SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 14 November 2019

doi: 10.2903/j.efsa.2020.5923

Scientific Opinion on Flavouring Group Evaluation 61 Revision 2 (FGE.61Rev2): consideration of aliphatic acetals evaluated by JECFA (57th, 63rd and 68th meetings) structurally related to acetals evaluated by EFSA in FGE.03Rev2

EFSA Panel on Food Additives and Flavourings (FAF),
Maged Younes, Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Peter Moldeus, Agneta Oskarsson, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle, Romualdo Benigni, Claudia Bolognesi, Kevin Chipman, Eugenia Cordelli, Gisela Degen, Daniel Marzin, Camilla Svendsen, Maria Carfi, Carla Martino and Wim Mennes

Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 12 flavouring substances attributed to the Flavouring Group Evaluation 61 (FGE.61), using the Procedure as outlined in the Commission Regulation (EC) No 1565/2000. Nine substances have already been considered in FGE.61 and FGE.61Rev1 [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037, 06.081]. The remaining three substances [FL-no: 06.025, 06.031 and 06.072] have been cleared with respect to genotoxicity in FGE.200Rev1 and are considered in this revision 2 of FGE.61. 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 the 12 substances gives rise to safety concerns at their levels of dietary intake, 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 nine flavouring substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037 and 06.081], use levels are still needed to calculate the modified Theoretical Added Maximum Daily Intake (mTAMDI) values in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly.

Keywords: Flavourings, acetals, α,β-unsaturated carbonyls and precursors, FGE.61Rev1, JECFA

Requestor: European Commission

Question numbers: EFSA-Q-2018-00841, EFSA-Q-2018-00842, EFSA-Q-2018-00843

Correspondence: fip@efsa.europa.eu

Panel members: Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Wim Mennes, Peter Moldeus, Agneta Oskarsson, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle and Maged Younes.

Acknowledgements: The Panel wishes to thank the following for the support provided to this scientific output: Esraa Elewa and Giorgia Vianello. The Panel wishes to acknowledge the hearing experts: Vibe Meister Beltoft and Karin Nørby for the support provided to this scientific output.

Suggested citation: EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Frutos Fernandez MJ, Fürst P, Gundert-Remy U, Gürtler R, Husøy T, Moldeus P, Oskarsson A, Shah R, Waalkens-Berendsen I, Wölfle D, Benigni R, Bolognesi C, Chipman K, Cordelli E, Degen G, Marzin D, Svendsen C, Carfì M, Martino C and Mennes W, 2020. Scientific Opinion on Flavouring Group Evaluation 61 Revision 2 (FGE.61Rev2): consideration of aliphatic acetals evaluated by JECFA (57th, 63rd and 68th meetings) structurally related to acetals evaluated by EFSA in FGE.03Rev2. EFSA Journal 2020;18(1):5923, 26 pp. https://doi.org/10.2903/j.efsa.2020.5923

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

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1. Introduction

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of three aliphatic acetals (i.e. [FL-no: 06.025, 06.031, 06.072]) which are precursors of α,β-unsaturated carbonyl substances and they have been evaluated with respect to genotoxicity in FGE.200Rev1. According to the Mandate and Term 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[1] and of Regulation (EU) No 1334/2008[2]. The mandate for FGE.200Rev1 is cited below.

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

1.1.1. Background to Mandate from FGE.200Rev1 (M-2018-0041)

The use of flavourings is regulated under Regulation (EC) No 1334/2008[2] 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 872/2012[3]. The list includes a number of flavouring substances for which the safety evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000[1].

In February 2011, the EFSA Panel had evaluated a first dossier submitted by Industry in response to the requested data for representative substances in FGE. 200. These data were not considered adequate to alleviate the genotoxicity concern for the substance in subgroup 1.1.1 and the Panel recommended at that time 'to perform *in vivo* dietary Comet assays (in drinking water or in feed, not by gavage) for the three linear representatives of subgroup 1.1.1 [FL-no: 05.073, 05.058 and 05.060]'.

Additional data were submitted in February and June 2013 by Industry related to one representative substance of subgroup 1.1.1, hex-2(*trans*)-enal [FL-no: 05.073] and two other substances of the group.

On 21 May 2014 the EFSA CEF Panel adopted an opinion on this Flavouring Group Evaluation 200 (FGE.200). The Panel confirmed the need for an *in vivo* Comet assay performed in duodenum and liver for hex-2(*trans*)-enal [FL-no: 05.073]. For the two representative substances of subgroup 1.1.1 (nona-2 (*trans*), 6(*cis*)-dienal [FL-no: 05.058] and oct-2-enal [FL-no: 05.060]), a combined *in vivo* Comet assay and micronucleus assay would be required and evidence of bone marrow exposure should be provided.

New data concerning the three representative substances of this group addressing the EFSA opinion have been submitted during 2017. The data also included updated poundage and use levels concerning these substances.

The list of the substances referred to in this letter is included in Annex II.[4]

1.1.2. Terms of Reference of Mandate from FGE.200Rev1 (M-2018-0041)

The European Commission requests the European Food Safety Authority (EFSA) to evaluate the new information submitted and, depending on the outcome, proceed to full evaluation of the substances in this group in accordance with Commission Regulation (EC) No 1565/2000[1]. In accordance with the usual practice by the CEF panel, the first step (assessment of the genotoxicity) should be completed within 9 months. An additional 9 months if necessary is also established for the second step (evaluation through the CEF Procedure). In case the genotoxic potential cannot be ruled out or the procedure cannot be applied in the first step, EFSA is asked to quantify the exposure.

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

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

[3] Commission implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex Ito 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] Annex II refers here to the annex of the mandate letter from the European Commission to EFSA related to FGE.200Rev1.

1.2. Interpretation of the Terms of Reference

Flavouring substances [FL-no: 06.025, 06.031, 06.072] were first allocated to FGE.200Rev1 for evaluation with respect to genotoxicity. Based on new genotoxicity data submitted, the Panel concluded that these three flavouring substances do not give rise to concern with respect to genotoxicity and can accordingly be evaluated through the Procedure in the present revision of FGE.61 (FGE.61Rev2), in accordance with Commission Regulation (EC) No 1565/2000.

In addition, since the publication of FGE.61Rev1, data on EU production volumes and data on stereoisomerism and/or compositional information of the substances [FL-no: 06.004, 06.005, 06.037 and 06.081] have been provided by industry. Therefore, their safety evaluation through the Procedure can also be finalised in the current revision.

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

1.2.1. History of the evaluation of the substances in FGE.61

FGE.61 (EFSA AFC Panel, 2008) included seven aliphatic acetals [FL-no: 06.001, 06.008, 06.009, 06.015, 06.028, 06.037 and 06.081], which have been evaluated by The Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 57th meeting (JECFA, 2002) in a group of 10 flavouring substances consisting of aliphatic acyclic acetals. Three of the JECFA-evaluated substances, [FL-no: 06.004, 06.005 and 06.025], may be metabolised to α,β-unsaturated aldehydes. Since α,β-unsaturated carbonyls, or precursors for that, were considered by the Panel as structural alert for genotoxicity (EFSA, 2008), these three substances were given special considerations. Particularly, the concern for genotoxicity for two of these three candidates, citral diethyl acetal and citral dimethyl acetal [FL-no: 06.004 and 06.005], was ruled out in FGE.202 (EFSA CEF Panel, 2009a), and they were evaluated through the procedure in FGE.61Rev1 (EFSA CEF Panel, 2009b). Whereas, for the third substance, 1,1-diethoxynona-2,6-diene [FL-no: 06.025], a conclusion on its genotoxic potential could not be reached and additional data were requested in FGE.200 (EFSA CEF Panel, 2014).

Therefore, FGE.61Rev1 only dealt with the safety evaluation of two aliphatic acetals [FL-no: 06.004 and 06.005] in addition to the seven flavouring substances previously evaluated in FGE.61 (EFSA AFC panel, 2008). These substances were considered structurally related to 58 acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated aldehydes, and one orthoester of formic acid, evaluated in FGE.03Rev1.

The Panel agreed with the way the application of the Procedure which has been performed by JECFA for all nine substances considered in FGE.61Rev1. However, for four substances, the Panel had reservations, i.e. no European production volumes available for [FL-no: 06.081], preventing evaluation using the Procedure; and/or missing information on stereoisomerism for [FL-no: 06.004, 06.005, 06.037]. For the remaining five substances [FL-no: 06.001, 06.008, 06.009, 06.015 and 06.028], the Panel agreed with the JECFA conclusion 'no safety concern at estimated levels of intake as flavouring substances' based on the Maximised Survey-derived Daily Intake (MSDI) approach. For all nine substances, use levels are needed to calculate the modified Theoretical Added Maximum Daily Intakes (mTAMDIs) in order to identify those flavouring substances that need more refined exposure assessment.

The present revision of FGE.61, FGE.61Rev2, includes the safety evaluation of 1,1-diethoxynona-2,6-diene [FL-no: 06.025], evaluated by JECFA in its 57th meeting (JECFA, 2002) and cleared with respect to genotoxicity in FGE.200Rev1 (EFSA FAF Panel, 2018) following the assessment of the requested additional genotoxicity data by EFSA. Moreover, FGE.61Rev2 also considers two additional flavouring substances [FL-no: 06.031 and 06.072], evaluated by JECFA in its 63rd and 68th meetings, respectively (JECFA, 2005, 2007). By expert judgement, they have been included in FGE.61Rev2 on the basis of their structural similarity with the substances considered in this group. These flavouring substances were considered of no concern for genotoxicity in FGE.200Rev1 (EFSA FAF Panel, 2018) and accordingly they can be evaluated through the Procedure.

Together with the nine substances that were already considered in FGE.61Rev1, the current revision comprises 12 substances. The five flavouring substances for which the evaluation was finalised in FGE.61Rev1 will not further be discussed. Nevertheless, for the sake of completion their information is maintained in the various tables in this FGE.

EU production volumes and/or data on stereoisomerism have been provided for four flavouring substances [FL-no: 06.004, 06.005, 06.037 and 06.081], considered in the previous revision (FGE.61Rev1). This information is included and taken into account in this revision 2 of FGE.61.

FGE	Adopted by EFSA	Link	No of substances
FGE.61	3 July 2007	https://www.efsa.europa.eu/en/efsajournal/pub/688	7
FGE.61Rev1	26 March 2009	https://www.efsa.europa.eu/en/efsajournal/pub/1026	9
FGE.61Rev2	14 November 2019	https://www.efsa.europa.eu/en/efsajournal/pub/5923	12

FGE: Flavouring Group Evaluation.

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 2 of FGE.61 (FGE.61Rev2)

FL-no	Chemical name	Data provided for the current revision 2 of FGE.61	Appendix (Table nr) and relevant section of the opinion	Documentation provided to EFSA nr:
06.004	Citral diethyl acetal	Specifications	Appendix B (Table B.1)	Documentation provided to EFSA n. 1
06.005	Citral dimethyl acetal	Specifications	Appendix B (Table B.1)	Documentation provided to EFSA n. 1
06.025	1,1-Diethoxynona-2,6-diene	Specifications, EU poundage data (MSDI), Use levels (mTAMDI)	Appendix B (Table B.1) Appendix C (Tables C.1 and C.4)	Documentation provided to EFSA n. 2 and 4
06.031	1,1-Diethoxyhex-2-ene	Specifications, EU poundage data (MSDI), Use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Tables C.1 and C.4)	Documentation provided to EFSA n. 2 and 4
06.037	1,1-Diethoxyhept-4-ene (*cis* and *trans*)	Specifications	Appendix B (Table B.1)	Documentation provided to EFSA n. 1
06.072	1,1-Dimethoxyhex-2 (*trans*)-ene	EU poundage data (MSDI), Use levels (mTAMDI)	Appendix C (Tables C.1 and C.4)	Documentation provided to EFSA n. 2 and 4
06.081	(*Z*)-1-Ethoxy-1-(3-hexenyloxy) ethane	Specifications, EU poundage data (MSDI)	Appendix B (Table B.1); Appendix C (Table C.4)	Documentation provided to EFSA n. 1 and 3

FL-no: FLAVIS number; FLAVIS: Flavour Information System (database); MSDI: Maximised Survey-derived Daily Intake; mTAMDI: modified Theoretical Added Maximum Daily Intake.

In addition, the following data have been used in FGE.61Rev2:

- JECFA specifications for the three candidate substances [FL-no: 06.025, 06.031 and 06.072] (JECFA, 2002, 2005, 2007);
- Genotoxicity data evaluated in FGE.200 and FGE.200Rev1 (EFSA CEF Panel 2008; EFSA FAF Panel, 2018);
- 57th, 63rd and 68th JECFA reports (JECFA, 2002, 2005, 2007) and 54th JECFA toxicology monograph (JECFA, 2006);
- EFSA Scientific Opinion on FGE.61 (EFSA AFC Panel, 2008);
- EFSA Scientific Opinion on FGE.61Rev1 (EFSA CEF panel, 2009a,b);
- EFSA Scientific Opinion on FGE.03Rev2 ((EFSA CEF Panel, 2011).

2.2. Methodologies

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

2.2.1. Procedure for the safety evaluation of flavouring substances

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

2.2.2. Approach used for the calculation of exposure

The approach used for calculation of the intake of the flavouring substances is described in Appendix A (point '(a) Intake') and in Appendix C (Section C.2 'mTAMDI calculation').

3. Assessment

3.1. Specifications

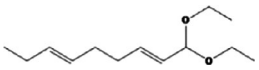
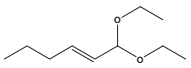
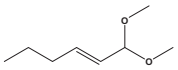
JECFA status

The JECFA specifications are available for all the 12 flavouring substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.025, 06.028, 06.031, 06.037, 06.072 and 06.081] considered in the present opinion (FGE.61Rev2) (JECFA, 2002, 2005, 2007).

EFSA considerations

Table 2 shows the chemical structure of the candidate substances which are considered in this revision of FGE.61 (FGE.61Rev2).

Table 2: Flavouring substances under evaluation in FGE.61Rev2

FL-no	Chemical name	Structural formula	Structural class*
06.025	1,1-Diethoxynona-2,6-diene		Class I
06.031	1,1-Diethoxyhex-2-ene		Class I
06.072	1,1-Dimethoxyhex-2(*trans*)-ene		Class I

FL-no: FLAVIS number; FLAVIS: Flavour Information System (database); FGE: Flavouring Group Evaluation.
*: Determined with OECD Toolbox (version 4.3).

Additional information for two candidate flavouring substances [FL-no: 06.025 and 06.031], related to the defined composition of the stereoisomeric mixtures, have been submitted by industry (Documentation provided to EFSA n. 2). The Panel considered these updated specifications adequate to describe the materials of commerce for these flavouring substances. Based on this updated information on stereoisomerism, the chemical name for flavouring substance [FL-no: 06.025] should be changed in the Union List (UL) to 1,1-diethoxynona-(2*E*,6*Z*)-diene, to reflect the stereochemical configuration of the flavouring substance. In addition, also the chemical name and the CAS number for flavouring substance [FL-no: 06.031] should be changed in the UL to 1,1-diethoxyhex-(2*E*)-ene, CAS nr: 67746-30-9, to reflect the stereochemical configuration of the flavouring substance (see 'EFSA comments' column in Table B.1 – Appendix B). For the third candidate flavouring substance [FL-no: 06.072], the JECFA specifications were considered adequate.

In addition, the purity requirements for flavouring substances [FL-no: 06.025, 06.031 and 06.037] should be updated in the UL in accordance with the specifications provided. For flavouring substance [FL-no: 06.037], the chemical name and the CAS number should be changed to 1-diethoxyhept-(4*Z*)-ene, CAS nr: 18492-65-4, to reflect the stereochemical configuration of the flavouring substance (see 'EFSA comments' column in Table B.1 – Appendix B).

For flavouring substances [FL-no: 06.004 and 06.005], which are citral derivatives, further information on their stereochemistry was requested in the previous revision of this FGE (FGE.61Rev1). Industry informed that the material of commerce for these two substances is a mixture, at least 98% pure, of *E/Z*-stereoisomers plus hemiacetal and citral. The Panel noted that the trivial name 'citral' refers to a nearly equimolar mixture of *E*- stereoisomer (geranial) and *Z*- stereoisomer (neral), by which the stereochemical composition of the respective acetals [FL-no: 06.004 and 06.005] is also

defined. Therefore, the additional information provided was considered adequate by the Panel. With respect to flavouring substance [FL-no: 06.081], the Panel requested information (in FGE.61Rev1) on the configuration of the molecule. Industry informed that this flavouring substance is a racemate.

The most recent specifications data for all 12 substances in FGE.61Rev2 are summarised in Table B.1 – Appendix B.

3.2. Estimation of intake

JECFA status

For 11 flavouring substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037, 06.025, 06.031 and 06.072], evaluated through the JECFA Procedure, intake data are available for the EU (JECFA, 2002, 2005, 2007). For one substance [FL-no: 06.081], a production figure is only available for the US and thus the MSDI value for the EU cannot be calculated for this substance.

EFSA considerations

Updated EU production figures for the three newly allocated flavouring substances [FL-no: 6.025, 06.031, 06.072] have been submitted (Documentation provided to EFSA n. 4). Additionally, for one flavouring substance [FL-no: 06.081], considered in the previous version of this FGE (FGE.61Rev1), EU production volumes have been provided (Documentation provided to EFSA n. 3) and therefore, the EU MSDI value can now be calculated. The MSDI values range from 0.024 to 200 μg/capita per day (Table C.4 – Appendix C).

For the three newly allocated flavouring substances [FL-no: 6.025, 06.031, 06.072], normal and maximum use levels have been submitted (Documentation provided to EFSA n. 2) and mTAMDI intake values can be calculated. The mTAMDI intake estimates calculated from these data are all below the threshold of concern for their structural class I.

No normal and maximum use levels have been provided for the nine flavouring substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037 and 06.081], previously considered in FGE.61Rev1.

The MSDI values for the 12 flavouring substances and the mTAMDI intake estimates for [FL-no: 6.025, 06.031, 06.072] are shown in Table C.4 – Appendix C.

3.3. Biological and toxicological data

3.3.1. ADME data

According to JECFA, (57th, 63rd and 68th meetings), the three candidate aliphatic acetals [FL-no: 06.025, 06.031 and 06.072] undergo acidic hydrolysis in the stomach to yield the corresponding alcohols and α,β-unsaturated aldehydes which are readily absorbed through the gastrointestinal tract. The resulting alcohols and aldehydes are oxidised by cytochrome P450 enzymes to the corresponding acids, which are further metabolised through β-oxidation and subsequently via the citric acid cycle. In addition to the oxidative metabolism, also conjugation with glutathione (GSH) has been described. Experimental studies indicate that acetals may also be hydrolysed enzymatically in the liver and probably also in other tissues. Nevertheless, hydrolysis data on acetals show that it cannot be excluded that a fraction of an oral dose of the parent acetals may reach the systemic circulation (JECFA, 2002; EFSA CEF Panel, 2011). Therefore, acetals can be anticipated to be metabolised to innocuous substances through (acidic or enzymatic) hydrolysis, oxidation and normal fatty acid metabolism, including β-oxidation and citric acid cycle, which finally leads to their total oxidation. Based on this information, JECFA concluded that these flavouring substances [FL-no: 06.025, 06.031, 06.072], now subject of this revision of FGE.61, can be evaluated along the A-side of the Procedure (see Appendix A).

EFSA considerations

In accordance with JECFA, the Panel agrees that flavouring substances [FL-no: 06.025, 06.031 and 06.072] can be expected to be hydrolysed to the corresponding saturated alcohols and α,β-unsaturated aldehydes. The substances [FL-no: 06.025 and 06.031] would be hydrolysed to ethanol and 2,6-nonadienal and 2-hexenal, respectively (JECFA, 2002, 2005). Ethanol was evaluated by JECFA as no safety concern at its 46th meeting (JECFA, 1997) and accordingly it was introduced in the Union List ([FL-no: 02.078]). With respect to 2,6-nonadienal, the stereoisomer nona-2(*trans*),6(*cis*)-dienal [FL-no: 05.058] has been evaluated by EFSA in FGE.70Rev1 (EFSA FAF Panel, 2019a) as no safety

concern. With respect to 2-hexenal [FL-no: 05.189] and its stereospecific *trans*-isomer [FL-no: 05.073], they have been evaluated by EFSA in FGE.05Rev3 (EFSA FAF Panel, 2019b) and in FGE.71Rev1 (EFSA FAF Panel, 2020), respectively, as of no safety concern.

For the other acetal [FL-no: 06.072], which is substituted with two dimethoxy groups, the Panel observed that this would be hydrolysed to methanol and *trans*-2-hexenal. Methanol is not an authorised food flavouring substance.

The Panel considered that the possible release of methanol, amounting to 8.8×10^{-5} μg/kg body weight (bw) per day[5] following hydrolysis of 1,1-dimethoxyhex-2(*trans*)-ene [FL-no: 06.072]. This amount of methanol corresponds to an increase in plasma methanol concentration of less than 1%, which would not pose a safety concern (EFSA ANS Panel, 2013).

Overall, the Panel concurs with JECFA view that the three candidate substances [FL-no: 06.025, 06.031 and 06.072] in FGE.61Rev2 can be evaluated along the A-side.

3.3.2. Genotoxicity data

This revision involves the inclusion of three flavouring substances, for which in FGE.19 a concern for genotoxicity had been identified based on the presence of a structural alert (i.e. α,β-unsaturated carbonyl substance or precursor for that), preventing their evaluation through the Procedure (see also Appendix A). Because of this, these substances needed further attention in FGE.200 and its revision 1 (FGE.200Rev1), where their genotoxic potential has been assessed and ruled out (EFSA CEF Panel, 2014; EFSA FAF Panel, 2018). Therefore, the safety evaluation through the Procedure can be performed for flavouring substances [FL-no: 06.025, 06.031 and 06.072].

3.3.3. Toxicological data

In the JECFA evaluations at its 63rd meeting (JECFA, 2005), an acute toxicity study on the candidate substance 1,1-diethoxyhex-2-ene [FL-no: 06.031] was considered. An oral median lethal dose (LD_{50}) of 860 mg/kg bw for rats has been reported (study by Moreno, 1977 as cited in JECFA, 2006).

No subacute, subchronic/chronic toxicity and carcinogenicity studies are available on the candidate substances or on structurally related substances.

3.4. Application of the procedure

Application of the Procedure to three aliphatic, linear, α,β-unsaturated, acetals by JECFA (2002, 2005, 2007)

JECFA allocated the three candidate flavouring substances [FL-no: 06.025, 06.031 and 06.072], currently under evaluation in FGE.61Rev2, to structural class I according to the decision tree approach presented by (Cramer et al., 1978).

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

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

EFSA considerations

The FAF Panel agrees with JECFA with respect to the allocation of the three candidate flavouring substances to Cramer class I. The Panel agrees with the way of the application of the Procedure that has been performed by JECFA for flavouring substances [FL-no: 06.025, 06.031 and 06.072]. The MSDI exposure estimates for the three candidate flavouring substances [FL-no: 06.025, 06.031 and 06.072] are below the threshold of concern for structural class I (i.e. 1,800 μg/person per day) (see Table C.4 – Appendix C). Therefore, the FAF Panel concludes, at step A3 of the Procedure scheme, that the candidate flavouring substances do not raise a safety concern when used as flavouring substances at the current levels of use, based on the MSDI approach.

For one flavouring substance [FL-no: 06.081], considered in the previous revision of this FGE (FGE.61Rev1), EFSA could not conclude on the safety of this substance as the European production

[5] Calculated from the exposure to 1,1-dimethoxyhex-2(*trans*)-ene [FL-no: 06.072] at the level of MSDI (see Table C.4 – Appendix C).

figures were not available. In the present revision, the evaluation of this substance has been finalised as EU production data became available. The resulting MSDI is below the threshold of concern for class I and accordingly the Panel concluded [FL-no: 06.081] at step A3 of the procedure to be of no safety concern, based on the MSDI approach.

4. Discussion

This revision 2 of FGE.61 comprises in total 12 flavouring substances, nine of which have already been considered in FGE. 61 and FGE.61Rev1. The remaining three substances [FL-no: 06.025, 06.031 and 06.072] have been included in this revision, following an extensive evaluation in FGE.200Rev1 of their genotoxic potential due to the presence of a structural alert for genotoxicity (i.e. α,β-unsaturated carbonyl or precursors for that).

Based on consideration of structural class, metabolism data and absence of genotoxic potential *in vivo*, and the MSDI exposure estimates, the FAF Panel concludes that the flavouring substances considered in this revision of FGE.61 (FGE.61Rev2) do not raise a safety concern at step A3 of the Procedure.

For all three substances considered in FGE.61Rev2, normal and maximum use levels have been provided, from which mTAMDI exposure estimates have been calculated. For these three candidate substances, the mTAMDI values are below the threshold of concern for their structural class (I). For the previously (in FGE.61Rev1) considered nine substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037 and 06.081], no normal or maximum use levels have been provided. For these nine substances, normal and maximum use levels are needed to calculate the mTAMDI estimates in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly. To determine whether the conclusions for the 12 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 the 12 flavouring substances [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.025, 06.028, 06.031, 06.037, 06.072 and 06.081].

5. Conclusions

In conclusion, for all 12 flavouring substances in FGE.61Rev2, the Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach. For nine substances, use levels are still 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.

6. Recommendation

The Panel recommends the European Commission to consider:

- to request normal and maximum use levels for [FL-no: 06.001, 06.004, 06.005, 06.008, 06.009, 06.015, 06.028, 06.037 and 06.081];
- in accordance with the latest specifications for the materials of commerce provided by industry:
  a) to change the chemical name in the Union List for flavouring substance [FL-no: 06.025] (see Table B.1 of Appendix B);
  b) to change the chemical name and CAS number for flavouring substances [FL-no: 06.031 and 06.037] (see Table B.1 of Appendix B);
  c) to update the purity requirements in the Union List for flavouring substances [FL-no: 06.025, 06.031 and 06.037] (see Table B.1 of Appendix B).

Documentation provided to EFSA

1) EFFA (European Flavour Association), 2010a. EFFA Letters to EFSA on clarification of specifications and isomerism for which data were requested in published FGEs.
2) EFFA (European Flavour Association), 2019. EFFA Submission of additional information on isomeric composition of substances within FGE.61 Rev2 (FGE.19 Subgroup 1.1.1) and refined use levels. August 2019.

3) EFFA (European Flavour Association), 2010b. European production volumes for selected flavouring substances (footnote 8 substances). Private communication from EFFA to DG SANCO. February 2010.
4) EFFA (European Flavour Association), 2018a. EFFA 2015 poundage information for 74 substances from FGE.19 subgroup 1.1.1 corresponding to FGE.200. Unpublished data submitted from EFFA to EFSA. Dated August 2018.
5) EFFA (European Flavour Association), 2002. Letter from EFFA to Dr. Joern Gry, Danish Veterinary and Food Administration. Dated 31 October 2002. Re.: Second group of questions. FLAVIS/8.26.

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Abbreviations

ADME	absorption, distribution, metabolism, elimination
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
ANS	Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFFA	European Flavour Association
FAF	Panel on food Additives and Flavourings
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation

FLAVIS (FL)	Flavour Information System (database)
GSH	glutathione
ID	Identity
IR	infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	median lethal dose
MS	mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NMR	nuclear magnetic resonance
No	Number
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
(Q)SAR	(quantitative) structure–activity relationship
SC	secondary components
SCF	Scientific Committee on Food
TTC	Threshold of Toxicological Concern
UL	Union List
WHO	World Health Organization

Appendix A – Procedure of the safety evaluation

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000, named the 'Procedure', is shown in schematic form in Figure A.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995, 1996, 1997, 1999), hereafter named the 'JECFA Procedure'.[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 products[7] (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)? Are the flavourings or their metabolites endogenous[8] (step A4)?
- Does a NOAEL exist on the flavourings or on structurally related substances (steps A5 and B4)?

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

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

[7] *Innocuous products*: products that are known or readily predicted to be harmless to humans at th 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).

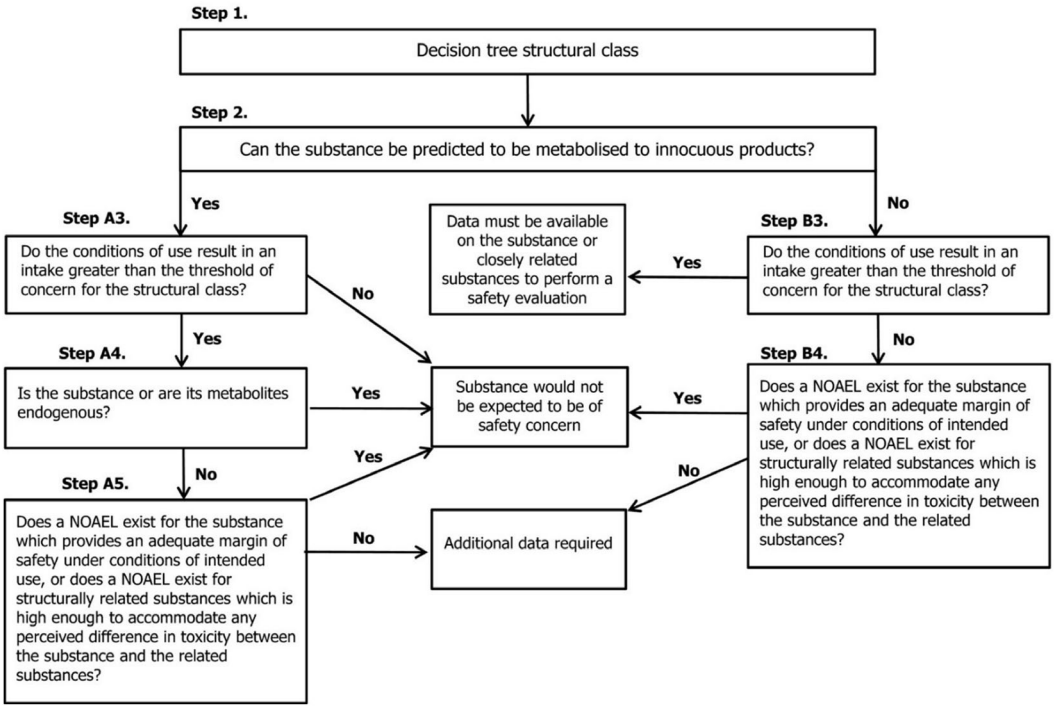


Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances

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 List[10] of flavouring substances for which this is the case, the Panel will need European Union (EU) production figures in order to finalise the evaluation.

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

[9] EU MSDI: Amount added to food as flavour in (kg/year) × 10^9/(0.1 × population in Europe (= 375 × 10^6) × 0.6 × 365) = μg/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 Ito 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.

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 μg/person per day (step B5) used by JECFA

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

'The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 μg/person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents, used at the 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 μg per day?')' (JECFA, 1999).

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

c) Genotoxicity

As reflected in the opinion of the 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.61Rev2, for chemical structures see Appendix D

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. index[f] Spec. gravity[g]**	
06.001 941 2002 35 105-57-7	1,1-Diethoxyethane	(b)	Liquid $C_6H_{14}O_2$ 118.18	Slightly soluble Miscible	102 IR 95%	1.378–1.386 0.822–0.831	
06.004 948 2304 38 7492-66-2	Citral diethyl acetal	At least 98% (sum of isomers + hemiacetals + citral)	Liquid $C_{14}H_{26}O_2$ 226.36	Insoluble Miscible	230 IR 98% (mixture of (*Z*)- and (*E*)-isomers and SC: citral (< 11%) and hemiacetal (< 6%))	1.445–1.455 0.864–0.879	
06.005 944 2305 39 7549-37-3	Citral dimethyl acetal	At least 98% (sum of isomers + hemiacetals + citral)	Liquid $C_{12}H_{22}O_2$ 198.31	Insoluble Miscible	105–106 (13 hPa) IR 98% (mixture of (*Z*)- and (*E*)-isomers and SC: citral (< 6%) and hemiacetal (< 6%))	1.450–1.463 0.881–0.893	
06.008 942 2798 42 10022-28-3	1,1-Dimethoxyoctane	(b)	Liquid $C_{10}H_{22}O_2$ 174.28	Insoluble Miscible	185 IR 95%	1.410–1.420 0.841–0.851	
06.009 945 2363 43 7779-41-1	1,1-Dimethoxydecane	(b)	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Miscible	218 IR 95%	1.420–1.430 0.830–0.852	

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. index[f] Spec. gravity[g]**	
06.015 940 3426 510 534-15-6	1,1-Dimethoxyethane	(b)	Liquid $C_4H_{10}O_2$ 90.12	Miscible Miscible	64 IR 96%	1.365–1.367 0.850–0.860	
06.025 946 3378 660 67674-36-6	1,1-Diethoxynona-2,6-diene	(b)	Liquid $C_{13}H_{24}O_2$ 212.33	Insoluble Miscible	125 (5 hPa) IR 90% sum of isomers (82% (2*E*,6*Z*)-isomer and 8% other geometric isomers: 2–6% (2*E*,6*E*), 1–4% (2*Z*,6*E*) and 1–2% (2*Z*,6*Z*) SC: 8% 2-nonenal diethyl acetal	1.441–1.448 0.860–0.868	The chemical name should be changed to 1,1-Diethoxynona-(2*E*,6*Z*)-diene, to reflect the stereochemical configuration of the flavouring substance. The purity requirement for the named compound [FL-no: 06.025] in the UL should be updated according to the specifications provided. (Documentation provided to EFSA n. 2)
06.028 947 2541 2015 10032-05-0	1,1-Dimethoxyheptane	(b)	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Miscible	164–165 IR 98%	1.405–1.415 0.844–0.849	

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. index[f] Spec. gravity[g]**	
06.031 1383 4047 2135 54306-00-2	1,1-Diethoxyhex-2-ene	(b)	Liquid $C_{10}H_{20}O_2$	Practically insoluble or insoluble Freely soluble	76–77 (15 mmHg) MS Mixture of 92–93% of 2*E*-isomer and 3–5% of 2*Z*-isomer	1.418–1.426 0.843–0.849	The chemical name should be changed to 1,1-Diethoxyhex-(2*E*)-ene and its CAS nr to (67746-30-9), to reflect the stereochemical configuration of the flavouring substance The purity requirement for the named compound [FL-no: 06.031] in the UL should be updated according to the specifications provided (Documentation provided to EFSA n. 2)
06.037 949 3349 10011 1192738-48-9	1,1-Diethoxyhept-4-ene (*cis* and *trans*)	(b)	Liquid $C_{11}H_{22}O_2$ 186.29	Insoluble Miscible	93 (20 hPa) IR Sum > 97% mixture of (*Z*)-isomer (75–79%) and (*E*)-isomer (19–21%)	1.420–1.440 0.840–0.860	The chemical name should be changed to 1,1-diethoxyhept-(4*Z*)-ene and its CAS nr to (18492-65-4), to reflect the stereochemical configuration of the flavouring substance The purity requirement for the named compound [FL-no: 06.037] in the UL should be updated according to the specifications provided (Documentation provided to EFSA n. 1)
06.072 1728 4098 – 18318-83-7	1,1-Dimethoxyhex-2 (*trans*)-ene	(b)	Liquid $C_8H_{16}O_2$ 144.2	Practically insoluble to insoluble in water Freely soluble	158 NMR 95% (*E*-isomer)	1.420–1.424 0.867–0.871	

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. index[f] Spec. gravity[g]**	
06.081 943 3775 10034 28069-74-1	(*Z*)-1-Ethoxy-1-(3-hexenyloxy)ethane	(b)	Liquid $C_{10}H_{20}O_2$ 172.27	Insoluble Miscible	85 (9 hPa) IR 97% (racemate)	1.430–1.435 0.846–0.856	According to the applicant the substance is a racemate (*R*/*S*) (Documentation provided to EFSA n. 1)

FL-no: FLAVIS number; FLAVIS: Flavour Information System (database); JECFA: The Joint FAO/WHO Expert Committee on Food Additives; FEMA: Flavor and Extract Manufacturers Association; CoE: Council of Europe; CAS: Chemical Abstract Service; ID: Identity; IR: infrared spectroscopy; MS: mass spectrometry; NMR: nuclear magnetic resonance; SC: secondary components; UL: Union List.
(a): JECFA (2002, 2005, 2007); EFSA CEF Opinion (2009); 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.

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.61Rev2 in food categories listed in Annex III of Reg. (EC) 1565/2000 (Documentation provided to EFSA n. 4)

FL-no		Food categories																	
		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
06.025	5.7 12	1.5 14.25	– –	– –	5 5.03	5.5 14.46	6.02 20.87	4.8 11.55	6 17	0.9 2.98	– –	– –	– –	2 5		2 4.43	1 2	2.5 4.5	– –
06.031	5.7 12	1.5 14.25	– –	– –	5 5.03	5.5 14.46	6.02 20.87	4.8 11.55	6 17	0.9 2.98	– –	– –	– –	2 5		2 4.43	1 2	2.5 4.5	– –
06.072	– –	– –	– –	– –	– –	10 10	– –	– –	5 5	– –	– –	– –	– –	2 2		22	– –	2 2	– –

JECFA: The Joint FAO/WHO Expert Committee on Food Additives; FGE: Flavouring Group Evaluation; FL-no: FLAVIS number; FLAVIS: Flavour Information System (database).
(a): 'Normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages (Documentation provided to EFSA n. 5).
(b): Additional food category 05.3 (chewing-gum as per Annex II part D of Reg. (EC) 1333/2008) for which EFFA submitted use levels (Documentation provided to EFSA n. 2). 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)

SCF: Scientific Committee on Food.

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

- Beverages (SCF, 1995) correspond to food Table C.3): category 14.1
- Foods (SCF, 1995) correspond to the food categories 1, 2, 3, 4.1, 4.2, 6, 7, 8, 9, 10, 13, and/or 16
- Exception a (SCF, 1995) corresponds to food category 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		

mTAMDI: modified Theoretical Added Maximum Daily Intake; SCF: Scientific Committee on Food.

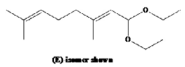
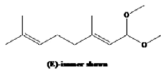
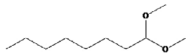
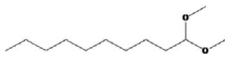
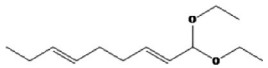
Table C.4: Estimated intakes based on the MSDI approach and the mTAMDI approach for substances in FGE.61Rev2

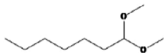
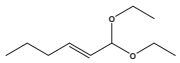
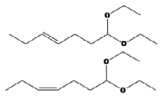
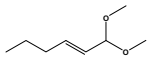
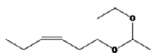
FL-no	EU Register name	MSDI EU[(a)] (μg/capita per day)	MSDI USA[(b)] (μg/capita per day)	mTAMDI[(c)] (μg/person per day)	Structural class	Threshold of concern (μg/person per day)
06.001	1,1-Diethoxyethane	200	640	–	Class I	1,800
06.004	Citral diethyl acetal	3.4	0	–	Class I	1,800
06.005	Citral dimethyl acetal	2.6	5	–	Class I	1,800
06.008	1,1-Dimethoxyoctane	0.97	0	–	Class I	1,800
06.009	1,1-Dimethoxydecane	0.024	0	–	Class I	1,800
06.015	1,1-Dimethoxyethane	61	11	–	Class I	1,800
06.025	1,1-Diethoxynona-2,6-diene	0.012	0.01	1,700	Class I	1,800
06.028	1,1-Dimethoxyheptane	0.037	0.26	–	Class I	1,800
06.031	1,1- Diethoxyhex-2-ene	0.012	–	1,700	Class I	1,800
06.037	1,1-Diethoxyhept-4-ene (*cis* and *trans*)	0.037	0	–	Class I	1,800
06.072	1,1- Dimethoxyhex-2(*trans*)-ene	0.012	–	1,700	Class I	1,800
06.081	(*Z*)-1-Ethoxy-1-(3-hexenyloxy)ethane	4.6	0	–	Class I	1,800

MSDI: Maximised Survey-derived Daily Intake; mTAMDI: modified Theoretical Added Maximum Daily Intake; FGE: Flavouring Group Evaluation; FL-no: FLAVIS number; FLAVIS: Flavour Information System (database).
(a): Based on EU production figures from JECFA (2002, 2005, 2007) and submitted by industry (Documentation provided to EFSA n. 3).
(b): Based on US production figures from JECFA (2002, 2005, 2007).
(c): Based on use levels submitted by industry (Documentation provided to EFSA n. 2).

Appendix D – Summary of safety evaluations

Table D.1: Summary of safety evaluations performed by JECFA (2002, 2005, 2007) and EFSA conclusions on flavouring substances in FGE.61 and its revisions

			JECFA conclusions	EFSA conclusion
FL-no JECFA-no	**EU Union List chemical name**	**Structural formula**	**Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI[c] approach**	**Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce**
06.001 941	1,1-Diethoxyethane		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	No safety concern Concluded in FGE.61
06.004 948	Citral diethyl acetal		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61Rev1
06.005 944	Citral dimethyl acetal		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61Rev1
06.008 942	1,1-Dimethoxyoctane		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61
06.009 945	1,1-Dimethoxydecane		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61
06.015 940	1,1-Dimethoxyethane		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61
6.025 946	1,1-Diethoxynona-2,6-diene		Class I A3: Intake below threshold No safety concern	No safety concern The chemical name should be changed and the purity requirement should be updated in the Union List (see 'EFSA comments' column in Table B.1 – Appendix B) Concluded in FGE.61Rev2

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 conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce
06.028 947	1,1-Dimethoxyheptane		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61
06.031 1383	1,1-Diethoxyhex-2-ene		Class I A3: Intake below threshold No safety concern	No safety concern The chemical name, CAS number should be changed and purity requirement should be updated (see 'EFSA comments' Table B.1 Appendix B) Concluded in FGE.61Rev2
06.037 949	1,1-Diethoxyhept-4-ene (*cis* and *trans*)		Class I A3: Intake below threshold No safety concern	No safety concern The chemical name, CAS number should be changed and purity requirement should be updated (see 'EFSA comments' Table B.1 Appendix B) Concluded in FGE.61
06.072 1728	1,1-Dimethoxyhex-2(*trans*)-ene		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61Rev2
06.081 943	(*Z*)-1-Ethoxy-1-(3-hexenyloxy)ethane		Class I A3: Intake below threshold No safety concern	No safety concern Concluded in FGE.61

MSDI: Maximised Survey-derived Daily Intake; JECFA: The Joint FAO/WHO Expert Committee on Food Additives; FGE: Flavouring Group Evaluation; FL-no: FLAVIS number; FLAVIS: Flavour Information System (database);
(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) × 10^9/(0.1 × population in Europe (= 375 × 10^6) × 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. 3 and 4).