point, °C ID test Assay minimum (isomers distribution/SC)	Refrac. index ^(f) Spec. gravity ^(g)	
09.501 835 2416 2241 620-79-1	Ethyl 2-acetyl-3phenylpropionate	(b)	Liquid C13H16O3 220.27	Insoluble Miscible	276 IR 97% (racemate)	1.498–1.502 1.033–1.037	(Documentation provided to EFSA nr. 3)

SC: Secondary components; UL: Union List.

(a): JECFA, 2002a,b; EFSA AFC Panel, 2008a; EFSA CEF Panel, 2011. Documentation provided to EFSA nr: 1. and 3.

(b): At least 95% unless otherwise specified.

(c): Solubility in water, if not otherwise stated.

(d): Solubility in 95% ethanol, if not otherwise stated.

(e): At 1,013.25 hPa, if not otherwise stated.

(f): At 20°C, if not otherwise stated.

(g): At 25°C, if not otherwise stated.

Appendix C – Exposure estimates

C.1. Normal and Maximum Use Levels

Table C.1: Normal and maximum use levels (mg/kg) of JECFA evaluated flavouring substances in FGE.69Rev1 in food categories listed in Annex III of Reg. (EC) 1565/2000 (Documentation provided to EFSA nr. 2 and 4)

FL-no	Food categories																	
	Normal use levels(a) (mg/kg)																	
	Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
02.066	3.76 20.66	– –	– –	– –	– –	3.07 11.97	3.33 11.97	3.89 5.03	– –	– –	– –	– –	– –	– –	0.57 2.26	0 0	– –	– –
07.013	0.064 0.16	– –	– –	– –	– –	0.14 2.3	0.0016 0.16	– –	– –	– –	– –	– –	– –	2E-5 0.00099	0.017 0.017	– –	0.0016 0.0024	– –
07.024	1.59 2.9	0.02 0.2	– –	– –	– –	4.44 8.72	1.59 2.9	5.25 10	– –	– –	– –	– –	– –	– –	0.89 1.72	1.28 1.92	– –	– –
07.027	16.55 19.1	– –	– –	– –	– –	11.9 13.13	16.55 19.1	12.83 14.23	– –	– –	– –	– –	– –	– –	7.63 10.25	0 0	– –	– –
07.028	3.8E-5 0.00035	0 0	– –	– –	– –	0.00016 0.0017	– –	– –	– –	– –	– –	– –	– –	– –	0.00016 0.0014	– –	– –	– –
07.032	– –	– –	0.01 0.089	– –	– –	0.022 0.12	0.01 0.074	0.01 0.076	– –	– –	– –	– –	– –	– –	– –	– –	– –	0.02 0.15
07.086	– –	– –	– –	– –	– –	0.006 0.04	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –

(a): 'Normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages (Documentation provided to EFSA n. 5).

C.2. mTAMDI calculations

The method for calculation of modified theoretical added maximum daily intake (mTAMDI) values is based on the approach used by the SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amount of flavourable foods and beverages listed in Table C.2. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

Table C.2: Estimated amount of flavourable foods, beverages and exceptions assumed to be consumed per person per day (SCF, 1995)

Class of product category	Intake estimate (g/day)
Beverages (non-alcoholic)	324.0
Foods	133.4
Exception a: Candy, confectionery	27.0
Exception b: Condiments, seasonings	20.0
Exception c: Alcoholic beverages	20.0
Exception d: Soups, savouries	20.0
Exception e: Others, e.g. chewing gum	E.g. 2.0 (chewing gum)

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 and reported by the Flavour Industry in the following way (see

- Beverages (SCF, 1995) correspond to food Table C.3): category 14.1
- Foods (SCF, 1995) correspond to the food categories 1, 2, 3, 4.1, 4.2, 6, 7, 8, 9, 10, 13, and/or 16
- Exception a (SCF, 1995) corresponds to food categories 5 and 11
- Exception b (SCF, 1995) corresponds to food category 15
- Exception c (SCF, 1995) corresponds to food category 14.2
- Exception d (SCF, 1995) corresponds to food category 12
- Exception e (SCF, 1995) corresponds to others, e.g. chewing gum.

Table C.3: Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 into the seven SCF food categories used for mTAMDI calculations (SCF, 1995)

Key	Food categories according to Commission Regulation 1565/2000	Distribution of the seven SCF food categories		
	Food category	Foods	Beverages	Exceptions
01.0	Dairy products, excluding products of category 02.0	Foods		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Foods		
03.0	Edible ices, including sherbet and sorbet	Foods		
04.1	Processed fruit	Foods		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Foods		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Foods		
07.0	Bakery wares	Foods		
08.0	Meat and meat products, including poultry and game	Foods		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Foods		
10.0	Eggs and egg products	Foods		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Foods		
14.1	Non-alcoholic ('soft') beverages, excl. dairy products		Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts			Exception c
15.0	Ready-to-eat savouries			Exception b
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01.0–15.0	Foods		

Table C.4: Estimated intakes based on the MSDI approach and the mTAMDI approach for substances in FGE.69Rev1

FL-no	Union list name	MSDI EU ^(a) (µg/capita per day)	MSDI US ^(b) (µg/capita per day)	mTAMDI ^(c) (µg/person per day)	Structural class	Threshold of concern (µg/person per day)
02.033	1-Phenylpropan-1-ol	0.24	0.1		Class I	1,800
02.034	1-Phenylpentan-2-ol	0.12	1		Class I	1,800
02.036	4-Phenylbutan-2-ol	1.2	0.3		Class I	1,800
02.064	1-Phenylethan-1-ol	27	72		Class I	1,800
02.066	4-Phenylbut-3-en-2-ol	0.061	0.1	790	Class I	1,800
02.080	1-(p-Tolyl)ethan-1-ol	0.12	1		Class I	1,800
07.004	Acetophenone	15	170		Class I	1,800
07.022	4-Methylacetophenone	22	37		Class I	1,800
07.023	2,4-Dimethylacetophenone	0.24	0.01		Class I	1,800
07.024	4-Phenylbut-3-en-2-one	1.2	7	1,100	Class I	1,800
07.026	4-(p-Tolyl)butan-2-one	0.012	0.4		Class I	1,800
07.027	3-Methyl-4-phenylbut-3-en-2-one	0.012	0.1	5,000	Class I	1,800
07.029	4-(4-Methoxyphenyl)butan-2-one	4.5	840		Class I	1,800
07.038	4-Methoxyacetophenone	130	84		Class I	1,800
07.040	1-Phenylpropan-1-one	0.012	0.03		Class I	1,800
07.042	4-Isopropylacetophenone	0.012	0.4		Class I	1,800
07.087	4-Methoxyphenylacetone	0.12	0.1		Class I	1,800
09.144	1-Phenethyl propionate	0.97	27		Class I	1,800
09.178	1-Phenethyl acetate	170	650		Class I	1,800
09.179	1-Phenethyl formate	0.037	0.4		Class I	1,800
09.189	1-Phenylpropyl butyrate	0.24	0.3		Class I	1,800
09.200	1-Methyl-3-phenylpropyl acetate	6.1	7		Class I	1,800
09.231	1-Phenethyl butyrate	1.1	0.01		Class I	1,800
09.249	1-Methyl-2-phenethyl butyrate	0.12	0.1		Class I	1,800
09.476	Ethyl 3-phenyl-3-oxopropionate	0.012	140		Class I	1,800
09.486	1-Phenethyl isobutyrate	24	1		Class I	1,800
09.501	Ethyl-2-acetyl-3-phenylpropionate	0.37	0.4		Class I	1,800
02.065	4-Methyl-1-phenylpentan-2-ol	24	3		Class II	540
07.025	4-Methyl-1-phenylpentan-2-one	8.5	0.3		Class II	540
07.070	3-Benzylheptan-4-one	0.05	1		Class II	540

FL-no	Union list name	MSDI EU ^(a) (µg/capita per day)	MSDI US ^(b) (µg/capita per day)	mTAMDI ^(c) (µg/person per day)	Structural class	Threshold of concern (µg/person per day)
07.079	1-Phenylpropan-1,2-dione	4.9	0.1		Class II	540
07.013	Methyl 2-naphthyl ketone	6.3	48	21	Class III	90
07.028	Benzoin	6.2	21	0.064	Class III	90
07.032	Benzophenone	23	11	3.7	Class III	90
07.086	1,3-Diphenylpropan-2-one	0.12	0.1	0.28	Class III	90

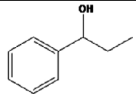
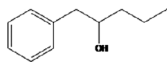
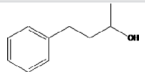
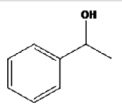
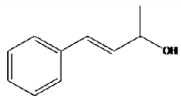
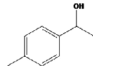
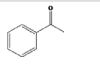
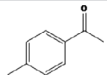
(a): Based on EU production figures from JECFA (JECFA, 2002a,b) and submitted by industry (Documentation provided to EFSA nr. 1 and 3).

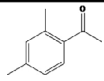
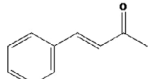
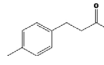
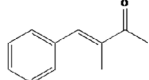
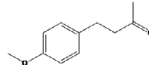
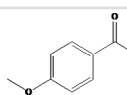
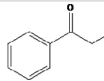
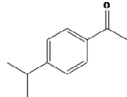
(b): Based on US production figures from JECFA (JECFA, 2002a,b).

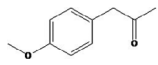
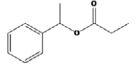
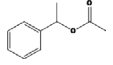
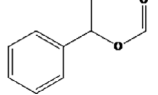
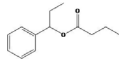
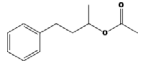
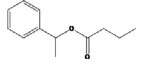
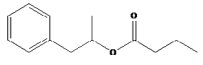
(c): Based on use levels submitted by industry (Documentation provided to EFSA nr. 2 and 4).

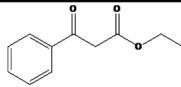
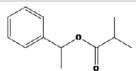
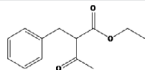
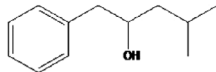
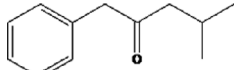
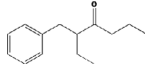
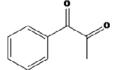
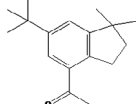
Appendix D – Summary of safety evaluations

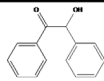
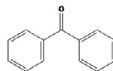
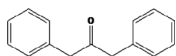
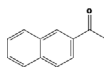
Table D.1: Summary of safety evaluations performed by JECFA (2002a, 2002b) and EFSA conclusions on flavouring substances in FGE.69 and its revisions

FL-no JECFA-no	Union list name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusion Procedural path if different from JECFA, conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
02.033 822	1-Phenylpropan-1-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
02.034 825	1-Phenylpentan-2-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
02.036 815	4-Phenylbutan-2-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
02.064 799	1-Phenylethan-1-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
02.066 819	4-Phenylbut-3-en-2-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69Rev1
02.080 805	1-(p-Tolyl)ethan-1-ol		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.004 806	Acetophenone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.022 807	4-Methylacetophenone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69

FL-no JECFA-no	Union list name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusion Procedural path if different from JECFA, conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.023 809	2,4-Dimethylacetophenone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.024 820	4-Phenylbut-3-en-2-one		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69Rev1
07.026 817	4-(p-Tolyl)butan-2-one		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach
07.027 821	3-Methyl-4-phenylbut-3-en-2-one		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69Rev1
07.029 818	4-(4-Methoxyphenyl)butan-2-one		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.038 810	4-Methoxyacetophenone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Composition of the mixture of positional isomers to be specified for the material of commerce Concluded in FGE.69
07.040 824	1-Phenylpropan-1-one		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.042 808	4-Isopropylacetophenone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Composition of the mixture of positional isomers to be specified for the material of commerce Concluded in FGE.69

FL-no JECFA-no	Union list name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusion Procedural path if different from JECFA, conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.087 813	4-Methoxyphenylacetone		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
09.144 802	1-Phenethyl propionate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
09.178 801	1-Phenethyl acetate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
09.179 800	1-Phenethyl formate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach The purity requirements should be updated in the UL, as in accordance with the specifications provided (see Table B.1 – Appendix B) Concluded in FGE.69
09.189 823	1-Phenylpropyl butyrate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.96
09.200 816	1-Methyl-3-phenylpropyl acetate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.96
09.231 803	1-Phenethyl butyrate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
09.249 814	1-Methyl-2-phenethyl butyrate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69

FL-no JECFA-no	Union list name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusion Procedural path if different from JECFA, conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
09.476 834	Ethyl 3-phenyl-3-oxopropionate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach The purity requirements should be updated in the UL, as in accordance with the specifications provided Concluded in FGE.69
09.486 804	1-Phenethyl isobutyrate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
09.501 835	Ethyl 2-acetyl-3-phenylpropionate		Class I A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.96
02.065 827	4-Methyl-1-phenylpentan-2-ol		Class II A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.025 828	4-Methyl-1-phenylpentan-2-one		Class II A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.070 830	3-Benzylheptan-4-one		Class II A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.96
07.079 833	1-Phenylpropan-1,2-dione		Class II A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.133	4-Acetyl-6-t-butyl-1,1-		Class II B3: Intake below threshold B4: No adequate NOAEL	Additional toxicity data required in FGE.69 No longer supported by Industry and was not included in the Union list

FL-no JECFA-no	Union list name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusion Procedural path if different from JECFA, conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.028 836	Benzoin		Class IIIA3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.032 831	Benzophenone		Class III A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.086 832	1,3-Diphenylpropan-2-one		Class III A3: Intake below threshold	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69
07.013 811	Methyl 2-naphthyl ketone		Class III B3: Intake below threshold B4: Adequate NOAEL exists	No safety concern at the estimated level of intake based on the MSDI approach Concluded in FGE.69

(a): Thresholds of concern: Class I = 1,800 µg/person per day, Class II = 540 µg/person per day, Class III = 90 µg/person per day.

(b): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.

(c): EU MSDI: Amount added to food as flavour in (kg/year) × 10⁹ / (0.1 × population in Europe (= 375 × 10⁶) × 0.6 × 365) = µg/capita per day.

(d): Refer to Appendix C for MSDI values considered by EFSA based on EU production figures submitted by industry (Documentation provided to EFSA n.: 1 and 3).