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Scientific Opinion on Flavouring Group Evaluation 63, Revision 4 (FGE.63Rev4): consideration of aliphatic secondary saturated and unsaturated alcohols, ketones and related esters evaluated by JECFA (59th and 69th meetings) structurally related to flavouring substances evaluated by EFSA in FGE.07Rev6

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Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 43 flavouring substances assigned to the Flavouring Group Evaluation 63 (FGE.63), using the Procedure as outlined in the Commission Regulation (EC) No 1565/2000. Twenty-nine substances have already been considered in FGE.63 and its revisions ([FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 02.252, 07.015, 07.069, 07.081, 07.099, 07.100, 07.101, 07.102, 07.114, 07.123, 07.151, 07.190, 07.240, 07.247, 07.249, 07.256, 09.281, 09.282, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936]). The remaining 14 flavouring substances have been cleared with respect to genotoxicity in FGE.204Rev1 ([FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244]) and they are considered in this revision 4 of FGE.63. The substances were evaluated through a stepwise approach that integrates information on the structure–activity relationships, intake from current uses, toxicological threshold of concern (TTC) and available data on metabolism and toxicity. The Panel concluded that none of these 43 substances gives rise to safety concerns at their levels of dietary intake, when estimated on the basis of the 'Maximised Survey-derived Daily Intake' (MSDI) approach. Besides the safety assessment of the flavouring substances, the specifications for the materials of commerce have also been considered and found adequate for 43 flavouring substances. However, for 14 of these flavouring substances in the present revision and for 10 of the substances in the previous revision (FGE.63Rev3), the 'modified Theoretical Added Maximum Daily Intakes' (mTAMDI) values are equal to or above the TTCs for their structural classes (I and II). For 15 substances previously evaluated in FGE.63Rev3, use levels are still needed to calculate the mTAMDI estimates. Therefore, in total for 39 flavouring substances, more data on uses and use levels should be provided to finalise their safety evaluations.

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Requestor: European Commission

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1. Introduction

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of 14 α,β -unsaturated aliphatic secondary alcohols and ketones ([FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121,¹ 07.139, 07.177, 07.188 and 07.244]) which have been evaluated with respect to genotoxicity in FGE.204Rev1. 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 1565/2000 and of Regulation (EU) No 1334/2008.

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

1.1.1. Background to Mandate from FGE.204Rev1 (M-2015-0114)

The use of flavourings is regulated under Regulation (EC) No 1334/2008² 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 1565/2000⁴.

On 21 November 2012, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids adopted an opinion on Flavouring Group Evaluation 204 (FGE.204): Consideration of genotoxicity data on 18 monounsaturated, aliphatic, α,β -unsaturated ketones and precursors from chemical subgroup FGE.204 (FGE.19 s.g. 1.2.1).

The Panel concluded that for the representative substance 7-Methyl-3-octen-2-one [FL-no: 07.177] of subgroup 1.2.1 of FGE.19, the Panel's concern with respect to genotoxicity could not be ruled out and consequently additional data are requested.

On 31 September 2014 (Ares (2014) 207551) the applicant submitted to the Commission and to EFSA data on the potential presence of the substance FL-no 07.177 in plasma (analytical data).

On 9 January 2015 (Ares (2015) 202297) the applicant submitted additional studies on the representative substance [FL-no: 07.177] in relation to this EFSA evaluation. This additional data examines the systemic exposure of rats following oral administration of this substance, using the same dosing regimen employed in the combined micronucleus and comet test previously submitted. The data on this representative substance is intended to cover the following 15 substances in this group, namely [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.187, 07.188, 07.244 and 07.258].

1.1.2. Terms of Reference of Mandate from FGE.204Rev1 (M-2015-0114)

The European Commission requests the European Food Safety Authority (EFSA) to evaluate this new information and, depending on the outcome, proceed to the full evaluation of the flavouring substances mentioned above in accordance with Commission Regulation (EC) No 1565/2000.

1.2. Interpretation of the Terms of Reference

Flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] were evaluated by JECFA (JECFA, 2002a, 2008 (59th and 69th meetings)) and will be considered in the current revision of FGE.63.

¹ This substance, dec-3-en-2-one, is currently under evaluation as active substance under Regulation (EC) 1107/2009 (EFSA-Q-2017-00813).

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.

⁴ Commission Regulation 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.

Flavouring substances [FL-no: 07.187 and 07.258] were not evaluated by JECFA and they have been evaluated in the revision 6 of FGE.07 (EFSA FAF Panel, 2022). For the flavouring substance 6-methyl-3-hepten-2-one [FL-no: 07.258], the industry informed that this substance is no longer supported (EFSA FAF Panel, 2022). On the basis that this flavouring substance is no longer supported by any interested party, the European Commission on 18/5/2020 (Ares(2020)2601393 – 18/5/2020) informed that it is going to proceed with the withdrawal of [FL-no: 07.258] from the Union List of flavourings. Accordingly, the EFSA evaluation of this flavouring substance is closed and [FL-no: 07.258] is no longer included in FGE.07Rev6.

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

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 4 of FGE.63 (FGE.63Rev4)

FL-no	Chemical name	Data provided for the current revision 4 of FGE.63	Appendix (Table nr) and relevant section of the opinion	Documentation provided to EFSA nr:
07.244	trans-6-Methyl-3-hepten-2-one	Specifications, EU poundage data (MSDI), use levels, ADME data	Appendix B (Table B.1) Appendix C (Tables C.1 and C.4), Section 3.3.1	Documentation provided to EFSA nr: 1 and 3
07.082	Oct-2-en-4-one	Specifications, EU poundage data (MSDI), use levels, ADME data	Appendix B (Table B.1) Appendix C (Tables C.1 and C.4), Section 3.3.1	Documentation provided to EFSA nr: 1, 3 and 4
07.188	Non-3-en-2-one	Specifications, EU poundage data (MSDI), use levels	Appendix B (Table B.1) Appendix C (Tables C.1 and C.4)	Documentation provided to EFSA nr: 1 and 2
07.177	7-Methyl-3-octenone-2			
07.139	5-Methylhept-2-en-4-one			
07.121	Dec-3-en-2-one			
07.106	5-Methylhex-3-en-2-one			
07.105	Hept-3-en-2-one			
07.104	Hept-2-en-4-one			
07.048	4-Hexen-3-one			
07.044	Pent-3-en-2-one			
02.193	Oct-2-en-4-ol			
02.102	Oct-3-en-2-ol			
07.107	Oct-3-en-2-one			

In addition, the following documentation has been consulted for the safety evaluation of FGE.63Rev4:

- JECFA specifications for the 14 flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] (JECFA, 2002a);
- Genotoxicity data evaluated in FGE.204Rev1 (EFSA FAF Panel, 2019);
- 59th JECFA report (JECFA, 2002b);
- EFSA Scientific Opinion on FGE.63Rev3 (and the previous revisions) (EFSA CEF Panel, 2016a);
- EFSA Scientific Opinion on FGE.07Rev5 (EFSA CEF Panel, 2017).

2.1.1. History of the evaluation of the substances in FGE.63

In the first version of Flavouring Group Evaluation 63 (FGE.63) (EFSA AFC Panel, 2008), EFSA considered a group of 13 aliphatic saturated and unsaturated secondary alcohols, ketones and related esters ([FL-no: 07.015, 07.069, 07.100, 07.114, 07.123, 07.151, 07.240, 07.249, 09.657, 09.658, 09.923, 09.924 and 09.925]) which had been evaluated by the JECFA at its 59th meeting (JECFA, 2002b).

The revision 1 of FGE.63, FGE.63Rev1 (EFSA CEF Panel, 2012a) was prepared due to the inclusion of six additional substances [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936] evaluated by JECFA at their 59th and 69th meetings. Furthermore, information on the stereoisomeric composition for six substances ([FL-no: 07.069, 07.114, 09.657, 09.658, 09.923 and 09.925]) and European poundage data for three substances ([FL-no: 07.069, 07.100 and 09.658]) had been submitted since the first publication of FGE.63.

The second revision of FGE.63, FGE.63Rev2 (EFSA CEF Panel, 2013) included the consideration of one additional substance, 4-methylpent-3-en-2-one [FL-no: 07.101]. This substance is an α,β -unsaturated ketone and was originally allocated in FGE.204 (EFSA CEF Panel, 2012a) where the concern for genotoxicity was assessed and ruled out.

The third revision of FGE.63, FGE.63Rev3 (EFSA CEF Panel, 2016a) dealt with the consideration of six additional substances ([FL-no: 02.023, 02.099, 02.104, 02.136, 07.081 and 07.102]), evaluated at the 59th meeting of JECFA, and three substances ([FL-no: 02.155, 09.281 and 09.282]), evaluated at the 69th meeting of JECFA. These substances are α,β -unsaturated secondary alcohols and ketones and they were originally evaluated in FGE.205 (EFSA CEF Panel, 2012b) and FGE.205Rev1 (EFSA CEF Panel, 2016b) to assess their genotoxicity potential. Since the concern for genotoxicity was ruled out for all nine substances, they had been evaluated through the Procedure in FGE.63Rev3. In addition, specifications, use levels and poundage data have also become available for these substances and this information was considered by the Panel in FGE.63Rev3.

For all 29 JECFA-evaluated aliphatic secondary alcohols, ketones and related esters [FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 02.252, 07.015, 07.069, 07.081, 07.099, 07.100, 07.101, 07.102, 07.114, 07.123, 07.151, 07.190, 07.240, 07.247, 07.249, 07.256, 09.281, 09.282, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936] considered in FGE.63Rev3, the Panel agreed with the JECFA conclusion: 'No safety concern at current levels of intake when used as flavouring agents, based on the 'Maximized Survey-derived Daily Intake' (MSDI).

For 14 of the 29 substances in FGE.63Rev3 use levels have been provided ([FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 02.252, 07.081, 07.099, 07.101, 07.102, 07.190, 09.281, 09.282 and 09.936]). Four flavouring substances [FL-no: 02.252, 07.099, 07.101 and 09.936] have mTAMDI intake estimates below the toxicological threshold of concern (TTC) for their structural class. For 10 substances [FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 07.081, 07.102, 07.190, 09.281 and 09.282], the mTAMDI values are above the TTC for their structural class II. Therefore, for these 10 substances, more reliable data on uses and use levels are required in order to finalise the evaluation.

For the remaining 15 [FL-no: 09.657, 09.658, 09.923, 09.924, 09.925, 07.015, 07.081, 07.100, 07.114, 07.123, 07.151, 07.240, 07.247, 07.249, 07.256] substances, evaluated through the Procedure in FGE.63Rev3, use levels are still missing.

The present revision 4 of FGE.63 (FGE.63Rev4) deals with 14 flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] which were evaluated by JECFA in its 59th meeting (JECFA, 2002b). These substances were evaluated by EFSA in FGE.204Rev1 (EFSA FAF Panel, 2019), where it was concluded that the concern for genotoxicity for these substances could be ruled out. Therefore, they could be evaluated through the Procedure.

Together with the 29 substances that were already considered in FGE.63Rev3, the current revision comprises 43 substances. The 29 flavouring substances, for which the evaluation was finalised in FGE.63Rev3, will not be further discussed. Nevertheless, for the sake of completeness, the information for all the 43 substances is maintained in the various tables in this FGE.

FGE	Adopted by EFSA	Link	No of substances
FGE.63	7 July 2007	https://www.efsa.europa.eu/en/efsajournal/pub/706.htm	13
FGE.63Rev1	26 September 2012	https://www.efsa.europa.eu/en/efsajournal/pub/2900.htm	19
FGE.63Rev2	09 April 2013	https://www.efsa.europa.eu/en/efsajournal/pub/3188	20
FGE.63Rev3	30 November 2016	https://www.efsa.europa.eu/en/efsajournal/pub/4662	29
FGE.63Rev4	15 December 2021	https://www.efsa.europa.eu/en/efsajournal/pub/7102	43

2.2. Methodologies

This opinion was elaborated 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 C.2 mTAMDI calculation).

3. Assessment

3.1. Specifications

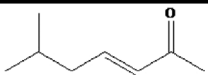
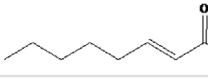
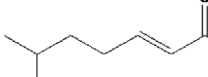
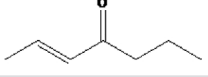
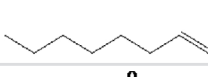
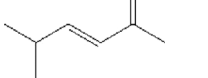
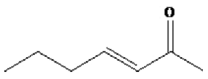
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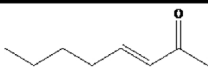
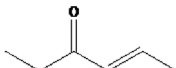
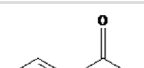
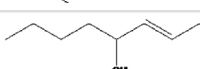
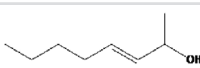
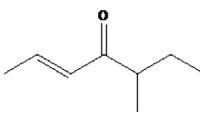
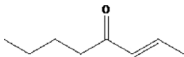
JECFA specifications are available for all the flavouring substances in FGE.63Rev4, including the 14 newly included flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] (JECFA, 2002a).

EFSA considerations

Table 1 shows the chemical structures of the candidate substances which are considered in this revision of FGE.63 (FGE.63Rev4).

Table 2: Flavouring substances under evaluation in FGE.63Rev4

FL-no	Chemical name	Structural formula	Structural class*
07.244	trans-6-Methyl-3-hepten-2-one		Class I
07.188	Non-3-en-2-one		Class I
07.177	7-Methyl-3-octenone-2		Class I
07.104	Hept-2-en-4-one		Class I
07.121	Dec-3-en-2-one		Class I
07.106	5-Methylhex-3-en-2-one		Class I
07.105	Hept-3-en-2-one		Class I

FL-no	Chemical name	Structural formula	Structural class*
07.107	Oct-3-en-2-one		Class I
07.048	4-Hexen-3-one		Class I
07.044	Pent-3-en-2-one		Class I
02.193	Oct-2-en-4-ol		Class II
02.102	Oct-3-en-2-ol		Class II
07.139	5-Methylhept-2-en-4-one		Class II
07.082	Oct-2-en-4-one		Class II

*: Determined with OECD Toolbox (version 4.3.1 available at <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>).

The newly included flavouring substances in FGE.63Rev4 can exist as geometrical stereoisomers due to the presence of a double bond.

With regard to composition of the stereoisomeric mixtures, adequate information to describe the materials of commerce for these flavouring substances has been submitted by industry (Documentation provided to EFSA nr: 1). Based on this information on stereoisomerism, the chemical names and the CAS numbers for flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177 and 07.188] should be changed in the Union List (UL) to reflect their stereochemical configuration (see 'EFSA comments' column in Table B.1 – Appendix B).

Flavouring substances [FL-no: 02.102 and 02.193] can exist also as optical stereoisomers due to the presence of a chiral centre in their structures. Industry informed that these flavouring substances occur as racemates (Documentation provided to EFSA nr: 2).

In addition, with regard to flavouring substance [FL-no: 07.123], previously considered in FGE.63Rev3, the Panel noted that its chemical name should be changed to (*E*)-geranylacetone.

The most recent specifications data for all 43 substances in FGE.63Rev4 are summarised in Table B.1 – Appendix B.

3.2. Estimation of intake

JECFA status

For 43 flavouring substances in FGE.63Rev4, including 11 newly allocated flavouring substances [FL-no: 02.102, 07.044, 07.048, 07.082, 07.104, 07.105, 07.107, 07.121, 07.139, 07.188 and 07.244], intake data are available for the EU (JECFA, 2002b). For flavouring substances [FL-no: 02.193 (JECFA-no: 1141), 07.106 (JECFA-no: 1132) and 07.177 (JECFA-no: 1135)], no EU poundage data were available to JECFA and they concluded on the basis of USA poundage data (JECFA, 2002b).

EFSA considerations

For all 14 candidate substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] updated EU production figures have been submitted by industry (Documentation provided to EFSA nr. 1 and 3). The MSDI values range from 0.01 to 41.44 $\mu\text{g}/\text{capita}$ per day (Table C.4 – Appendix C).

For these 14 newly included flavouring substances, normal and maximum use levels have been submitted (Documentation provided to EFSA nr. 1) and mTAMDI intake values can be calculated. The mTAMDI intake estimates calculated from these data for two substances [FL-no: 07.044 and 07.048] are equal to the toxicological threshold of concern (TTC) of their structural class I. For the remaining 12 substances ([FL-no: 02.102, 02.193, 07.104, 07.139, 07.082, 07.105, 07.106, 07.107, 07.121,

07.177, 07.188, 07.244]), the mTAMDI intake estimates are above the TTC for their structural classes (I and II). Therefore, for all 14 flavouring substances, more detailed data on uses and use levels should be provided in order to refine the exposure assessment and to finalise their safety evaluation.

No normal and maximum use levels have been provided for 15 flavouring substances [FL-no: 09.657, 09.658, 09.923, 09.924, 09.925, 07.015, 07.081, 07.100, 07.114, 07.123, 07.151, 07.240, 07.247, 07.249, 07.256], previously considered in FGE.63Rev3.

The MSDI values and the mTAMDI intake estimates for the flavouring substances in FGE.63Rev4 are shown in Table C.4 – Appendix C.

3.3. Biological and toxicological data

3.3.1. ADME data

At its 59th meeting, JECFA evaluated a group of aliphatic acyclic secondary alcohols and ketones and esters derived from aliphatic secondary alcohols (JECFA, 2002b). JECFA describes that alcohols and their corresponding ketones are interconvertible under physiological conditions and the principal elimination pathway for ketones is their reduction to their corresponding secondary alcohols and subsequent conjugation with glucuronic acid and excretion. If the substance is α,β unsaturated, such as the candidate substances in the present revision of this FGE, conjugation with glutathione can also occur. The glutathione conjugates are transformed to their corresponding mercapturic acid derivatives and excreted.

JECFA concluded that none of the flavouring substances within this flavouring group would be expected to be metabolised to noxious metabolites and agreed to evaluate these substances along the A-side of the Procedure.

EFSA consideration

Based on the data described in FGE.07Rev5 (EFSA CEF Panel, 2017; see Appendix D), and in line with JECFA, the main elimination pathway expected for aliphatic ketones with chain lengths equal to or above five carbon atoms, such as the candidate substances in the present revision, would be the (enzymatic) reduction of the carbonyl function to the corresponding secondary alcohol followed by subsequent conjugation to glucuronic acid and excretion. However, ω - and $\omega-1$ oxidation (i.e. oxidation of the terminal or one-but-last carbon atoms of a chain) are alternative metabolic pathways that can be competing with the ketone reduction pathway at high tissue concentrations (Topping et al., 1994). While ω oxidation would lead to the formation of primary alcohols, which are converted into carboxylic acids; $\omega-1$ oxidation of a ketone results in a hydroxy-ketone which subsequently can be oxidised to a diketone. If the two ketone functions are in γ position relative to each other, such diketones are known to be neurotoxic (e.g. axonal swelling, axonal atrophy) (Topping et al.; 1994). For substances that are subject to ω -oxidation, no formation of such a diketone is possible. One of the candidate substances, 6-Methyl-(3E)-hepten-2-one [FL-no: 07.244], is structurally related to 5-methylheptan-3-one [FL-no: 07.182] which can be oxidised to a γ -diketone as outlined in FGE.07Rev5 (EFSA CEF Panel, 2017). The Panel investigated the metabolism of [FL-no: 07.244] using the OECD QSAR Toolbox (V. 4.3.1; *in vivo* rat metabolism simulator). The toolbox did not predict the formation of a γ -diketone, although it indicated formation of hydroxy-ketones. The Panel noted that such hydroxy-ketones might be converted into γ -diketones.

If such a γ -diketone were formed, its conversion into stable pyrrole-protein adducts would be required to express neuropathy. Such stable protein-pyrrole adducts result from a first nucleophilic attack by a free protein amine to the γ -diketones leading to imines in equilibrium with a secondary amine which, upon ring closure, yields a dihydro pyrrolidino moiety. Abstraction of two water molecules from this intermediate results in the formation of the stable neurotoxic protein-pyrrole adduct (Documentation provided to EFSA nr: 3). This mechanism underlying neurotoxicity is analogous to that reported for 2,5 hexanedione (Couri and Milks, 1982).

The formation of the putative stable protein-pyrrole adduct from the respective γ -diketone outlined above is depicted in Figure 1.

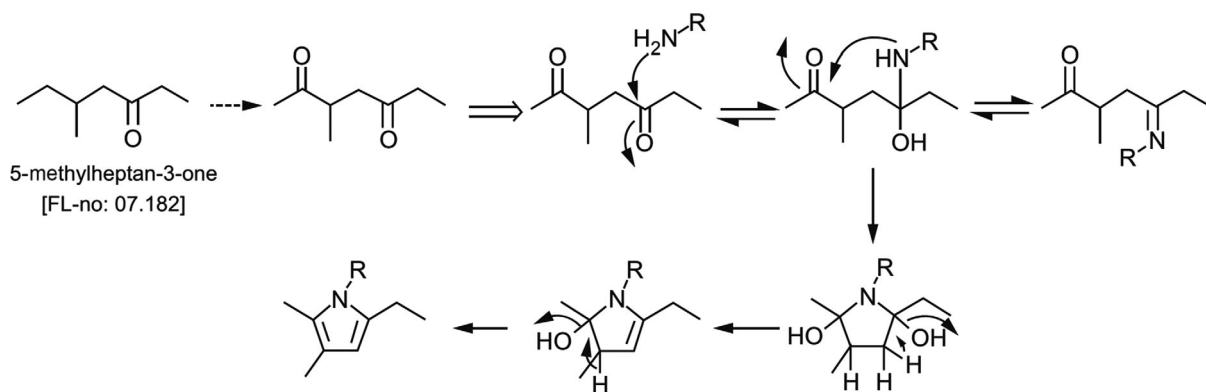


Figure 1: Proposed mechanism of conversion of 5-methylheptan-3-one [FL-no: 07.182] to a stable pyrrole-protein adduct (R = protein portion) (Documentation provided to EFSA nr: 3)

For this reaction sequence, the capacity of proton abstraction from C3 and C4 of the intermediate dihydro pyrrolidino moiety is of critical importance for the formation of the neurotoxic protein-pyrrole adduct. This is supported by the fact that the γ -diketone 3,3-dimethyl-2,5-hexanedione does not cause neurotoxic effects because the lack of hydrogen at C3 does not allow the formation of a pyrrole (Sayre et al., 1986). Conversely, the γ -diketone 3,4-dimethyl-2,5-hexanedione can undergo pyrrolisation (i.e. ring closure followed by loss of water), as this structure includes protons which can be abstracted at both C3 and C4; consequently, this compound displays neurotoxic effects (Sayre et al., 1986).

Taking this knowledge of the mechanism of the formation of neurotoxic protein-pyrrole adducts from γ -diketones into account, the Panel considered whether this might also be applicable to the flavouring substance 6-Methyl-(3*E*)-hepten-2-one [FL-no: 07.244] and requested industry provide evidence documenting that this flavouring substance could, or could not, be oxidised to a neurotoxic γ -diketone. In this respect, the industry stated that upon oxidation at position C5 of [FL-no: 07.244], an unsaturated γ -diketone, i.e. 6-methyl-3-heptene-2,5-dione, would be generated. This γ -diketone would be prone to undergo nucleophilic attack by a free protein amine, leading to an imine. A ring closure and the formation of a dihydro pyrrolidino moiety may energetically not be favoured due to the conformational restrictions around the 3,4 olefinic bond. Even if this dihydro pyrrolidino moiety were formed, the subsequent conversion to a stable protein-pyrrole adduct is not expected since this would require abstraction of the protons in positions 3 and 4 across the double bond with concomitant loss of two water molecules (Figure 2) (Documentation provided to EFSA nr: 3).

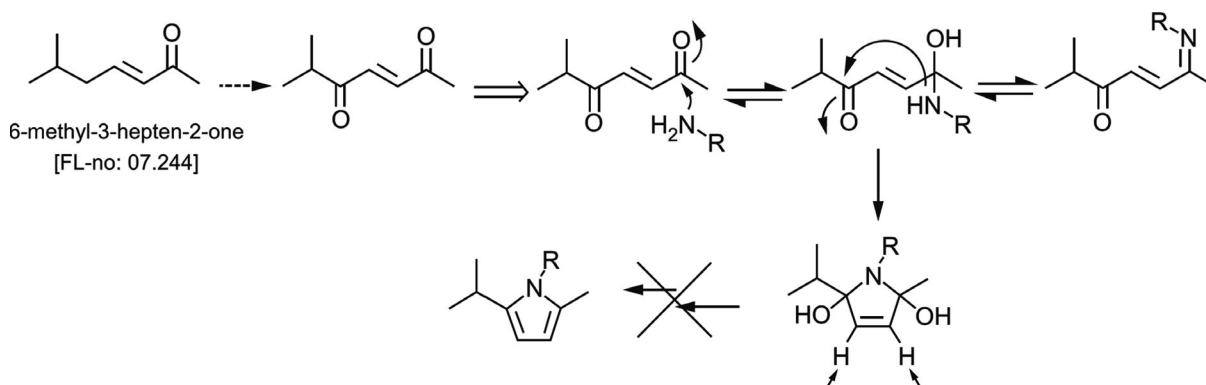


Figure 2: Proposed mechanism of potential formation of stable protein-pyrrole adducts from γ -diketone derived from flavouring substance [FL-no: 07.244] (Documentation provided to EFSA nr: 3)

The Panel concurred with the proposed mechanism described by industry, that ω -1 or ω -2 oxidation and formation of γ -diketones along the unsaturated part of the aliphatic chain would not be expected to form stable neurotoxic protein-pyrrole adducts.

Thus, the Panel considered that the formation of a neurotoxic stable pyrrole-protein is not expected for flavouring substance [FL-no: 07.244] since the concerned γ -diketone would be formed along the

unsaturated part of the carbon chain and this would not allow the formation of the neurotoxic protein-pyrrole adduct. Similarly, this would also be the case for candidate flavouring substances [FL-no: 02.102, 07.105, 07.107, 07.121, 07.177 and 07.188] (see Table 3). In addition, in flavouring substances [FL-no: 02.102, 07.107, 07.121, 07.177, 07.188 and 07.244], the oxidation leading to the formation of the γ -diketone would be at mid-chain (ω -3, ω -4 or ω -5). This oxidation would not be sufficiently energetically favourable to get sufficient γ -diketone formed to result in neurotoxicity (levels of γ -diketone not toxicologically relevant) (EFSA CEF Panel, 2015). In flavouring substances [FL-no: 07.044, 07.048, 07.104, 07.106 and 07.139], there is no carbon atom at a γ position that can be oxidised to yield a γ -diketone (at the γ -position only primary or tertiary alcohols can be formed) (Topping et al., 1994) (see Table 3). Therefore, the Panel concluded that flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] can be evaluated along the A-side of the Procedure.

The Panel observed that, for the candidate substance oct-2-en-4-one [FL-no: 07.082] and the corresponding alcohol oct-2-en-4-ol [FL-no: 02.193], if ω -1 oxidation occurs, γ -diketones would be generated along the saturated part of the aliphatic chain (see Table 3). Therefore, the double bond in [FL-no: 07.082 and 02.193] cannot prevent the formation of the neurotoxic protein-pyrrole adduct for these flavouring substances.

For oct-2-en-4-ol [FL-no: 02.193], the Panel noted that, according to FGE.25Rev3 (EFSA CEF Panel, 2015) for secondary alcohols, the γ -diketone formation is not expected to be relevant, because these alcohols are readily conjugated with e.g. glucuronic acid. This would reduce the amount of secondary alcohol available for conversion into a γ -diketone. Further supporting this view is a paper by Sanz et al. (1995) in which different derivatives of *n*-hexane and *n*-heptane have been tested *in vitro* for their neurotoxic potential (the pyrrole-protein adduct formation capability in rat liver microsomal fraction was tested, but also the potential to induce neurotoxicity *in vivo* was studied). The paper indicated that the neurotoxic potencies of 2-hexanol and 2-heptanol are much less than those of the ketone derivatives. Additionally, as stated in FGE.07Rev5 (EFSA CEF Panel, 2017), the length of the aliphatic chain would affect the neurotoxic potency of the formed γ -diketones. Therefore, the Panel considered that the secondary alcohol oct-2-en-4-ol [FL-no: 02.193] does not raise a concern with respect to neurotoxicity and it can be evaluated along the A-side of the Procedure.

Conversely, for the candidate substance oct-2-en-4-one [FL-no: 07.082], the Panel requested industry to investigate the possible generation of the γ -diketone oct-2-en-4,7-dione and its neurotoxic potency. To this aim, following a clarification teleconference⁵ in November 2020, industry provided an *in vitro* biotransformation study of oct-2-en-4-one [FL-no: 07.082] using cryopreserved rat and human hepatocytes (Documentation provided to EFSA nr: 4). The *in vitro* biotransformation of 2-hexanone was studied in parallel, as confirmation of the potential for formation of a diketone metabolite (2,5-hexanedione). Incubations were carried out in crimp-sealed vials with suspensions of one commercial batch of pooled human hepatocytes from 10 male donors and with one commercial batch of pooled rat hepatocytes from 24 male donors. For both species, cell viability was confirmed to be approximately 90% using the trypan blue exclusion test. The specifications for the human hepatocytes stated metabolic proficiency for several cytochrome P450 substrates. For the rat hepatocytes, only a clarification that the cells were proficient in 7-ethoxycoumarin deethylation was noted. For both human and rat hepatocytes, proficiency for 7-ethoxycoumarin deethylation was experimentally confirmed by the test laboratory, showing adequate formation of 7-hydroxycoumarin and its glucuronide and sulfate conjugates. For oct-2-en-4-one biotransformation, incubations were done in triplicate; for biotransformation of 2-hexanone, incubations were done in duplicate. Chromatographic methods were developed for the quantitative measurement of oct-2-en-4,7-dione and 2,5-hexanedione using LC-MS/MS. Limits of quantification and detection were 0.05 $\mu\text{g/mL}$ and 0.01 $\mu\text{g/mL}$, respectively, for both metabolites.

Results with rat hepatocytes

Following the incubation of 10 $\mu\text{mol/L}$ (1.260 $\mu\text{g/mL}$) oct-2-en-4-one with rat hepatocytes for 4 h, in one of the replicates, oct-2-en-4,7-dione was generated at a concentration above the limit of detection but it remained below the limit of quantification. Following the incubation of 10 $\mu\text{mol/L}$ (1.002 $\mu\text{g/mL}$) 2-hexanone (positive control) with rat hepatocytes for 4 h, the specific metabolite product 2,5-hexanedione was not generated in detectable amounts, but it was observed above the limit of detection in one incubate at incubation time 0.

⁵ As foreseen by the EFSA's Catalogue of support initiatives during the lifecycle of applications for regulated products.

Results with human hepatocytes

Following the incubation of 10 $\mu\text{mol/L}$ of oct-2-en-4-one with human hepatocytes for 4 h, in two of the replicates, oct-2-en-4,7-dione was generated at a concentration above the limit of detection, but it remained below the limit of quantification. Following the incubation of 10 $\mu\text{mol/L}$ of 2-hexanone (positive control) with human hepatocytes for 4 h, the specific metabolite 2,5-hexanedione was not generated in quantities greater than the limit of detection.

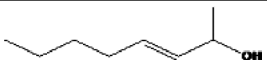
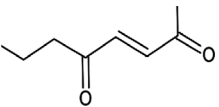
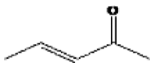
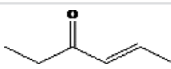
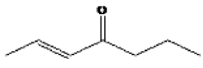

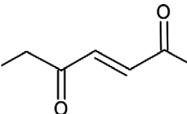
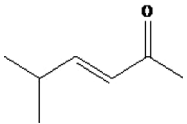
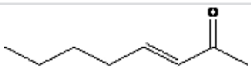
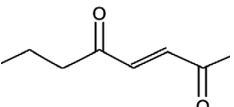
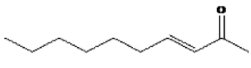
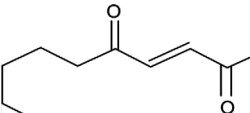
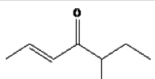
For both starting substances, peaks co-eluting with the diketones were observed in incubates where biotransformation was not anticipated: a peak at the retention time of the octenedione standard was seen in an incubate without hepatocytes at incubation time $T = 0$ and a peak at the retention time of the hexadione standard was observed in a rat hepatocyte incubate also at $T = 0$ (see above). Both peaks were below the limit of quantification.

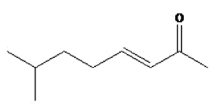
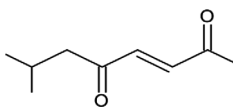
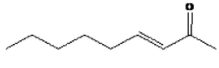
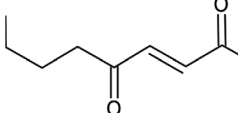

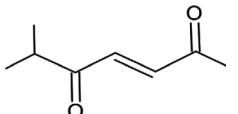
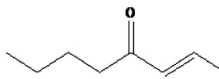
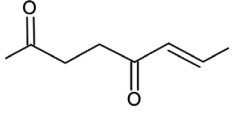
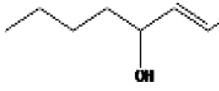
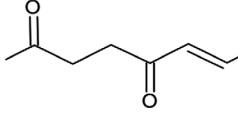
In relation to this *in vitro* biotransformation study, the Panel noted the following:

- 1) The limits of detection and quantification determined for the target metabolites demonstrated that the chosen analytical approach was suitable for investigation of the potential formation of the respective γ -diketones.
- 2) The demonstration of metabolic proficiency using 7-ethoxycoumarin as an indicator substrate is limited. The specifications for the human cells are helpful in this respect because they indicated biotransformation activity for several types of reactions. Nevertheless, for the formation of the putative diketones, ω -1 oxidation is necessary. Use of a substrate that would show the metabolic proficiency for this particular biotransformation would have been informative.
- 3) It is of concern that the positive control (2-hexanone) was not metabolised into detectable amounts of the corresponding γ -diketone 2,5-hexanedione. This puts the sensitivity of the experimental design into question.
- 4) The concentration of the substrate is quite low (1 $\mu\text{g/mL}$), but no explanation is given for this choice. Although the sensitivity of the analytical method is sufficient, with such a low substrate concentration, it is not clear that detectable amount of metabolites could be formed.
- 5) Additional studies with hepatic microsomes, supersomes and/or other *in vitro* models for metabolism would have been informative. With respect to risk assessment, results using microsomes/supersomes are of limited relevance since they have limited capacity for phase II metabolism. Therefore, they may not reflect the real formation and liberation of metabolites.
- 6) No other metabolites were monitored. When the intermediate for the diketones (i.e. the corresponding keto-alcohol) is formed, then this may be conjugated so quickly in hepatocytes that subsequent detectable oxidation of hydroxylated ketones is not seen. In that respect, a higher substrate concentration might have revealed the formation of the diketone. In addition, if the keto-alcohols reach the blood stream, they may also be oxidised to the diketones in extra-hepatic tissues.
- 7) The observations of peaks assigned by the study authors to the putative metabolites under conditions where such metabolism would not have been possible, casts doubt on the relevance of the peaks in the incubates where biotransformation could have occurred.

Overall, the Panel concluded that the information provided is not sufficient to judge whether oct-2-en-4-one [FL-no: 07.082] can be converted to the corresponding γ -diketone oct-2-en-4,7-dione. In particular, the fact that the positive control (2-hexanone) was not metabolised into detectable amounts of 2,5-hexanedione demonstrates the non-suitability of the experimental design. Consequently, the flavouring substance [FL-no: 07.082] should be evaluated along the B-side of the Procedure.

Table 3: Flavouring substances in FGE.63Rev4 and the potentially resulting γ -diketones

FL-no	Chemical name	Chemical structure	γ -diketone	Comments
02.102	oct-3-en-2-ol			via ω -3 oxidation: no neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.044	pent-3-en-2-one		Not possible	oxidation at the γ position results in a primary alcohol and not in a ketone
07.048	4-hexen-3-one		Not possible	oxidation at the γ position results in a primary alcohol and not in a ketone
07.104	hept-2-en-4-one		Not possible	oxidation at the γ positions results in primary alcohols and not in ketones
07.105	hept-3-en-2-one			Via ω -2 oxidation: no neurotoxicity is expected because of prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.106	5-methylhex-3-en-2-one		Not possible	ω -1 oxidation results in a tertiary alcohol and not in a ketone at the γ position; ω oxidation results in the formation of a primary alcohol at the δ position (relative to the keto-function)
07.107	oct-3-en-2-one			Via ω -3 oxidation: no neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.121	dec-3-en-2-one			Via ω -5 oxidation: no neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.139	5-methylhept-2-en-4-one		Not possible	Oxidation at the γ positions results in primary alcohols and not in ketones

FL-no	Chemical name	Chemical structure	γ -diketone	Comments
07.177	7-Methyl-3-octenone-2			Via ω -4 oxidation: No neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.188	Non-3-en-2-one			Via ω -4 oxidation: no neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.244	trans-6-methyl-3-hepten-2-one			Via ω -3 oxidation: no neurotoxicity is expected because of limited formation of the γ -diketone and prevention of formation of the stable pyrrole-protein adduct by the unsaturation
07.082	oct-2-en-4-one			Via ω -1 oxidation: neurotoxicity may be expected because of probable formation of stable pyrrole-protein adduct and no prevention by the unsaturation
02.193	oct-2-en-4-ol		 Corresponding γ -diketone is the same as for [FL-no: 07.082] but formation is very limited.	Via ω -1 oxidation: no neurotoxicity is expected because of ready conjugation of the secondary alcohol with e.g. glucuronic acid and long aliphatic chain (C > 7).

3.3.2. Genotoxicity data

This revision involves the inclusion of 14 flavouring substances ([FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244]), which have a structural alert for genotoxicity (i.e. α,β -unsaturated carbonyl substance or precursor), preventing their evaluation through the Procedure (see also Appendix A). Therefore, these substances were evaluated in FGE.204Rev1 where their genotoxic potential has been assessed and ruled out (EFSA FAF Panel, 2019). Accordingly, the safety evaluation through the Procedure can be performed for these 14 flavouring substances.

3.3.3. Toxicological data

No subacute, subchronic/chronic toxicity and carcinogenicity studies are available on any of the candidate substances.

For structurally related substances in FGE.07Rev5, acute, subacute and subchronic toxicity studies and developmental and reproductive toxicity studies are listed in FGE.07Rev5 (see Appendix E of EFSA CEF Panel, 2017). Particularly, for flavouring substance 5-methylheptan-3-one [FL-no: 07.182], evaluated in FGE.07, a subchronic 13-week study is available in which a no observed adverse effect

level (NOAEL) of 82 mg/kg body weight (bw) per day was identified based on neurotoxicity endpoints (behavioural effects) and microscopic changes. The details of the study are available in FGE.07Rev5 (EFSA CEF Panel, 2017).

EFSA considerations

The Panel noted that flavouring substance 5-methylheptan-3-one [FL-no: 07.182], according to its chemical structure, can be considered structurally related to the flavouring substance oct-2-en-4-one [FL-no: 07.082]. Based on the available information on absorption, distribution, metabolism and excretion (ADME) from the CEF Panel opinion on FGE.07Rev5 (see Appendix D of EFSA CEF Panel, 2017), 5 methylheptan-3-one [FL-no: 07.182], similar to the candidate substance [FL-no: 07.082], may potentially undergo ω -1 oxidation leading first to a hydroxy-ketone and then to a γ -diketone (3-methyl-2,5-heptanedione). The Panel also noted that in the γ -diketone, potentially generated by 5-methylheptan-3-one [FL-no: 07.182], there is a single methyl group on one of the carbons located between the two carbonyl groups of the γ -diketone (see Figure 1); this would increase the potential neurotoxicity of the compound (Topping et al., 1994). Thus, the use of 5-methylheptan-3-one [FL-no: 07.182] as reference substance represents a conservative scenario with regard to the formation of neurotoxic metabolites. Therefore, the Panel used the NOAEL of 82 mg/kg bw per day identified for 5-methylheptan-3-one [FL-no: 07.182] from a 13-week study to derive a margin of safety for the flavouring substance oct-2-en-4-one [FL-no: 07.082].

3.4. Application of the Procedure

Application of the Procedure to 14 aliphatic α,β unsaturated secondary alcohols and aldehydes by JECFA (2002a)

JECFA allocated six flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.104 and 07.139], currently under evaluation in FGE.63Rev4, to structural class I according to the decision tree approach presented by Cramer et al. (1978). The remaining eight flavouring substances [FL-no: 07.082, 07.105, 07.106, 07.107, 07.121, 07.177, 07.188 and 07.244] were allocated to structural class II.

JECFA considered that these flavouring substances can be anticipated to be metabolised to innocuous products (step 2). The intakes, based on MSDI approach, for all 14 substances are below the thresholds of concern for structural class I and II (1,800 and 540 $\mu\text{g}/\text{person}$ per day, respectively) (step A3). Therefore, JECFA concluded that these 14 flavouring substances would pose no safety concern at their estimated level of use, based on the MSDI approach.

The JECFA safety evaluations of the flavouring substances in FGE.63Rev4 are summarised in Table D.1 – Appendix D.

EFSA considerations

The FAF Panel partially agrees with JECFA with respect to the allocation to structural class of the 14 flavouring substances. According to the predictions run in OECD (Q)SAR Toolbox (version 4.3), four out of the 14 candidate substances ([FL-no: 02.102, 02.193, 07.082 and 07.139]) are assigned to structural class II. The remaining 10 substances ([FL-no: 07.244, 07.188, 07.177, 07.104, 07.121, 07.106, 07.105, 07.107, 07.048 and 07.044]) are structural class I.

The FAF Panel agrees with the way of the application of the Procedure that has been performed by JECFA for all flavouring substances with the exception of oct-2-en-4-one [FL-no: 07.082]. The MSDI exposure estimates for the all flavouring substances are below the thresholds of concern for their structural classes (I and II) (see Table C.4 – Appendix C). Therefore, the FAF Panel concludes, at step A3 of the Procedure scheme, that flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] do not raise a safety concern when used as flavouring substances at the current levels of use, based on the MSDI approach.

For flavouring substance oct-2-en-4-one [FL-no: 07.082], the Panel considers that the available NOAEL on the structurally related substance 5 methylheptan-3-one [FL-no: 07.182] is suitable for a further evaluation of this substance (see EFSA considerations in Section 3.3.3). Comparison of the MSDI of [FL-no: 07.082] (13.78 $\mu\text{g}/\text{capita}$ per day) with the NOAEL of the 90-day study with 5 methylheptan-3-one [FL-no: 07.182] (82 mg/kg bw per day) provides an adequate margin of safety of 360,000 for the candidate substance [FL-no: 07.082].

Therefore, the Panel concluded, at step B4 of the Procedure scheme, that the flavouring substance oct-2-en-4-one [FL-no: 07.082] does not pose a safety concern when used as a flavouring substance at the estimated levels of intake, based on MSDI approach.

For all the 14 flavouring substances, normal and maximum use levels are available and mTAMDI values have been calculated (see Table C.4 – Appendix C). The mTAMDI intake estimates for two substances [FL-no: 07.044 and 07.048] are equal to the toxicological threshold of concern (TTC) of their structural class I. For the remaining 12 substances ([FL-no: 02.102, 02.193, 07.104, 07.139, 07.082, 07.105, 07.106, 07.107, 07.121, 07.177, 07.188, 07.244]), the mTAMDI intake estimates are above the TTC for their structural classes (I and II). Therefore, for all 14 flavouring substances, more detailed data on uses and use levels should be provided in order to refine the exposure assessment and to finalise their safety evaluation.

4. Discussion

This revision 4 of FGE.63 comprises in total 43 JECFA-evaluated flavouring substances, 29 of which have already been considered in FGE.63 and its three revisions. The remaining 14 substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244] have been included in this revision, following evaluation in FGE.204Rev1 of their genotoxic potential due to the presence of a structural alert for genotoxicity (i.e. α,β -unsaturated carbonyl or precursors for that) in which the concern for the genotoxicity was ruled out.

The FAF Panel concludes in this revision of FGE.63 as follows:

- i) at step A3 of the Procedure: the flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244];
- ii) at step B4 of the Procedure: the flavouring substance oct-2-en-4-one [FL-no: 07.082]

do not raise a safety concern at the estimated levels of exposure, when based on MSDI approach.

For all 14 flavouring substances, normal and maximum use levels have been provided. The mTAMDI intake estimates for two substances [FL-no: 07.044 and 07.048] are equal to the toxicological threshold of concern (TTC) of their structural class I. For the remaining 12 substances ([FL-no: 02.102, 02.193, 07.104, 07.139, 07.082, 07.105, 07.106, 07.107, 07.121, 07.177, 07.188, 07.244]), the mTAMDI intake estimates are above the TTC for their structural classes (I and II). Therefore, for all 14 flavouring substances, more detailed data on uses and use levels should be provided in order to refine the exposure assessment and to finalise their safety evaluation.

No normal and maximum use levels have been provided for 15 flavouring substances [FL-no: 09.657, 09.658, 09.923, 09.924, 09.925, 07.015, 07.081, 07.100, 07.114, 07.123, 07.151, 07.240, 07.247, 07.249, 07.256], previously considered in FGE.63Rev3. Therefore, for these 15 flavouring 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. The Panel also noted that in the previous revision (FGE.63Rev3), 10 substances [FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 07.081, 07.102, 07.190, 09.281 and 09.282] had mTAMDI values above their respective TTCs. For these 10 substances, more reliable data on uses and use levels are required in order to finalise the evaluation.

To determine whether the conclusions for the 43 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 all 43 flavouring substances in FGE.63Rev4.

5. Conclusions

In conclusion, for all 43 flavouring substances in FGE.63Rev4, the FAF Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' when based on the MSDI approach.

However, for 14 of these candidate substances in the present revision ([FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188 and 07.244]) and for 10 of the substances in the previous revision (FGE.63Rev3) ([FL-no: 02.023, 02.099, 02.104, 02.136, 02.155, 07.081, 07.102, 07.190, 09.281 and 09.282]), the mTAMDI values are equal to or above the TTCs for their structural classes (I and II). For 15 substances [FL-no: 09.657, 09.658, 09.923, 09.924, 09.925, 07.015, 07.081, 07.100, 07.114, 07.123, 07.151, 07.240, 07.247, 07.249 and

07.256], previously evaluated in FGE.63Rev3, use levels are still needed to calculate the mTAMDI estimates. Therefore, in total for 39 flavouring substances, more data on uses and use levels should be provided in order to finalise their safety evaluations.

6. Recommendations

The Panel recommends the European Commission to consider:

- requesting normal and maximum uses and use levels for [FL-no: 09.657, 09.658, 09.923, 09.924, 09.925, 07.015, 07.081, 07.100, 07.114, 07.123, 07.151, 07.240, 07.247, 07.249, 07.256];
- requesting more detailed data on uses and use levels for substances ([FL-no: 02.023, 02.099, 02.102, 02.104, 02.193, 02.136, 02.155, 07.044, 07.048, 07.081, 07.082, 07.102, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177, 07.188, 07.190, 07.244, 09.281 and 09.282]. When these data are received, the assessment for these flavouring substances should be updated accordingly and expanded if necessary (i.e. request of additional toxicity data);
- in accordance with the latest specifications for the materials of commerce provided by industry, changing the chemical names and the CAS numbers in the Union List for flavouring substances [FL-no: 02.102, 02.193, 07.044, 07.048, 07.082, 07.104, 07.105, 07.106, 07.107, 07.121, 07.139, 07.177 and 07.188] to reflect their stereochemical configuration (see Table B.1 of Appendix B);
- changing the chemical name in the Union List for flavouring substance [FL-no: 07.123], previously considered in FGE.63Rev3, as indicated in Table B.1 of Appendix B.

7. Documentation provided to EFSA

- 1) EFFA (European Flavour Association), 2019. Submission of additional information on isomeric composition, poundage and refined use levels data of substances of FGE.204 Rev1 (FGE.19 Subgroup 1.2.1).
- 2) EFFA (European Flavour Association), 2020. Submission of additional information on stereoisomers for two substances of FGE.204 ([FL-no: 02.102 and 02.193]) for evaluation in FGE.63 Rev4.
- 3) EFFA (European Flavour Association), 2020a. Submission of additional information on EU poundage data, info on use and potential oxidation of substances of FGE.204 Rev1 (FGE.19 Subgroup 1.2.1).
- 4) EFFA (European Flavour Association), 2021. Submission of an *in vitro* comparative metabolism study of oct-2-en-4-one ([FL-no: 07.082]).

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
bw	body weight
EFFA	European Flavours Association
FGE	Flavouring Group Evaluation
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	modified Theoretical Added Maximum Daily Intakes
NOAEL	No observed adverse effect level
SCF	Scientific Committee on Food
TTC	toxicological threshold of concern

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'.⁶

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 products⁷ (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous⁸ (step A4)?
- Does an 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.

⁶ The FAF Panel is aware that a revised Procedure for the Safety Evaluation of Flavouring agents has been agreed by JECFA (JECFA, 2016). The EFSA Scientific Committee has 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.

⁷ Innocuous products: products that are known or readily predicted to be harmless to humans at the estimated intake of the flavouring agent (JECFA, 1997).

⁸ 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).

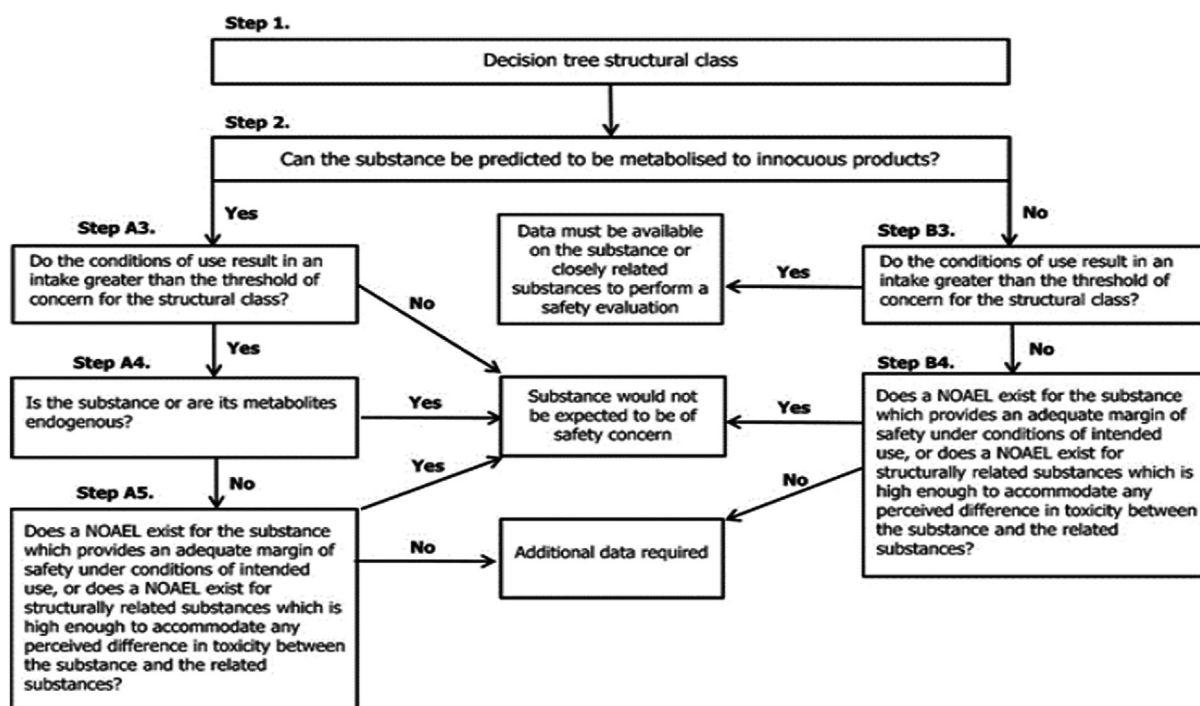


Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances

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)⁹ 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 List¹⁰ 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

⁹ EU MSDI: Amount added to food as flavour in (kg/year) $9\ 109 / (0.1\ 9\ \text{population in Europe} (= 375\ 9\ 106) \ 9\ 0.6\ 9\ 365) = \mu\text{g/capita per day}$.

¹⁰ 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.

estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods' (JECFA, 2005).

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 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 j.tg/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 j.tg/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 forty-sixth 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 j.tg 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 j.tg 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.63Rev4, 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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
02.023 1152 2805 72 3391-86-4	Oct-1-en-3-ol	(b)	Liquid C ₈ H ₁₆ O 128.22	Insoluble Miscible	175–175.2 NMR 96%	1.431–1.442 0.835–0.845	
02.099 1150 3584 11717 616-25-1	Pent-1-en-3-ol	(b)	Liquid C ₅ H ₁₀ O 86.13	Sparsely soluble Miscible	114 NMR 98% (racemate)	1.419–1.427 0.831–0.837	
02.102 1140 3602 76649-14-4	Oct-3-en-2-ol	(b)	Liquid C ₈ H ₁₆ O 128.22	Insoluble Miscible	73–76 (13 hPa) IR NMR MS 95% (<i>E</i>)-isomer (racemate)	1.422–1.428 0.826–0.836	The chemical name should be changed to Oct-(3 <i>E</i>)-en-2-ol and the CAS number to 57648-55-2 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1 and 2)
02.104 1151 3608 10220 4798-44-1	Hex-1-en-3-ol	(b)	Liquid C ₆ H ₁₂ O 100.16	Insoluble Miscible	133.5–134 NMR 98% (racemate)	1.425–1.431 0.830–0.836	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
02.136 1153 3824 51100-54-0	Dec-1-en-3-ol	(b)	Liquid C ₁₀ H ₂₀ O 156.27	Slightly soluble Miscible	215 NMR MS 97% (racemate)	1.439–1.446 0.836–0.842	
02.155 1842 4129 10218 4938-52-7	1-Hepten-3-ol	(b)	Liquid C ₇ H ₁₄ O 114.19	Practically insoluble or insoluble Freely soluble	155 MS 97%(racemate)	1.431–1.437 0.834–0.837	
02.193 1141 3888 4798-61-2	Oct-2-en-4-ol	(b)	Liquid C ₈ H ₁₆ O 128.22	Insoluble 50% Soluble in ethanol	174–176 IR NMR MS % (<i>E</i>)-isomer 1–2% (<i>Z</i>) isomer (racemate)	1.438–1.442 0.830–0.838	The chemical name should be changed to Oct-(2 <i>E</i>)-en-4-ol and the CAS number to 20125-81-9 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1 and 2)
02.252 1841 4102 67845-50-5	4,8-Dimethyl-3,7-nonadien-2-ol	(b)	Liquid C ₁₁ H ₂₀ O 168	Insoluble Soluble	70 (2.6 hPa) IR NMR 95% (racemate and mixture of <i>E/Z</i> stereoisomers: 50–80% (<i>E</i>))	1.465–1.473 0.860–0.870	
07.015 1120 2707 149 110-93-0	6-Methylhept-5-en-2-one	(b)	Liquid C ₈ H ₁₄ O 126.19	Insoluble Miscible	173.1 NMR 97%	1.435–1.445 0.846–0.854	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.044 1124 3417 666 625-33-2	Pent-3-en-2-one	^(b)	Liquid C ₅ H ₈ O 84.12	Slightly soluble Miscible at room temp.	122 NMR At least 75% (<i>E</i>)-isomer 25% (<i>Z</i>)-isomer	1.433–1.437 0.860–0.865	The chemical name should be changed to pent-(3 <i>E</i>)-en-2-one and the CAS number to 3102-33-8 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.048 1125 3352 718 2497-21-4	4-Hexen-3-one	^(b)	Liquid C ₆ H ₁₀ O 98.15	Slightly soluble Miscible	93 (195 hPa) NMR 90–95% (<i>E</i>)-isomer 4–5% (<i>Z</i>)-isomer	1.437–1.443 0.855–0.861	The chemical name should be changed to hex-(4 <i>E</i>)-en-3-one and the CAS number to 50396-87-7 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.069 1121 3059 2053 4433-36-7	Tetrahydro-pseudo-ionone	^(b)	Liquid C ₁₃ H ₂₄ O 196.33	Insoluble Miscible	234 NMR 95% (racemate)	1.449–1.455 0.865–0.875	
07.081 1148 3515 2312 4312-99-6	Oct-1-en-3-one	^(b)	Liquid C ₈ H ₁₄ O 126.20	Insoluble Miscible	37–38 (3 hPa) NMR 96%	1.428–1.439 0.813–0.819	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.082 1129 3603 2313 4643-27-0	Oct-2-en-4-one	(b)	Liquid C ₈ H ₁₄ O 126.20	Insoluble Miscible at room temp.	81 (26–27 hPa) IR NMR 90–91% (<i>E</i>)-isomer 5–6% (<i>Z</i>)-isomer	1.440–1.446 0.835–0.842	The chemical name should be changed to oct-(2 <i>E</i>)-en-4- one and the CAS number to 22286-99-3 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.099 1134 3363 11143 1604-28-0	6-Methylhepta-3,5-dien-2- one	(b)	Liquid C ₈ H ₁₂ O 124.18	Almost insoluble Miscible	190 NMR 96% (mixture of <i>E/Z</i> stereoisomers: 60–90% (<i>E</i>))	1.528–1.537 0.895–0.899	
07.100 1119 3365 11150 3240-09-3	5-Methylhex-5-en-2-one	(b)	Liquid C ₇ H ₁₂ O 112.17	Insoluble Miscible	148–149 NMR 97%	1.428–1.433 0.862–0.868	
07.101 1131 3368 11853 141-79-7	4-Methylpent-3-en-2-one	(b)	Liquid C ₆ H ₁₀ O 98.14	Slightly soluble Miscible	126.76 NMR 95%	1.442–1.447 0.862–0.868	
07.102 1147 3382 11179 1629-58-9	Pent-1-en-3-one	(b)	Liquid C ₅ H ₈ O 84.12	Insoluble Miscible	68–70 (260 hPa) NMR 97%	1.417–1.422 0.842–0.848	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.104 1126 3399 11093 4643-25-8	Hept-2-en-4-one	^(b)	Liquid C ₇ H ₁₂ O 112.17	Slightly soluble Miscible	156–157 IR NMR 95% (<i>E</i>)-isomer	1.440–1.445 0.845–0.852	The chemical name should be changed to hept-(2 <i>E</i>)-en-4-one and the CAS number to 22286-99-3 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.105 1127 3400 11094 1119-44-4	Hept-3-en-2-one	^(b)	Liquid C ₇ H ₁₂ O 112.17	Slightly soluble Miscible	162 NMR 95% (<i>E</i>)-isomer	1.439–1.448 0.841–0.847	The chemical name should be changed to hept-(3 <i>E</i>)-en-2-one and the CAS number to 5609-09-6 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.106 1132 3409 11149 5166-53-0	5-Methylhex-3-en-2-one	^(b)	Liquid C ₇ H ₁₂ O 112.17	Insoluble Miscible	77.5 (65 hPa) NMR 95% (<i>E</i>)-isomer	1.437–1.441 0.838–0.843	The chemical name should be changed to 5-Methylhex-(3 <i>E</i>)-en-2-one and the CAS number to 1821-29-0 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.107 1128 3416 11170 1669-44-9	Oct-3-en-2-one	At least 94%; secondary component 4-6% 4-octen-2-one	Liquid C ₈ H ₁₄ O 126.19	Insoluble Miscible at room temp.	75–79 (26 hPa) NMR 90–91% (<i>E</i>)-isomer 3–4% (<i>Z</i>)-isomer SC: 4-6% 4-octen-2-one	1.445–1.449 0.834–0.839	The chemical name should be changed to Oct-(3 <i>E</i>)-en-2-one and the CAS number to 18402-82-9 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.114 1123 3442 11206 762-29-8	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	^(b)	Liquid C ₁₈ H ₃₀ O 262.44	Soluble Miscible	147–148 NMR 96% (mixture of (5 <i>E</i> ,9 <i>E</i>)-, (5 <i>Z</i> ,9 <i>Z</i>)-, (5 <i>E</i> ,9 <i>Z</i>)- and (5 <i>Z</i> ,9 <i>E</i>)-isomers)	1.478–1.483 0.885–0.895	
07.121 1130 3532 11751 10519-33-2	Dec-3-en-2-one	^(b)	Liquid C ₁₀ H ₁₈ O 154.25	Almost insoluble Miscible at room temp.	125–126 NMR 95% (<i>E</i>)-isomer	1.446–1.452 0.809–0.813	The chemical name should be changed to Dec-(3 <i>E</i>)-en-2-one and the CAS number to 18402-84-1 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1)
07.123 1122 3542 11088 3796-70-1	Geranyl acetone	^(b)	Liquid C ₁₃ H ₂₂ O 194.32	Slightly soluble Miscible	247 NMR 95% (<i>E</i>)-isomer	1.463–1.471 0.861–0.867	Chemical name in the Union List should be changed to (<i>E</i>)-geranyl acetone
07.139 1133 3761 81925-81-7	5-Methylhept-2-en-4-one	^(b)	Liquid C ₈ H ₁₄ O 126.19	Slightly soluble Miscible	86–87 (78 hPa) NMR 91–95% (<i>E</i>)-isomer 1–5% (<i>Z</i>)-isomer (racemate)	1.440–1.445 0.845–0.852	The chemical name should be changed to 5-Methylhept-(2 <i>E</i>)-en-4-one and the CAS number to 102322-83-8 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1).

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.151 1118 3966 11056 928-80-3	Decan-3-one	(b)	Liquid C ₁₀ H ₂₀ O 156.27	Insoluble Miscible	204-205 NMR 97%	1.421–1.427 0.820–0.830	
07.177 1135 3868 33046-81-0	7-Methyl-3-octenone-2	At least 94%; secondary components 2-4% 7-methyl-4-octen-2-one, 5,6- dimethyl-3-hepten-2-one and 3-nonen-2-one	Liquid C ₉ H ₁₆ O 140.2	Slightly soluble Miscible	198 n.a. IR NMR MS % (E)-isomer SC: 2-4% 7-methyl-4-octen-2-one, 5,6-dimethyl-3-hepten-2-one and 3-nonen-2-one	1.446–1.451 0.838–0.847	The chemical name should be changed to 7-Methyl-oct-(3E)-en-2-one and the CAS number to 1004754-77-1 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1).
07.188 1136 3955 11163 14309-57-0	Non-3-en-2-one	(b)	Liquid C ₉ H ₁₆ O 140.22	Insoluble Miscible at room temp.	198 IR MS 95% (E)-isomer	1.443–1.452 0.843–0.846	The chemical name should be changed to Non-(3E)-en-2-one and the CAS number to 18402-83-0 to reflect the stereochemical configuration. (Documentation provided to EFSA nr: 1).
07.190 1848 4405 65213-86-7	Octa-1,5-dien-3-one	(b)	Liquid C ₈ H ₁₂ O 124.18	Practically insoluble or insoluble Freely soluble	169 MS 95% (mixture of E/Z stereoisomers: 60–90% (E))	1.438–1.444 0.823–0.829	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.240 1156 4000 13019-20-0	2-Methylheptan-3-one	(b)	Liquid C ₈ H ₁₆ O 128.2	Insoluble Miscible	158–160 NMR 98%	1.408–1.413 0.811–0.821	
07.244 1138 4001 20859-10-3	(6 <i>E</i>)-Methyl-3-hepten-2-one	(b)	Liquid C ₈ H ₁₄ O 126.2	Insoluble Miscible at room temp.	170–180 NMR 96% (<i>E</i>)-isomer < 1% (<i>Z</i>)-isomer	1.438–1.447 0.840–0.850	
07.247 1139 4008 30086-02-3	(<i>E,E</i>)-3,5-Octadien-2-one	(b)	Liquid C ₈ H ₁₂ O 124.2	Insoluble Miscible	220 NMR 95%	1.508–1.516 0.880–0.890	
07.249 1155 4022 927-49-1	Undecan-6-one	(b)	Liquid C ₁₁ H ₂₂ O 170.3	Insoluble Miscible	228 NMR 97%	1.424–1.430 0.826–0.836	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
07.256 1137 3969 817-88-9	(E) & (Z)-4,8-Dimethyl-3,7-nonadiene-2-one	94% Secondary component: 3–4% 4,8-dimethyl-3,7-nonadien-2-ol	Liquid C ₁₁ H ₁₈ O 166.26	Insoluble Freely soluble	200–201 n.a. IR NMR % (Mixture of E/Z stereoisomers: 60–90% (E)) Secondary component: 3–4% 4,8-dimethyl-3,7-nonadien-2-ol	1.473–1.477 0.869–0.875	
09.281 1836 3582 11716 2442-10-6	Oct-1-en-3-yl acetate	^(b)	Liquid C ₁₀ H ₁₈ O ₂ 170.25	Practically insoluble or insoluble Freely soluble	80 (2 hPa) NMR 97% (racemate)	1.418–1.428 0.865–0.886	
09.282 1837 3612 16491-54-6	Oct-1-en-3-yl butyrate	^(b)	Liquid C ₁₂ H ₂₂ O ₂ 198.32	Practically insoluble or insoluble Freely soluble	81 (0.46 hPa) IR NMR MS 95% (racemate)	1.418–1.428 0.865–0.875	
09.657 1146 4012 10761 626-38-0	1-Methylbutyl acetate	^(b)	Liquid C ₇ H ₁₄ O ₂ 130.2	Insoluble Partially Soluble	135 NMR 98% (racemate)	1.369-1.400 0.862-0.866	

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 ^(h))	Refrac. Index ^(f) Spec. gravity ^(g)	
09.658 1142 3893 10763 60415-61-4	1-Methylbutyl butyrate	(b)	Liquid C ₉ H ₁₈ O ₂ 158.24	Insoluble 50% Soluble	185–186 IR NMR MS 99% (racemate)	1.409–1.415 0.862–0.868	
09.923 1144 3981 39026-94-3	Hept-2-yl butyrate	(b)	Liquid C ₁₁ H ₂₂ O ₂ 186.3	Insoluble Miscible	210 NMR 98% (racemate)	1.413–1.417 0.855–0.860	
09.924 1143 3980 5921-83-5	3-Heptyl acetate (mixture of R and S)	(b)	Liquid C ₉ H ₁₈ O ₂ 158.2	Insoluble Miscible	185 NMR 98% (racemate)	1.406–1.414 0.858–0.867	
09.925 1145 4007 60826-15-5	Nonan-3-yl acetate	(b)	Liquid C ₁₁ H ₂₂ O ₂ 186.3	Insoluble Miscible	225 NMR 98% (racemate)	1.416–1.423 0.854–0.864	
09.936 1847 4103 91418-25-6	4,8-Dimethyl-3,7-nonadien- 2-yl acetate	(b)	Liquid C ₁₃ H ₂₂ O ₂ 210	Insoluble Soluble	75–83 (3 hPa) IR NMR 95% (racemate and mixture of <i>E/Z</i> stereoisomers: 50–80% (<i>E</i>))	1.451–1.459 0.890–0.900	

UL: Union List.

(a): JECFA (2002a), EFSA CEF Panel (2016a); Documentation provided to EFSA nr: 1 and 2.

(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.
- (h): Secondary components.

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.63Rev4 in food categories listed in Annex III of Reg. (EC) 1565/2000 (EFSA CEF Panel, 2016a and Documentation provided to EFSA n. 1 and 3)

FL-no	Normal use levels (mg/kg) ^(a)																		
	Maximum use levels (mg/kg)																		
	01.0	02.0	03.0	04.1	04.2	05.0	05.3 ^{b)}	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
02.023	0.63 1.8	0.5 1	1 2	– –	11.85 18.4	1.14 1.8	– –	0.56 1.8	3.81 10.5	3.74 5.7	1 5	1 5	1 5	2 5	1 2	0.56 1.2	0.3 1	0.35 0.7	2 10
02.099	5 35	2 25	3 50	– –	7 35	4 50	– –	5 25	5 50	2 10	1 10	1 10	1 10	5 25	3 50	3 25	4 50	5 100	2 25
02.102	5 11.5	0.5 1.25	1.55 2.28	– –	4.6 8.36	6.92 11.63	2 6.63	5 10.4	5 15	2.13 2.6	1 1	– –	– –	2 5.6	– –	2.5 4.63	0.67 10	1 2	– –
02.104	5 35	2 25	3 50	– –	7 35	4 50	– –	5 25	5 50	2 10	1 10	1 10	1 10	5 25	3 50	3 25	4 50	5 100	2 25
02.136	5 35	2 25	3 50	– –	7 35	4 50	– –	5 25	5 50	2 10	1 10	1 10	1 10	5 25	3 50	3 25	4 50	5 100	2 25
02.155	7 35	5 25	10 50	7 35	– –	10 50	– –	5 25	10 50	2 10	2 10	– –	– –	5 25	10 50	5 25	10 50	20 100	5 25
02.193	5 11.5	0.5 1.25	1.55 2.28	– –	4.6 8.36	6.92 11.63	2 6.63	5 10.4	5 15	2.13 2.6	1 1	– –	– –	2 5.6	– –	2.5 4.63	0.67 10	1 2	– –
02.252	0.0005 0.025	0.0005 0.025	0.005 0.25	0.0005 0.025	0.0005 0.025	0.05 2.5	– –	– –	0.005 0.25	0.0005 0.025	0.0005 0.025	– –	– –	0.0005 0.025	– –	0.05 2.5	0.05 2.5	0.0005 0.025	0.0005 0.025
07.044	5 11.5	0.5 1.25	1.55 2.28	– –	4.6 8.36	6.92 11.63	2 6.63	5 10.4	5 15	2.13 2.6	1 1	– –	– –	2 5.6	– –	2.5 4.63	0.67 10	1 2	– –
07.048	5 11.5	0.5 1.25	1.55 2.28	– –	4.6 8.36	6.92 11.63	2 6.63	5 10.4	5 15	2.13 2.6	1 1	– –	– –	2 5.6	– –	2.5 4.63	0.67 10	1 2	– –
07.081	3 15	2 10	3 15	– –	2 10	4 20	– –	2 10	5 25	1 5	1 5	1 5	1 5	2 10	3 15	2 10	4 20	5 25	2 10
07.082	5 11.5	0.5 1.25	1.55 2.28	– –	4.6 8.36	6.92 11.63	2 6.63	5.71 10.4	8.75 15	2.13 2.6	1 1	– –	– –	2 5.6	– –	3 4.63	0.67 10	1 2	– –
07.099	0.05 0.05	– –	0.5 2	– –	– –	1.1 9	– –	1 4.5	1 4.5	– –	– –	– –	– –	0.5 2	1 4.5	0.05 0.05	0 0	– –	– –

FL-no	Normal use levels (mg/kg) ^(a)																		
	Maximum use levels (mg/kg)																		
	01.0	02.0	03.0	04.1	04.2	05.0	05.3 ^{b)}	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
07.101	0.4	–	0.75	–	–	1.12	–	–	2.25	–	–	–	–	0.5	0.5	–	0	–	–
	0.4	–	0.75	–	–	1.12	–	–	2.25	–	–	–	–	0.5	0.5	–	0	–	–
07.102	3	2	3	–	2	4	–	2	5	1	1	1	1	2	3	2	4	5	2
	5	10	15	–	10	20	–	10	25	5	5	5	5	10	15	10	20	25	10
07.104	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.105	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.106	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.107	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.121	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.139	5	0.5	1.55	–	4.6	6.92	2	5	5	2.13	1	–	–	2	–	2.5	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.177	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.188	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
07.190	3	2	3	2	–	4	–	2	5	1	1	–	–	2	3	2	4	5	2
	15	10	15	10	–	20	–	10	25	5	5	–	–	10	15	10	20	25	10
07.244	5	0.5	1.55	–	4.6	6.92	2	5.71	8.75	2.13	1	–	–	2	–	3	0.67	1	–
	11.5	1.25	2.28	–	8.36	11.63	6.63	10.4	15	2.6	1	–	–	5.6	–	4.63	10	2	–
09.281	7	5	10	7	–	10	–	5	10	2	2	–	–	5	10	5	10	20	5
	35	25	50	35	–	50	–	25	50	10	10	–	–	25	50	25	50	100	25
09.282	7	5	10	7	–	10	–	5	10	2	2	–	–	5	10	5	10	20	5
	35	25	50	35	–	50	–	25	50	10	10	–	–	25	50	25	50	100	25
09.936	0.0005	0.0005	0.005	0.0005	0.0005	0.05	–	–	0.005	0.0005	0.0005	–	–	0.0005	–	0.05	0.05	0.0005	0.0005
	0.025	0.025	0.25	0.025	0.025	2.5	–	–	0.25	0.025	0.025	–	–	0.025	–	2.5	2.5	0.025	0.025

(a): 'Normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages.

(b): Additional food category 05.3 (chewing gum as per Annex II part D of Reg. (EC) 1333/2008) for which EFSA submitted use levels (Documentation provided to EFSA n. 1 and 3). These data have been considered in the calculation of mTAMDI.

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 Table C.3)

- 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.63Rev4

Estimated intakes based on the MSDI approach and the mTAMDI approach						
FL-no	EU Union List name	MSDI – EU (µg/capita per day)	MSDI – USA (µg/capita per day)	mTAMDI (µg/person per day)	Structural class	TTC (µg/person per day)
02.102	Oct-3-en-2-ol	0.01	ND	1,700	Class II	540
02.193	Oct-2-en-4-ol	1.84	ND	1,700	Class II	540
02.252	4,8-Dimethyl-3,7-nonadien-2-ol	3	0.1	19	Class I	1,800
07.044	Pent-3-en-2-one	0.25	ND	1,800	Class I	1,800
07.048	4-Hexen-3-one	41.44	1	1,800	Class I	1,800
07.104	Hept-2-en-4-one	0.01	ND	2,400	Class I	1,800
07.139	5-Methylhept-2-en-4-one	32.60	1	1,700	Class II	540
09.657	1-Methylbutyl acetate	2.9	3	NA	Class I	1,800
09.658	1-Methylbutyl butyrate	0.47	1	NA	Class I	1,800
09.923	Hept-2-yl butyrate	3	3	NA	Class I	1,800
09.924	3-Heptyl acetate (mixture of R and S)	3	3	NA	Class I	1,800
09.925	Nonan-3-yl acetate	3	3	NA	Class I	1,800
02.023	Oct-1-en-3-ol	390	23	1,800	Class II	540
02.099	Pent-1-en-3-ol	4.3	1	2,300	Class II	540
02.104	Hex-1-en-3-ol	0.012	2	2,300	Class II	540
02.136	Dec-1-en-3-ol	0.012	0.1	2,300	Class II	540
02.155	1-Hepten-3-ol	0.13	–	3,900	Class II	540
07.015	6-Methylhept-5-en-2-one	100	44	NA	Class II	540
07.069	Tetrahydro-pseudo-ionone	0.012	0.01	NA	Class II	540
07.081	Oct-1-en-3-one	1.5	0.1	1,600	Class II	540
07.082	Oct-2-en-4-one	13.78	3	2,400	Class II	540
07.099	6-Methylhepta-3,5-dien-2-one	13	5	190	Class II	540
07.100	5-Methylhex-5-en-2-one	0.24	0.3	NA	Class II	540
07.101	4-Methylpent-3-en-2-one	0.34	ND	340	Class II	540
07.102	Pent-1-en-3-one	1.6	0.1	1,600	Class II	540
07.105	Hept-3-en-2-one	0.01	0.07	2,400	Class I	1,800
07.106	5-Methylhex-3-en-2-one	0.01	0.1	2,400	Class I	1,800
07.107	Oct-3-en-2-one	0.63	1	2,500	Class I	1,800
07.114	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	0.085	ND	NA	Class II	540

Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Union List name	MSDI – EU ($\mu\text{g}/\text{capita per day}$)	MSDI – USA ($\mu\text{g}/\text{capita per day}$)	mTAMDI ($\mu\text{g}/\text{person per day}$)	Structural class	TTC ($\mu\text{g}/\text{person per day}$)
07.121	Dec-3-en-2-one	0.17	ND	2,400	Class I	1,800
07.123	Geranylacetone	41	2	NA	Class II	540
07.151	Decan-3-one	3	3	NA	Class II	540
07.177	7-Methyl-3-octenone-2	0.04	2	2,400	Class I	1,800
07.188	Non-3-en-2-one	0.05	13	2,400	Class I	1,800
07.190	Octa-1,5-dien-3-one	0.061	ND	1,600	Class II	540
07.240	2-Methylheptan-3-one	3	3	NA	Class II	540
07.244	(6 <i>E</i>)-Methyl-3-hepten-2-one	0.01	3	2,400	Class I	1,800
07.247	(<i>E,E</i>)-3,5-Octadien-2-one	3	4	NA	Class II	540
07.249	Undecan-6-one	3	3	NA	Class II	540
07.256	(<i>E</i>) & (<i>Z</i>)-4,8-Dimethyl-3,7-nonadiene-2-one	6.1	6.6	NA	Class II	540
09.281	Oct-1-en-3-yl acetate	2.1	–	3,900	Class II	540
09.282	Oct-1-en-3-yl butyrate	0.0012	–	3,900	Class II	540
09.936	4,8-Dimethyl-3,7-nonadien-2-yl acetate	3	0.2	19	Class II	540

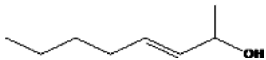
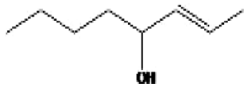
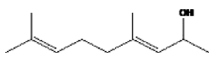

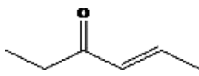
(a): Based on EU production figures from JECFA (JECFA 2002b and 2005) and submitted by industry (Documentation provided to EFSA nr. 1 and 3).

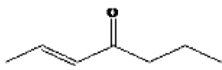
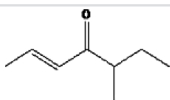
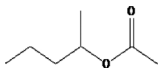
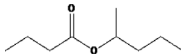
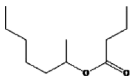
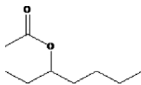
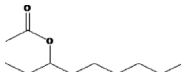
(b): Based on US production figures from JECFA (JECFA 2002b, 2005).

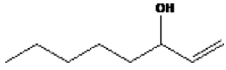
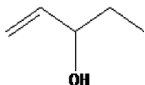
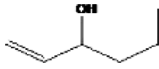
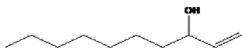

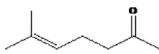
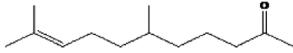
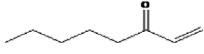
(c): Based on use levels submitted by industry (Documentation provided to EFSA nr. 1).

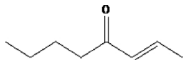
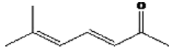
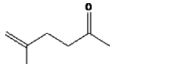
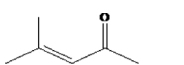
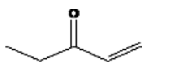

Appendix D – Summary of safety evaluations

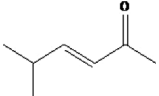
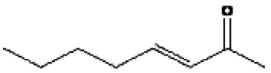

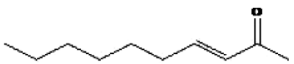
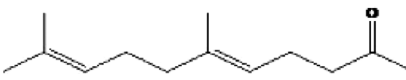
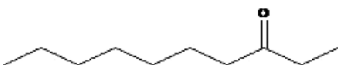
Table D.1: Summary of safety evaluations performed by JECFA (JECFA, 2002b, 2005) and EFSA conclusions on flavouring substances in FGE.63 and its revisions

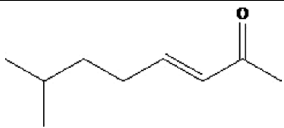

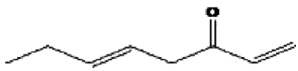
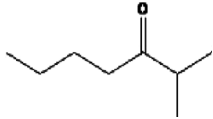
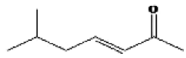
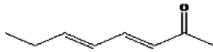
FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
02.102 1140	Oct-3-en-2-ol		Class I A3: Intake below threshold No safety concern	Class II A3: Intake below threshold No safety concern. The chemical name should be changed to Oct-(3E)-en-2-ol and the CAS number to 57648-55-2 Concluded in FGE.63Rev4
02.193 1141	Oct-2-en-4-ol		Class I A3: Intake below threshold No safety concern	Class II A3: Intake below threshold No safety concern. The chemical name should be changed to Oct-(2E)-en-4-ol and the CAS number to 20125-81-9 Concluded in FGE.63Rev4
02.252 1841	4,8-Dimethyl-3,7-nonadien-2-ol		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1
07.044 1124	Pent-3-en-2-one		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. The chemical name should be changed to Pent-(3E)-en-2-one and the CAS number to 3102-33-8 Concluded in FGE.63Rev4
07.048 1125	4-Hexen-3-one		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. The chemical name should be changed to Hex-(4E)-en-3-one and the CAS number to 50396-87-7 Concluded in FGE.63Rev4

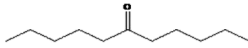
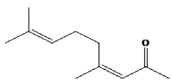
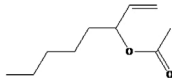
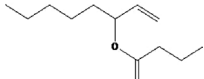
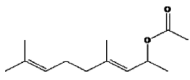
FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.104 1126	Hept-2-en-4-one		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. The chemical name should be changed to Hept-(2E)-en-4-one and the CAS number to 22286-99-3. Concluded in FGE.63Rev4
07.139 1133	5-Methylhept-2-en-4-one		Class I A3: Intake below threshold No safety concern	Class II A3: Intake below threshold No safety concern. The chemical name should be changed to 5-Methylhept-(2E)-en-4-one and the CAS number to 102322-83-8. Concluded in FGE.63Rev4
09.657 1146	1-Methylbutyl acetate		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
09.658 1142	1-Methylbutyl butyrate		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
09.923 1144	Hept-2-yl butyrate		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
09.924 1143	3-Heptyl acetate (mixture of R and S)		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
09.925 1145	Nonan-3-yl acetate		Class I A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
02.023 1152	Oct-1-en-3-ol		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
02.099 1150	Pent-1-en-3-ol		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
02.104 1151	Hex-1-en-3-ol		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
02.136 1153	Dec-1-en-3-ol		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
02.155 1842	1-Hepten-3-ol		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
07.015 1120	6-Methylhept-5-en-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
07.069 1121	Tetrahydro-pseudo-ionone		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
07.081 1148	Oct-1-en-3-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3

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07.082 1129	Oct-2-en-4-one		Class II A3: Intake below threshold No safety concern	Class II B3: intake below the threshold B4: Adequate NOAEL exists No safety concern. The chemical name should be changed to oct-(2E)-en-4-one and the CAS number to 22286-99-3 to reflect the stereochemical configuration. Concluded in FGE.63Rev4
07.099 1134	6-Methylhepta-3,5-dien-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1
07.100 1119	5-Methylhex-5-en-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
07.101 1131	4-Methylpent-3-en-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev2
07.102 1147	Pent-1-en-3-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
07.105 1127	Hept-3-en-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to hept-(3E)-en-2-one and the CAS number to 5609-09-6. Concluded in FGE.63Rev4

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.106 1132	5-Methylhex-3-en-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to 5-Methylhex-(3 <i>E</i>)-en-2-one and the CAS number to 1821-29-0. Concluded in FGE.63Rev4
07.107 1128	Oct-3-en-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to Oct-(3 <i>E</i>)-en-2-one and the CAS number to 18402-82-9. Concluded in FGE.63Rev4
07.114 1123	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
07.121 1130	Dec-3-en-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to Dec-(3 <i>E</i>)-en-2-one and the CAS number to 18402-84-1. Concluded in FGE.63Rev4
07.123 1122	Geranylacetone		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. The chemical change should be changed to (<i>E</i>)-geranylacetone Concluded in FGE.63
07.151 1118	Decan-3-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class ^(a) Evaluation procedure path ^(b) Outcome on the named compound based on the MSDI ^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI ^(d) approach on the named compound and on the material of commerce
07.177 1135	7-Methyl-3-octenone-2		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to 7-Methyl-oct-(3 <i>E</i>)-en-2-one and the CAS number to 1004754-77-1. Concluded in FGE.63Rev4
07.188 1136	Non-3-en-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. The chemical name should be changed to Non-(3 <i>E</i>)-en-2-one and the CAS number to 18402-83-0. Concluded in FGE.63Rev4
07.190 1848	Octa-1,5-dien-3-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1
07.240 1156	2-Methylheptan-3-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1
07.244 1138	(6 <i>E</i>)-Methyl-3-hepten-2-one		Class II A3: Intake below threshold No safety concern	Class I A3: Intake below threshold No safety concern. Concluded in FGE.63Rev4
07.247 1139	(<i>E,E</i>)-3,5-Octadien-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class^(a) Evaluation procedure path^(b) Outcome on the named compound based on the MSDI^(c) approach	EFSA conclusions Procedural path if different from JECFA Conclusion based on the MSDI^(d) approach on the named compound and on the material of commerce
07.249 1155	Undecan-6-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63
07.256 1137	(E) & (Z)-4,8-Dimethyl-3,7- nonadiene-2-one		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1
09.281 1836	Oct-1-en-3-yl acetate		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
09.282 1837	Oct-1-en-3-yl butyrate		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev3
09.936 1847	4,8-Dimethyl-3,7-nonadien- 2-yl acetate		Class II A3: Intake below threshold No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.63Rev1

(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).