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Scientific Opinion on Flavouring Group Evaluation 70, Revision 1 (FGE.70Rev1): consideration of aliphatic, linear, α,β-unsaturated, di- and trienals and related alcohols, acids and esters evaluated by JECFA (61st-68th-69th meeting)

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Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 29 flavouring substances attributed to the Flavouring Group Evaluation 70 (FGE.70), using the Procedure in Commission Regulation (EC) No 1565/2000. Seven substances have already been considered in FGE.70 [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840]. The remaining 22 substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] have been cleared with respect to genotoxicity in FGE.200Rev1 and FGE.203Rev2 and are considered in this revision. 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 29 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, except for [FL-no: 09.371 and 09.840]. For these two substances, data on the composition of the stereoisomeric mixture should be requested. Data on the identity and contents of secondary components should be requested for [FL no: 09.260]. Normal and maximum use levels should be provided for seven flavouring substances [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840]. For six flavouring substances [FL-no: 05.057, 05.058, 05.111, 05.120, 05.172 and 09.947] further information is required based on the comparison of the 'modified Theoretical Added Maximum Daily Intakes' (mTAMDIs) with the TTCs. This includes more reliable data on use and use levels and then, if required, additional toxicological data.

Keywords: flavourings, α,β-unsaturated carbonyls and precursors, FGE.70, JECFA

Requestor: European Commission

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1. Introduction

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of 22 α,β-unsaturated carbonyl substances or their precursors, i.e. [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573], which have been evaluated regarding genotoxicity in FGE.200Rev1 and 203Rev2. According to the Mandates and Terms of Reference of these two FGEs, 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 mandates for FGE.200Rev1 and FGE.203Rev2 are 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 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 that 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).

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

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

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

[4] Annex II refers here to the annex of the mandate letter from the EC to EFSA related to FGE.200Rev1.

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.

1.1.3. Background to Mandate from FGE.203Rev2 (M-2017-0003)

The use of flavouring 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 contains flavouring substances for which the scientific evaluation should be completed taking into account Commission Regulation (EC) No 1565/2000[1].

The genotoxicity of the twenty substances belonging to the group FGE.203 rev.1; alpha, beta-unsaturated aliphatic aldehydes and precursors from chemical subgroup 1.1.4 of FGE.19 were considered in the EFSA opinion of 26 March 2014.[5]

The Authority evaluated the genotoxicity of these substances on the basis of the data on the following two substances selected as representative of the group: the hexa-2(trans),4(trans)-dienal (FL-no: 05.057) and deca-2(trans),4(trans)-dienal (FL-no: 05.140). Overall, the Authority concluded that the safety concern regarding genotoxicity cannot be ruled out for both representative substances of the group and that this conclusion is likewise applicable to the other substances of this FGE.203.

These substances are included in the Union List with no restrictions.

Following this opinion, the applicant offered to carry out a number of additional toxicology studies to address the safety concerns raised in the opinion. This set of studies were not requested and not agreed with EFSA or the Commission.

The Commission requested information on poundage and use levels of the substances in order to calculate the exposure and quantify the risks. It also requested information regarding stereoisomerism in particular regarding the substances belonging to this group and not evaluated by JECFA and currently included in the Union List. This information is also attached in the submission.

The studies offered by industry and also the information requested by the Commission were submitted by industry on 22 September 2016.

The Commission submitted for vote at the Standing Committee on Plants, Animals, Food and Feed of the 25 November 2016 a draft Regulation amending the conditions of use of these substances establishing restrictions to the food categories actually in use and also establishing maximum levels for these uses (Ref Doc SANTE 10070/2016). This measure contains the exposure to these substances and also prevents further new uses. The measure was supported by a very substantial qualified majority of the Member States. The measure will continue its usual process of adoption.

1.1.4. Terms of Reference of Mandate from FGE.203Rev2 (M-2017-0003)

The European Commission requests the European Food Safety Authority (EFSA) to evaluate the studies in the submission and any new other safety information relevant, and depending on the outcome, proceed to the full evaluation on 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 Authority is also asked to characterise the hazards and also quantify the risks also in case its concern on genotoxicity cannot be ruled out and the EFSA CEF Panel procedure cannot be applied for any of the substances of the group.

1.2. Interpretation of the Terms of Reference

Flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947] were first allocated to FGE.200Rev1 for evaluation with respect to genotoxicity. Based on the new genotoxicity data submitted, the Panel concluded that these six 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.70 (FGE.70Rev1), in accordance with Commission Regulation (EC) No 1565/2000.

[5] Scientific Opinion on Flavouring Group Evaluation 203 Rev 1 (FGE.203 Rev1): alpha, beta-unsaturated aliphatic aldehydes and precursors from chemical subgroup 1.1.4 of FGE.19 with two or more conjugated double-bonds and with or without additional non-conjugated double-bonds. EFSA Journal 2014;12(4):3626, 31 pp. https://doi.org/10.2903/j.efsa.2014.32626. Available online: www.efsa.europa.eu/efsajournal

Flavouring substances [FL-no: 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] were first allocated to FGE.203Rev2 for evaluation with respect to genotoxicity. Based on the new genotoxicity data submitted, the Panel concluded that these sixteen 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.70 (FGE.70Rev1), in accordance with Commission Regulation (EC) No 1565/2000.

The above-mentioned flavouring substances belong to a group of structurally related substances which have been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in the past (JECFA, 2004a, 2007, 2008a) and which EFSA had already considered previously in FGE.70 (EFSA CEF Panel, 2009a). For substances that have been previously evaluated by JECFA, a full evaluation is not required but EFSA should consider whether the evaluation by JECFA can be agreed to or not. If not, EFSA should carry out a full evaluation of such substances (for further explanations see Appendix A).

In addition, since the publication of FGE.70, data on EU production volumes and data on stereoisomerism and/or compositional information of the isomers mixture have been provided by industry for the following four flavouring substances: [FL-no: 08.085, 09.371, 09.639 and 09.840]. Therefore, their safety evaluation through the Procedure can also be finalised in the current revision.

1.2.1. History of the evaluation of the substances in FGE.70

FGE.70 includes aliphatic, linear, α,β-unsaturated, di- and trienals and related alcohols, acids and esters, which have been evaluated before by JECFA in a group of 26 substances at their 61st meeting (JECFA, 2004a).

Two of the JECFA-evaluated substances were not in the Register.[6] These are (*E,E*)-2,4-octadien-1-ol and (*E,Z*)-2,6-nonadien-1-ol acetate (JECFA-no: 1180 and 1188). Seventeen substances are α,β-unsaturated aldehydes, or precursors, and they were considered by the Panel to be of concern for genotoxicity and were considered together with other α,β-unsaturated aldehydes and precursors in FGE.200 (EFSA CEF Panel, 2014a) and FGE.203 (EFSA CEF Panel, 2009b). Therefore, FGE.70 only dealt with seven dienoic and trienoic acids or esters thereof ([FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840]).

The Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) Panel concluded that no supporting FGE was available for the substances in FGE.70.

The Panel agreed with the way the application of the Procedure was performed by JECFA for all seven dienoic and trienoic acids or esters thereof dealt with in this opinion. However, for four substances [FL-no: 08.085, 09.371, 09.639 and 09.840], the Panel had reservations (no European production volumes available, preventing them to be evaluated using the Procedure, and/or missing data on stereoisomerism and/or compositional information of mixtures). For the remaining three substances [FL-no: 09.194, 09.260 and 09.300], the Panel agreed with the JECFA conclusion 'No safety concern at estimated levels of intake as flavouring substances, based on the MSDI approach'. For all seven substances, use levels are needed to calculate the modified Theoretical Added Maximum Daily Intake (mTAMDI) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

The seven substances that have been considered in FGE.70 will not be readdressed in the current revision, unless additional information is provided or data gaps are identified (e.g. on production volumes, use levels or specifications).

From the substances considered in the present revision of FGE.70 (FGE.70Rev1), 12 flavouring substances [FL-no: 02.139, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127 and 05.140] were evaluated by JECFA in its 61st meeting (JECFA, 2004a) and 3 of these substances [FL-no: 02.139, 02.162 and 02.188] were re-evaluated by JECFA in its 69th meeting (JECFA 2008a). These 12 candidate substances were evaluated by EFSA in FGE.203Rev2 for possible genotoxicity (EFSA CEF Panel, 2018). Additionally, five more substances from the 61st JECFA meeting [FL-no: 02.049, 05.058, 05.111, 05.120 and 05.172] were evaluated by EFSA in FGE.200Rev1 for possible genotoxicity (EFSA FAF Panel, 2018). The substance (*E,Z*)-2,6-nonadien-1-ol acetate (JECFA no. 1188), which was addressed by JECFA in its 61st and 69th meetings (JECFA, 2004a, 2008a), at that time was not in the Register.[6] This substance was added to the current revision 1 of FGE.70 as a newly notified substance in the EU ([FL-no: 09.947])[7]. In the meantime, this substance has been cleared for genotoxicity in FGE.200Rev1 (EFSA FAF Panel, 2018).

[6] Commission Decision 1999/217/EC.
[7] Mandate for 18 newly notified substances (NNS) sent by EC to EFSA in April 2009: 'Ref. SANCO/E3/SH/vj(2009) D/530356'.

In conclusion, these 18 flavouring substances were regarded of no genotoxic concern in FGE.200Rev1 (EFSA FAF Panel, 2018) and in FGE.203Rev2 (EFSA CEF Panel, 2018), and therefore, they can be evaluated in FGE.70Rev1 using the Procedure.

In addition, FGE.70Rev1 also considers four flavouring substances [FL-no: 02.153, 05.141, 05.173 and 09.573] evaluated by JECFA in its 68th meeting (JECFA, 2007). By expert judgement, they have been included in FGE.70Rev1 on the basis of their structural similarity with the substances considered in this group. These flavouring substances were considered of no genotoxic concern in FGE.203Rev2 (EFSA CEF Panel, 2018). Therefore, they can be evaluated through the Procedure.

Taken together with the seven substances that were already considered in FGE.70, the current revision comprises altogether 29 substances. However, the three flavouring substances for which the evaluation was finalised in FGE.70 will not further be discussed. For the sake of completion their information is maintained in the various tables in this FGE.

EU production volumes and/or data on stereoisomerism and/or compositional information of the isomers mixtures were provided for four flavouring substances [FL-no: 08.085, 09.371, 09.639 and 09.840], considered in the previous revision (FGE.70). This information will be included and considered in this revision 1 of FGE.70 (Documentation provided to EFSA n. 6 and 7).

FGE	Adopted by EFSA	Link	No. of Substances
FGE.70	23 July 2009	https://www.efsa.europa.eu/efsajournal/pub/1205	7
FGE.70Rev1	5 June 2019	http://www.efsa.europa.eu/en/efsajournal/pub/5749	29

FGE: Flavouring Group Evaluation.

2. Data and methodologies

2.1. Data

The present version of the opinion is based on the following data as provided by the applicant:

- Updated specifications and data on stability and on decomposition products submitted for 16 flavouring substances [FL-no: 02.139, 02.153, 02,162, 02.188, 05.157, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] in the context of FGE.203Rev2 application (Documentation provided to EFSA n. 4 and 5).
- JECFA specifications for six flavouring substances from FGE.200Rev1 [FL-no. 02.049, 05.058, 05.111, 05.120, 05.172 and 09.947] (JECFA, 2003, 2008b).
- Updated specifications related to the composition of stereoisomeric mixtures for flavouring substances [FL-no: 02.049, 02.139, 02.153, 02.162, 05.084, 05.120, 05.125, 05.173 and 05.071] submitted by the applicant during the assessment process in response to requests from EFSA sent on 6 February 2019 and 17 May 2019. (Documentation provided to EFSA n. 10 and 15).
- Updated specifications (data on stereoisomerism and/or compositional information of the isomers mixture) submitted for three flavouring substances [FL-no: 09.371, 09.639 and 09.840] following publication of the EFSA scientific opinion on FGE.70 (Documentation provided to EFSA n. 7).
- Poundage data and use levels submitted for six flavouring substances [FL-no. 02.049, 05.058, 05.111, 05.120, 05.172 and 09.947] in the context of FGE.200Rev1 application (Documentation provided to EFSA n. 1 and 2).
- Poundage data and use levels submitted for 16 flavouring substances [FL-no. 02.139, 02.153, 02,162, 02.188, 05.157, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] in the context of FGE.203Rev2 application (Documentation provided to EFSA n. 3).
- Poundage data submitted for three flavouring substances [FL-no: 08.085, 09.371 and 09.639] following publication of EFSA scientific opinion on FGE.70 (Documentation provided to EFSA n. 6).
- Absorption Distribution Metabolism and Excretion (ADME) data submitted for six flavouring substance [FL-no. 02.049, 05.058, 05.111, 05.120, 05.172 and 09.947] and toxicity data submitted for two flavouring substances [FL-no: 05.120, 05.064] in the context of FGE.200Rev1 application (Documentation provided to EFSA n. 8).
- Genotoxicity data evaluated in FGE.200, FGE.200Rev1, FGE.203, FGE.203Rev1 and FGE.203Rev2 [Refer to documentation provided to EFSA as reported in FGE.200 (EFSA CEF

Panel, 2014a), FGE.200Rev1 (EFSA FAF Panel, 2018), FGE.203 (EFSA CEF Panel, 2009b), FGE.203Rev1 (EFSA CEF Panel, 2014b) and FGE.203Rev2 (EFSA CEF Panel, 2018)].
- Toxicity data submitted for two flavouring substances [FL-no: 05.057 and 05.140] in the context of FGE.203Rev2 application (Documentation provided to EFSA n. 9).

The table below summarises all the data provided to EFSA for FGE.70Rev1:

FL-no	Chemical name	Data provided for the current revision 1 of FGE.70	Appendix (Table) and relevant section of the opinion
02.049	Nona-2,6-dien-1-ol	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1
05.058	Nona-2(*trans*),6(*cis*)-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1
05.111	Octa-2(*trans*),6(*trans*)-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1
05.120	Dodeca-2,6-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data, toxicity data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1 and Appendix E (Table E.1)
05.172	Nona-2(*trans*),6(*trans*)-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1
09.947	(*E,Z*)-2,6-Nonadienyl acetate	Specifications, EU poundage data (MSDI), use levels (mTAMDI), ADME data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Section 3.3.1
02.139	Deca-2,4-dien-1-ol	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
02.153	Hepta-2,4-dien-1-ol	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C1 and Table C.4)
02.162	Hexa-2,4-dien-1-ol	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
02.188	Nona-2,4-dien-1-ol	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.057	Hexa-2(*trans*),4(*trans*)-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), toxicity data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Appendix E (Table E.1 and Table E.3)
05.064	Trideca-2(*trans*),4(*cis*),7(*cis*)-trienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), toxicity data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Appendix E (Table E.1)
05.071	Nona-2,4-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.084	Hepta-2,4-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.101	Penta-2,4-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.108	Undeca-2,4-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.125	Dodeca-2,4-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.127	Octa-2(*trans*),4(*trans*)-dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.140	Deca-2(*trans*),4(*trans*)- dienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI), toxicity data	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4); Appendix E (Table E.1)

FL-no	Chemical name	Data provided for the current revision 1 of FGE.70	Appendix (Table) and relevant section of the opinion
05.141	Deca-2,4,7-trienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
05.173	Nona-2,4,6-trienal	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
08.085	(*E,E*)-Hexa-2,4-dienoic acid	EU poundage data (MSDI)	Appendix C (Table C.4)
09.371	Ethyl deca-2,4,7-trienoate	Specifications, EU poundage data (MSDI)	Appendix B (Table B.1); Appendix C (Table C.4)
09.573	Hexa-2,4-dienyl acetate	Specifications, EU poundage data (MSDI), use levels (mTAMDI)	Appendix B (Table B.1); Appendix C (Table C.1 and Table C.4)
09.639	Methyl (*E,Z*)-deca-2,4-dienoate	Specifications, EU poundage data (MSDI)	Appendix B (Table B.1); Appendix C (Table C.4)
09.840	Propyl 2,4-decadienoate	Specifications	Appendix B (Table B.1)

MSDI: maximised survey-derived daily intake; mTAMDI: modified Theoretical Added Maximum Daily Intake.

In addition, the following documentation was used:

- Scientific opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) on Flavouring Group Evaluation 70 (FGE.70): Consideration of aliphatic, alicyclic, linear, α,β-unsaturated, di- and trienals and related alcohols, acids and esters evaluated by JECFA (61st meeting). (EFSA CEF Panel, 2009a).
- Scientific opinion of the Panel on Food Additives and Flavourings (FAF) on re-evaluation of sorbic acid (E 200) and potassium sorbate (E 202) as food additives. (EFSA FAF Panel, 2019).

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 Guidelines 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 29 flavouring substances [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639, 09.840, 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] considered in the present opinion (FGE.70Rev1) (JECFA, 2003, 2008b).

EFSA considerations

Additional information on the purity, identity test (mass spectrometry (MS)), stereoisomerism and composition of the stereoisomeric mixtures have been submitted by the applicant for the following

flavouring substances: [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173, 09.639, 09.573] (Documentation provided to EFSA n. 4; 5; 7; 10 and 15). The Panel considered that the newly submitted specification data are adequate.

The most recent specifications data are summarised in Table B.1 – Appendix B.

For the following flavouring substances [FL-no: 02.139, 02.153, 05.084, 05.120, 05.125 and 05.173], the Panel noted that the chemical name should be changed in the EU Union list (UL) according to the most recent available information (see 'EFSA comments' column in Table B.1 – Appendix B). For flavouring substance [FL-no: 05.140], the Panel noted that the information on purity should be changed in the UL according to the most recent available information (see 'EFSA comments' column in Table B.1 – Appendix B)

For two flavouring substances [FL-no: 09.371 and 09.840], considered in the previous version of this FGE (FGE.70), the Panel noted that information on the composition of the stereoisomeric mixtures is still inadequate (Documentation provided to EFSA n. 7). Data on the identity and contents of secondary components should be requested for [FL no: 09.260] which was also previously considered in FGE.70.

3.2. Estimation of intake

JECFA status

For 26 flavouring substances [FL-no: 02.049, 02.139, 02.153, 02.162, 02.188, 05.057, 05.058, 05.064, 05.071, 05.084, 05.101, 05.108, 05.111, 05.120, 05.125, 05.127, 05.140, 05.141, 05.172, 05.173, 09.194, 09.260, 09.300, 09.573, 09.840 and 09.947], evaluated through the JECFA Procedure, intake data are available for the EU (JECFA, 2004a, 2007, 2008a).

For the remaining three flavouring substances [FL-no: 08.085, 09.371 and 09.639], production figures are only available for the USA.

EFSA considerations

Updated EU production figures for the 22 newly allocated flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] have been submitted by industry (Documentation provided to EFSA n. 1 and 3). Additionally, for three flavouring substances [FL-no: 08.085, 09.371 and 09.639], considered in the previous version of this FGE (FGE.70), EU production volumes have been provided (Documentation provided to EFSA n. 6) and therefore the MSDI values for EU can now be calculated.

For the 22 newly allocated flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947, 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573], normal and maximum use levels have been submitted (Documentation provided to EFSA n. 2 and 3) and mTAMDI intake values can be calculated.

The mTAMDI intake estimates resulted below to the threshold of concern for their structural class (I) for 16 flavouring substances [FL-no: 02.049, 02.139, 02.153, 02.162, 02.188, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573]. The remaining six flavouring substances [FL-no: 05.057, 05.058, 05.111, 05.120, 05.172 and 09.947] have mTAMDIs equal or above the threshold of concern. Therefore, for these flavouring substances, more reliable intake data 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 the seven flavouring substances ([FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840]) previously considered in FGE.70.

The MSDI figures and mTAMDI intake estimates for the 29 flavouring substances in FGE.70Rev1 are shown in Table C.4 – Appendix C.

3.3. Biological and toxicological data

3.3.1. ADME data

According to JECFA, (61st meeting), six 2,6-α,β-unsaturated flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 09.947 and 05.172] can be anticipated to be metabolised to innocuous substances through normal fatty acid metabolism, including β-oxidation and citric acid cycle, which finally leads to their total oxidation. In addition to the oxidative metabolism, also conjugation with

glutathione (GSH) has been described. The relevant data are summarised in the 61st JECFA toxicology monograph (JECFA, 2004b) and in FGE.200Rev1 (EFSA FAF Panel, 2018). Based on this information, JECFA concluded that these flavouring substances, discussed in the reports of their 61st and 69th meeting (JECFA, 2004a, 2008a) and now subject of this revision of FGE.70, can be evaluated along the A-side of the Procedure (see Appendix A). With respect to the sixteen 2,4 α,β-unsaturated derivatives, i.e. flavouring substances [FL-no: 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573], considered by JECFA in its 61st, 68th and 69th meeting, JECFA suggested that these cannot be predicted to be metabolised to innocuous products and therefore the evaluation proceeded via the B-side of the decision tree (JECFA, 2004a, 2007, 2008a).

EFSA considerations

In line with JECFA, the FAF Panel considers the six 2,6-α,β-unsaturated flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 09.947 and 05.172] in FGE.70Rev1, to be expected to be metabolised to innocuous products and hence to evaluate these substances along the A-side of the Procedure. For the sixteen 2,4-α,β-unsaturated derivatives in FGE.70Rev1, the Panel is of the opinion that the routes of the metabolism that JECFA described for these substances do not differ from those that JECFA mentioned for the 2,6-α,β-unsaturated substances and these substances were evaluated via the A-side. Moreover, the sixteen 2,4-α,β-unsaturated derivatives will be converted to the corresponding carboxylic acids and JECFA evaluated these compounds also via the A-side of the Procedure (JECFA, 2004a).

The Panel reconsidered the potential reactivity and metabolism of the 22 flavouring substances under evaluation in FGE.70Rev1. Although these substances can react with GSH and other cell constituents, among which DNA through Michael addition, the levels of the exposure are not high enough to result in GSH depletion that could lead to oxidative stress. Possible reactivity with DNA is not of concern because these substances are not genotoxic (EFSA CEF Panel, 2018 and EFSA FAF Panel, 2018). As far as toxicity data are available for substances in this FGE, their toxicity is less than predicted from their chemical structure based on the Cramer class TTC (Appendix E). The Panel concluded that these 16 flavouring substances can be evaluated via the A-side of the Procedure.

3.3.2. Genotoxicity data

This revision involves the inclusion of 22 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 22 flavouring substances needed further attention in FGE.200 or FGE.203.

The genotoxicity of flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172 and 09.947] has been assessed in FGE.200 (EFSA CEF Panel, 2014a) and FGE.200Rev1 (EFSA FAF Panel, 2018). Based on the genotoxicity data submitted, the Panel concluded that the concern with respect to genotoxicity could be ruled out for these flavouring substances.

The genotoxicity of flavouring substances [FL-no: 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] has been assessed in FGE.203 (EFSA CEF Panel, 2009b), FGE.203Rev1 (EFSA CEF Panel, 2014b) and FGE.203Rev2 (EFSA CEF Panel, 2018). Based on the genotoxicity data submitted, the Panel concluded that the concern with respect to genotoxicity could be ruled out for these flavouring substances.

Therefore, it is concluded that all 22 flavouring substances can now be evaluated through the Procedure.

3.3.3. Toxicological data

3.3.3.1. Repeated dose toxicity studies

In the JECFA evaluations at its 61st, 68th and 69th meetings (JECFA 2004a, 2007, 2008a), toxicity studies on 2,4-hexadienal [FL-no: 05.057], deca-2(*trans*),4(*trans*)-dienal [FL-no: 05.140], trideca-2(*trans*),4(*cis*),7(*cis*)-trienal [FL-no: 05.064] and 2-*trans*-6-*cis*-dodecadienal [FL-no: 05.120] were considered. These studies are fully described in the 61st JECFA toxicology monograph (JECFA, 2004b). According to JECFA, these studies have provided adequate 'No Observed Adverse Effect Levels'

(NOAELs) for the flavouring substances, and structurally related substances, evaluated along B-side of the Procedure (see Table E.1 – Appendix E).

EFSA considerations

In relation to the 14-week NTP study on 2,4-hexadienal [FL-no: 05.057] in rats and mice (NTP, 2003), JECFA derived NOAELs of 15 mg/kg body weight (bw) per day and 60 mg/kg bw per day for male and female rats, respectively. However, the Panel considered that based on the magnitude of the observed effect (body weight changes), which was only observed in male rats, the NOAEL in this study should be set at 60 mg/kg bw per day. Concerning the results observed in mice, JECFA derived a NOAEL at 30 mg/kg bw per day for male mice based on an increased absolute and relative organ weights. For female mice, JECFA did not derive a 'No Observed Effect Level' (NOEL) owing to the increased relative liver weights observed at all doses. However, the Panel noted that there was no indication of histopathological or clinical changes at any doses.

One of the flavouring substances evaluated in the previous revision of this FGE (FGE.70), i.e. (*E,E*)-hexa-2,4-dienoic acid [FL-no: 08.085], has been re-evaluated as preservative food additive (E200, sorbic acid) by FAF Panel (EFSA FAF Panel, 2019). The FAF Panel established a group ADI expressed as 11 mg sorbic acid/kg bw per day for sorbic acid (E 200) and its potassium salt (E 202), based on a lower confidence limit of the benchmark dose (BMDL) for reduced pup weight observed in an extended one-generation reproductive toxicity assay (EFSA FAF Panel, 2019). The Panel noted that the new ADI for sorbic acid is orders of magnitude higher than the exposure (estimated with the MSDI approach) related to the use of sorbic acid as flavouring substance (i.e. 1.01 μg/kg bw per day, see Table C.4 – Appendix C).

The relevant data on the above-mentioned reproductive toxicity study are summarised in Table E.2 – Appendix E.

The Panel considers the toxicity data coming from these studies consistent with the outcome of the Procedure for the safety evaluation of the flavouring substances in FGE.70Rev1.

All the available toxicity studies from JECFA are summarised in Table E.1 – Appendix E.

3.3.3.2. Carcinogenicity studies

One carcinogenicity study is available on hexa-2(*trans*),4(*trans*)-dienal [FL-no: 05.057] (NTP, 2003) already considered in FGE.203 (EFSA CEF Panel, 2009b). This study has also been considered by JECFA at their 61st meeting (JECFA, 2004a). JECFA reached the conclusion that the induction of neoplasms in the forestomach of rodents by this substance was not relevant for humans. In addition, EFSA in FGE.203Rev2 (EFSA CEF Panel, 2018) considered induction of squamous cell carcinomas of the tongue in two mice in the high-dose group.

EFSA considerations

Since the concern for genotoxicity could be ruled out for 2,4-hexadienal [FL-no: 05.057] in FGE.203Rev2, the Panel concluded that the effects induced by 2,4-hexadienal [FL-no: 05.057] in the 2-year carcinogenicity study (NTP, 2003) (i.e. increased incidence of neoplasms in the forestomach of male and female rats and mice; squamous cell carcinoma of the tongue observed in two mice of the high-dose group) are not due to a genotoxic activity of the substance. JECFA concluded that the carcinogenic effects of this substance are related to high local concentrations and subsequent tissue irritation. The FAF Panel concurs with this view.

The applicant provided studies on a slug mucosa irritation assay for 2,4-hexadienal [FL-no: 05.057], and four structurally related substances (documentation provided to EFSA n. 12; 13 and 14; FGE.203Rev2 (EFSA CEF Panel, 2018)) to support the hypothesis that neoplasm in the forestomach observed in the carcinogenicity study (NTP, 2003) was due to local irritation. The Panel noted that the slug mucosa irritation assay was developed to predict the mucosal irritation potency of pharmaceutical formulations and ingredients. This assay has not been validated for the assessment of carcinogenicity and is not further considered for this FGE.

The relevant data on carcinogenicity are summarised in Table E.3 – Appendix E.

3.4. Application of the Procedure

Application of the Procedure to twenty-two Aliphatic, Linear, α,β-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters by JECFA (2004a, 2007, 2008a)

In the respective meeting reports where the 22 flavouring substances included in this revision of FGE.70 are discussed, JECFA allocated all the flavouring substances to structural class I, using the decision tree approach presented by Cramer et al. (1978).

JECFA concluded for flavouring substances [FL-no: 02.049, 05.058, 05.111, 05.120, 05.172 and 09.947], that these can be anticipated to be metabolised to innocuous products (step A2) and the intakes (MSDIs) for all substances are below the threshold of concern for substances from structural class I (i.e. 1,800 μg/person per day) (step A3).

JECFA concluded for flavouring substances [FL-no: 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573] that these substances are not expected to be metabolised to innocuous products (step B2) and the intakes (MSDIs) are below the threshold of concern for the structural class I (step B3). JECFA concluded these substances at step B4 of the Procedure as adequate NOEALs for these substances or structurally related substances exist, which provide adequate margins of safety. Overall, JECFA evaluated all the 22 substances as to be of no safety concern.

The JECFA safety evaluations of the 22 substances, i.e. α,β-unsaturated aldehydes, dienals, alcohols and esters are summarised in Table D.1 – Appendix D.

EFSA considerations

The FAF Panel agrees with JECFA with respect to the allocation of the 22 candidate flavouring substances in 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: 02.049, 05.058, 05.111, 05.120, 05.172, 09.947]. For flavouring substances [FL-no: 02.139, 02.153, 02.162, 02.188, 05.057, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 05.141, 05.173 and 09.573], which JECFA evaluated along B-side of the Procedure, the FAF Panel deviates from JECFA and decides that these substances can be evaluated along the A-side of the Procedure as well (see Section 3.3.2).

The MSDI exposure estimates for the 22 flavouring substances are all below the threshold of concern for structural class I (see Table C.4 – Appendix C). Therefore, the FAF Panel concludes at step A3 of the Procedure 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.

4. Conclusions

This revision 1 of FGE.70 comprises in total 29 flavouring substances, 7 of which have already been considered before in FGE.70. The remaining 22 substances have been included in this revision, following an extensive evaluation in FGE.200Rev1 and FGE203Rev2 of their genotoxic potential due to a structural alert for genotoxicity (i.e. α,β-unsaturated carbonyl compounds and 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.70 (FGE.70Rev1) do not raise a safety concern at step A3 of the Procedure.

For all 22 substances considered in FGE.70Rev1, normal and maximum use levels have been provided, from which mTAMDI exposure estimates have been calculated. For 16 substances [FL-no: 02.049, 02.139, 02.162, 02.188, 05.064, 05.071, 05.084, 05.101, 05.108, 05.125, 05.127, 05.140, 02.153, 05.141, 05.173 and 09.573] the mTAMDI values are below the threshold of concern for their structural class (I). For six substances [FL-no: 05.057, 05.058, 05.111, 05.120, 05.172 and 09.947], the mTAMDIs are equal or above the threshold of concern. For these substances, more detailed information on uses is necessary to refine the exposure assessment and to finalise their evaluation. For the previously (in FGE.70) considered seven substances [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840], no normal or maximum use levels have been provided. For these seven substances normal and maximum use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusions for the 29 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 26 substances. For two substances [FL-no: 09.371 and 09.840], evaluated in FGE.70, information on the composition of the stereoisomeric mixtures is missing. For [FL no: 09.260], as well evaluated in FGE.70, the identity and

contents of secondary components should be clarified. In conclusion, for 26 flavouring substances in FGE.70Rev1 the Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach. For the remaining three flavouring substances [FL-no: 09.260, 09.371 and 09.840], considered in FGE.70, the Panel has reservations as there is incomplete information on their chemical identity.

5. Recommendations

- Normal and maximum use levels should be requested for [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840].
- More reliable data on use and use levels should be requested for [FL-no: 05.057, 05.058, 05.111, 05.120, 05.172 and 09.947], as the mTAMDI exposure estimates are equal or above the threshold of concern for structural class I.
- Data on the composition of the stereoisomeric mixtures should be requested for [FL-no: 09.371 and 09.840].
- Data on the identity and contents of secondary components should be requested for [FL no: 09.260]
- When the above data are received the assessment for these flavouring substances should be updated accordingly and expanded if necessary. This may include the need for additional toxicology data.
- In accordance with the latest information provided by the industry, the chemical name in the UL of flavouring substances [FL-no: 02.139, 02.153, 05.084, 05.120, 05.125 and 05.173] should be changed as indicated in Table B.1 of Appendix B ('EFSA comments').
- In accordance with the latest information provided by the industry, the information on the purity in the UL for flavouring substance [FL-no: 05.140] should be changed as indicated in Table B.1 of Appendix B ('EFSA comments').

Documentation provided to EFSA

1) 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.
2) EFFA (European Flavour Association), 2017a. Use levels survey for 84 substances from FGE.200. Unpublished data submitted from EFFA to EFSA. Dated 31/07/17.
3) EFFA (European Flavour Association), 2016 h. Aggregated Poundage (Volume of use) for 16 substances from FGE.203 for 2010 to 2015. Unpublished data submitted from EFFA to EFSA. dated 21/09/16.
4) EFFA (European Flavour Association), 2016i. Identification, characterisation and isomerism of 21 substances from FGE.203. Unpublished data submitted from EFFA to EFSA. Dated 21/09/16.
5) EFFA (European Flavour Association), 2018b. Stability and decomposition data for two representative substances from FGE.203. Unpublished data submitted from EFFA to EFSA. dated 15/02/18.
6) EFFA (European Flavour Association), 2010c. European production volumes for selected flavouring substances (footnote 8 substances). Private communication from EFFA to DG SANCO. February 2010.
7) EFFA (European Flavour Association), 2010a. EFFA Letters to EFSA on clarification of specifications and isomerism for which data were requested in published FGEs.
8) EFFA (European Flavour Association), 2017. Submission by the European Flavour Association to the European Food Safety Authority. Flavouring Group Evaluation 19 Subgroup 1.1.1(corresponding to FGE.200): Addendum to Flavouring Group Evaluation 19 Subgroup 1.1.1: 74 Flavouring Substances (Flavouring Substances) of the Chemical Group 3 (Annex I of 1565/2000/EC) Structurally Related to Straight-Chain Aliphatic Acyclic alpha,beta-Unsaturated Aldehydes, with or without Non Conjugated Double Bonds, Used as Flavouring Substances. 14 August 2017.
9) EFFA (European Flavour Association), 2013. Submission toxicity data on FGE.19 materials: Subgroup 1.1.4 – FGE.203.

10) EFFA (European Flavour Association), 2019. EFFA submission of additional information on isomeric composition of substances within FGE.203Rev2 (FGE.19 Subgroup 1.1.4) (FGE.70Rev1).
11) 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.
12) Adriaens E, 2013. Slug mucosal irritation assay, 1 day stinging itching burning. InvertTox study number: 13D26. Unpublished report submitted by EFFA to EFSA.
13) Adriaens E, 2014a. Slug mucosal irritation assay, 1 day stinging itching burning. InvertTox study number: 14F13. Unpublished report submitted by EFFA to EFSA
14) Adriaens E, 2014b. Slug mucosal irritation assay, 1 day stinging itching burning. InvertTox study number: 14I26. Unpublished report submitted by EFFA to EFSA.
15) EFFA (European Flavour Association), 2019. EFFA Submission of additional information on isomeric composition of substances within FGE.70 Rev1 (FGE.19 Subgroup 1.1.1 & 1.1.4)

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Edwards KB, 1973. Biological evaluation of 2,6-dodecadienal and 2,4,7-tridecatrienal. 4-week feeding study in rats. Unpublished report. Private communication to the Flavor and Extract Manufacturers Association. Submitted to WHO by the Flavor and Extract Manufacturers Association of the United States. , Washington DC, USA.

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2009a. Scientific Opinion on Flavouring Group Evaluation 70 (FGE.70): Consideration of aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters evaluated by JECFA (61st meeting). (Commission Regulation (EC) No 1565/2000 of 18 July). Adopted on 23 July 2009. EFSA-Q-2008-054. EFSA Journal 2009;7(9):1205, 19 pp. https://doi.org/10.2903/j.efsa.2009.1205

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EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2014b. Scientific Opinion on Flavouring Group Evaluation 203 Revision 1 (FGE.203Rev1): α,β-Unsaturated aliphatic aldehydes and precursors from chemical subgroup 1.1.4 of FGE.19 with two or more conjugated double-bonds and with or without additional non-conjugated double-bonds. EFSA Journal 2014;12(4):3626, 31 pp. https://doi.org/10.2903/j.efsa.2014.3626

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2018. Scientific Opinion on Flavouring Group Evaluation 203, Revision 2 (FGE.203Rev2): a,b-unsaturated aliphatic aldehydes and precursors from chemical subgroup 1.1.4 of FGE.19 with two or more conjugated double-bonds and with or without additional non-conjugated double-bonds. EFSA Journal 2018;16(7):5322, 39 pp. https://doi.org/10.2903/j.efsa.2018.5322

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Abbreviations

ADME	Absorption Distribution Metabolism and Excretion
BMDL	lower confidence limit of the benchmark dose
BMR	benchmark response
bw	body weight
CAS	Chemical Abstract Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids

CoE	Council of Europe
EFFA	European Flavour and Fragrance Association
FAF	EFSA 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)
GLP	Good Laboratory Practice
GSH	glutathione
ID	identity
IOFI	International Organization of the Flavour Industry
IR	infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MS	mass spectrometry
MSDI	maximised survey-derived daily intake
mTAMDI	modified Theoretical Added Maximum Daily Intake
MTD	maximum tolerated dose
NMR	nuclear magnetic resonance
No	number
NOAEL	no observed adverse effect level
NOEL	no observed effect level
(Q)SAR	(quantitative) structure–activity relationship
SCF	Scientific Committee on Food
TTC	toxicological thresholds of concern
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'.[8]

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[9] products (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous[9] (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.

[8] 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.

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

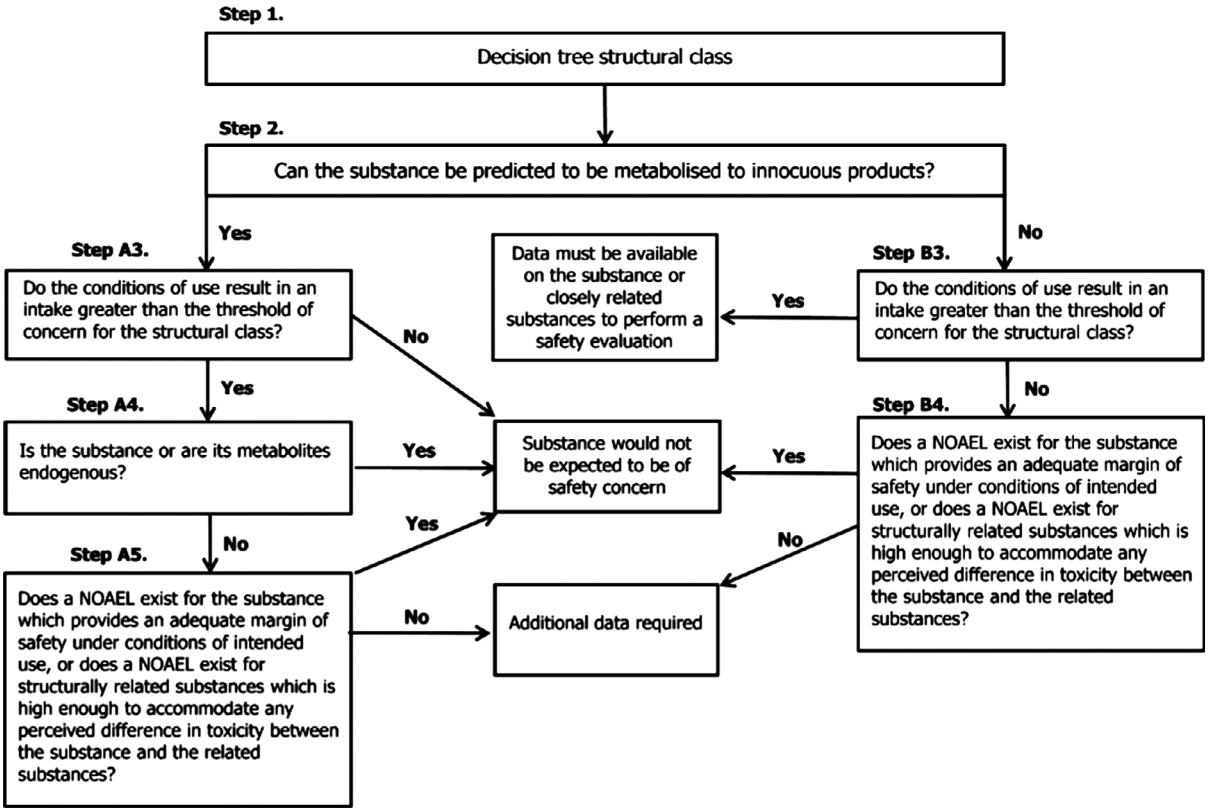


Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances.

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)[10] 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 of flavouring substances[11] 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,

[10] 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.

[11] 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.

considered 'how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods' (JECFA, 2006).

In the absence of more accurate information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a modified Theoretical Added Maximum Daily Intake (mTAMDI) approach based on the normal use levels reported by Industry (see Appendix C.2).

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

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

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

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

c) *Genotoxicity*

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

d) *Specifications*

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

e) *Structural Relationship*

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

Appendix B – Specifications

Table B.1: Summary table on specifications data for flavouring substances in FGE.70Rev1

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				
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]**	**EFSA Comments**
02.049 1184 2780 589 7786-44-9	Nona-2,6-dien-1-ol	[b]	Liquid $C_9H_{16}O$ 140.23	Insoluble Soluble	196 – IR NMR 95% not less than 92% (2*E*,6*Z*), 3-5% (2*E*,6*E*) < 3% (2*Z*,6*Z*) and (2*Z*,6*E*)	1.463–1.465 0.860–0.880	
02.139 1189 3911 11748 18409-21-7	Deca-2,4-dien-1-ol	[b]	Liquid $C_{10}H_{18}O$ 154.25	Insoluble Soluble	112 (13 hPa) – IR NMR MS 95% (sum of isomers) 92–95% (2*E*,4*E*); 2–5% (2*E*,4*Z*); 2–5% (2*Z*,4*E*); 0–2% (2*Z*,4*Z*)	1.485–1.495 0.861–0.871	The chemical name in the UL should be changed to deca-(2*E*,4*E*)-dien-1-ol, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)
02.153 1784 33467-79-7	Hepta-2,4-dien-1-ol	[b]	Liquid $C_7H_{12}O$ 112.17	Freely soluble	80 (19 hPa) – MS 95% 90–98% (2*E*,4*E*); 2–10% (2*E*,4*Z*); 2–10% (2*Z*,4*E*); 0–2% (2*Z*,4*Z*)	1.487–1.493	The chemical name in the UL should be changed to Hepta-(2*E*,4*E*)-dien-1-ol, in accordance with the CAs nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)

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]**	
02.162 1174 3922 111-28-4	Hexa-2,4-dien-1-ol	[b]	Solid $C_6H_{10}O$ 98.16	Insoluble Soluble	– 24–33 IR NMR MS 95% 95% or greater (2*E*,4*E*), up to 5% of (2*E*,4*Z*), < 3% (2*Z*,4*E*) and (2*Z*,4*Z*)	– –	
02.188 1183 3951 11802 62488-56-6	Nona-2,4-dien-1-ol	At least 92%; secondary component 3-4% 2-nonen-1-ol	Liquid $C_9H_{16}O$ 140.23	Insoluble Soluble	85 (0.7 hPa) – IR NMR MS 92% SC: 3–4% 2-nonen-1-ol	1.486–1.496 0.862–0.872	
05.057 1175 3429 640 142-83-6	Hexa-2 (*trans*),4 (*trans*)-dienal	[b]	Liquid C_6H_8O 96.13	Slightly soluble Soluble	64 (20 hPa) – MS 97% SC:(2–5%) hexa-(2*E*,4*Z*)-dienal, (1%) hexa-(2*Z*,4*Z*)- dienal, (1%) hexa-(2*Z*,4*E*)-dienal, (0.1%) 2,4-hexadecanoic acid)	1.538–1.543 0.896–0.902 (20°)	
05.058 1186 3377 659 557-48-2	Nona-2 (*trans*),6(*cis*)-dienal	At least 92%; secondary component 4-7% (*E,E*)-2,6-nonadienal	Liquid $C_9H_{14}O$ 138.21	Insoluble Soluble	94 – IR 92% SC: 4–7% (*E,E*)-2,6-nonadienal	1.470–1.475 0.850–0.870	

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]**	
05.064 1198 3638 685 13552-96-0	Trideca-2 (*trans*),4 (*cis*),7(*cis*)-trienal	At least 71%; secondary components 14% 4-*cis*-7-*cis*-tridecadienol; 6% 3-*cis*-7-*cis*-tridecadienol; 5% 2-*trans*-7-*cis*-tridecadienal; 3% 2-*trans*-4-*trans*-7-*cis*-tridecatrienal	Liquid $C_{13}H_{20}O$ 192.30	Insoluble Soluble	138 (0.4 hPa) – NMR MS 71% SC:14% (4Z,7Z)-tridecadienol; 6% (3Z,7Z)-tridecadienol; 5% (2E,7Z)-tridecadienal; 3% (2E,4E,7Z)-tridecatrienal	1.472–1.478 0.801–0.809	
05.071 1185 3212 732 6750-03-4	Nona-2,4-dienal	At least 89%; secondary components 5-6% 2,4-nonadien-1-ol and 1-2% 2-nonen-1-ol	Liquid $C_9H_{14}O$ 138.21	Insoluble Soluble	97 (13 hPa) – IR MS 89% 90–98% (2*E*,4*E*); 0.1–9% (2*E*,4*Z*); 0.1–9% (2*Z*,4*E*); 0–2% (2*Z*,4*Z*)	1.522–1.525 0.850–0.870	
05.084 1179 3164 729 4313-03-5	Hepta-2,4-dienal	At least 92%; Secondary components 2-4% (*E,Z*)-2,4-heptadienal and 2-4% 2,4-heptadienoic acid	Liquid $C_7H_{10}O$ 110.16	Insoluble Soluble	84 (1 hPa) – IR MS 92% 92–100% (2E,4E); 0.1–7% (2E,4Z); 1–5% (2Z,4E); 0–2% (2Z,4Z)	1.478–1.480 0.822–0.828	The chemical name in the UL should be changed to Hepta-(2*E*,4*E*)-dienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				
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]**	**EFSA Comments**
05.101 1173 3217 11695 764-40-9	Penta-2,4-dienal	[b]	Liquid C_5H_6O 82.13	n.a. Soluble	60 (91 hPa) – NMR MS 95% (predominantly *E,E*)	1.525–1.532 0.801–0.809	
05.108 1195 3422 10385 13162-46-4	Undeca-2,4-dienal	[b]	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Soluble	129 (17 hPa) – NMR MS 95% sum of isomers. Up to 95% (*E,E*) with (5-10%) (*E,Z*)	1.500–1.505 0.896–0.906	
05.111 1182 3466 10371 56767-18-1	Octa-2 (*trans*),6 (*trans*)-dienal	[b]	Liquid $C_8H_{12}O$ 124.19	Insoluble Soluble	97-99 (5 hPa) – IR NMR 96%	1.469–1.475 0.835–0.841	
05.120 1197 3637 21662-13-5	Dodeca-2,6-dienal	[b]	Liquid $C_{12}H_{20}O$ 180.28	Insoluble Soluble	130 (7 hPa) – NMR 97% > 95% (2*E*,6*Z*)-Dodeca-2,6-dienal	1.425–1.431 0.987–0.993	The chemical name in the UL should be changed to Dodeca-(2*E*,6*Z*)-dienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				
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]**	**EFSA Comments**
05.125 1196 3670 11758 21662-16-8	Dodeca-2,4-dienal	At least 85%; secondary component 11–12% 2-*trans*-4-*cis* isomer	Liquid $C_{12}H_{20}O$ 180.28	Slightly soluble Soluble Miscible in oils	130 – IR NMR MS 85% 90–98% (2*E*,4*E*); 0.1–9% (2*E*,4*Z*); 0.1–9% (2*Z*,4*E*); 0–2% (2*Z*,4*Z*)	1.470–1.476 0.983–0.989	The chemical name in the UL should be changed to Dodeca-(2*E*,4*E*)-dienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)
05.127 1181 3721 11805 30361-28-5	Octa-2 (*trans*),4 (*trans*)-dienal	[b]	Liquid $C_8H_{12}O$ 124.18	Insoluble Soluble	105–106 (10 hPa) – IR NMR MS 95% (90–98%) (*E,E*) with (0.1–8%) (*E,Z*)	1.519–1.525 0.832–0.839	
05.140 1190 3135 2120 25152-84-5	Deca-2 (*trans*),4 (*trans*)-dienal	At least 89%, Secondary components (3-4%) mixture of (2*Z*,4*Z*), (2*Z*,4*E*) and(2*E*,4*Z*) - decadienals; (3-4%) acetone plus trace of isopropanol	Liquid $C_{10}H_{16}O$ 152.24	Insoluble Soluble	104 – IR MS minimum 90% of the (*E,E*)-isomer and min. 95% (sum of isomers); SC: 4–5% (2*E*,4*Z*); < 1% (2Z,4Z); < 0.5% (2*Z*,4*E*); < 0,1% 2,4-decadienoic acid	1.512–1.517 0.866–0.876	The minimum purity assay should be updated to 90% minimum of the (*E, E*)-isomer; 95% (sum of isomers), in accordance with the latest data provided (Documentation provided to EFSA nr: 5)
05.141 1786 4089 51325-37-2	Deca-2,4,7-trienal	[b]	Liquid $C_{10}H_{14}O$ 150.22	Very slightly soluble Very soluble	233 – IR NMR MS 95% (81–83%) (6*E*,4*E*,7*Z*) (5–6%) (2*E*,4*Z*,7*Z*); (10–11%) (2*E*,4*E*,7E)	1.538–1.544 0.898–0.905	

Information included in the EU Union List Regulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				
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]**	**EFSA Comments**
05.172 1187 3766 17587-33-6	Nona-2 (*trans*),6 (*trans*)-dienal	[b]	Liquid $C_9H_{14}O$ 138.21	Insoluble Soluble	88 (14 hPa) – NMR 97%	1.439–1.445 0.856–0.864	
05.173 1785 4187 57018-53-8	Nona-2,4,6-trienal	[b]	Liquid $C_9H_{12}O$ 136.19	Freely soluble	194 – MS 95% (sum of isomers) > 95% (2*E*,4*E*,6*E*); < 5% other isomers; 0–1% (2*Z*,4*Z*,6*Z*)	1.550–1.556 0.867–0.873	The chemical name in the UL should be changed to Nona-(2*E*,4*E*,6*E*)-trienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10)
08.085 1176 3921 110-44-1	(*E,E*)-Hexa-2,4-dienoic acid	[b]	Solid $C_6H_8O_2$ 112.13	Slightly soluble Soluble	– 132–135 IR NMR 99%	– –	This flavouring substance is also called sorbic acid and corresponds to food additive (E-200)
09.194 1178 2459 635 2396-84-1	Ethyl (*E,E*)-hexa-2,4-dienoic acid	[b]	Liquid $C_8H_{12}O_2$ 140.18	Slightly soluble Soluble	195–196 – IR MS 98%	1.491–1.498 0.936–0.939	
09.260 1192 3148 10574 3025-30-7	Ethyl (*E,Z*)-deca-2,4-dienoate	[b]	Liquid $C_{12}H_{20}O_2$ 196.29	Insoluble	120 (9 hPa) – NMR 90% SC: (*E,E*)-ethyl 2,4-decadienoate	1.480–1.1486 0.917–0.920	The purity and content of the secondary components should be clarified

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]**	
09.300 1177 3714 689-89-4	Methyl (*E,E*)-hexa-2,4-dienoic acid	[b]	Liquid $C_7H_{10}O_2$ 126.16	Slightly soluble Soluble	180 – IR NMR 99%	1.501–1.505 0.933–0.938	
09.371 1193 3832 10576 78417-28-4	Ethyl deca-2,4,7-trienoate	[b]	Liquid $C_{12}H_{18}O_2$ 194.28	Soluble Soluble	134 (18 hPa) – IR NMR 95% (Mixture of (*Z*)- and (*E*)-isomer for all three C=C double bonds)	1.547–1.554 0.933–0.939	CAS nr in Union List does not specify stereoisomeric composition. Composition of stereoisomeric mixture to be specified
09.573 1780 10675 1516-17-2	Hexa-2,4-dienyl acetate	[b]	Liquid $C_{10}H_{20}O_2$ 140.18	Freely soluble	80 (20 hPa) – MS 95% (predominantly *E,E*-isomer)	1.470–1.476 0.908–0.914	
09.639 1191 3859 4493-42-9	Methyl (*E,Z*)-deca-2,4-dienoate	At least 93%; secondary component 2–5% (*E,E*) methyl 2,4-decadienoate	Liquid $C_{11}H_{18}O_2$ 182.26	Insoluble Soluble	67 (1 hPa) – IR NMR 93% (Material in commerce is min. 93% pure (2*E*,4*Z*)-isomer. Min. Purity > 95% (sum of isomers: other isomer mainly (2*E*,4*E*)-isomer)	1.488–1.494 0.917–0.923	
09.840 1194 3648 10889 84788-08-9	Propyl 2,4-decadienoate	[b]	Liquid $C_{13}H_{22}O_2$ 210.32	Insoluble Soluble	110 (0.5 hPa) – NMR 95% (Mixture of (*Z*)- and (*E*)-isomer for two C = C-double bonds)	1.468–1.475 0.913–0.919	Composition of the stereoisomeric mixture to be specified

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]**	
09.947 1188 3952 68555-65-7	(*E,Z*)-2,6-Nonadienyl acetate	[b]	Liquid $C_{11}H_{18}O_2$ 182.26	Sparingly soluble Soluble	231 - IR NMR MS 95%	1.448–1.458 0.905–0.907	

FGE: Flavouring Group Evaluation; FL-no: FLAVIS number; FLAVIS: Flavour Information System; 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; NMR: nuclear magnetic resonance; MS: mass spectrometry.
(a): JECFA (2003, 2007) and Documentation provided to EFSA nr.4;5;7;10 and 15.
(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 1013.25 hPa, if not otherwise stated.
(f): At 20°C, if not otherwise stated.
(g): At 25°C, if not otherwise stated.
(h): SC: 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.70Rev1 in food categories listed in Annex III of Reg. (EC) 1565/2000 (Documentation provided to EFSA n. 2 and 3)

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**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
02.049	0.42 0.89	0.05 0.05	– –	– –	0.02 0.03	0.44 1.04	0.17 0.54	0.25 0.63	– –	– –	– –	– –	0.01 0.01	– –	0.15 0.53	0.19 0.48	0.02 0.03	– –
02.139	– –	0.3 1.5	1 5	– –	– –	2 9	– –	3 15	1 5	– –	– –	– –	1 3	– –	0.5 2	0.1 1	– –	0.5 2
02.153	3 35	2 25	3 30	– –	2 50	4 50	2 25	5 50	1 10	1 10	– –	– –	2 100	0 0	2 25	0 0	5 50	2 25
02.162	– –	– –	1 4	– –	0.5 2	0.5 2	– –	– –	– –	– –	– –	– –	1 4	– –	1 4	0.2 1	0.1 1	0.5 2
02.188	0.5 2	1 5	1 5	– –	1 5	2 10	0.2 1	3 14.5	1 5	– –	– –	– –	2 10	– –	0.5 2	1 5	1 5	0.5 2.5
05.057	3 10	– –	3.5 10	– –	5 15	5 20	0.03 0.05	5 15	5 15	7 20	– –	7 50	1 4	– –	2 15	0.03 1	– –	3.5 10
05.058	5.7 12	1.5 14.25	0.9 2.98	– –	5 5.03	5.5 14.46	4.8 11.55	8 19.07	0.9 2.98	0.9 2.98	0.9 2.98	0.9 2.98	2 5	– –	2 4.43	1 2	2.5 4.5	0.9 2.98
05.064	– –	0.001 1	– –	– –	– –	– –	– –	– –	0.001 2	0.001 1	– –	– –	0.001 1	– –	– –	– –	0.05 1	– –
05.071	0.5 1.5	0.5 5	0.01 1	– –	0.01 1	1 5	0.051 1	1 5	3 5	2 5	0.01 1	0.01 1	3 10	– –	0.05 1	0.02 1	3 5	0.01 1
05.084	1 5	5 10	0.01 1	– –	1	0.5 5	0.05 0.5	1 10	1 6	1 6	0.01 1	0.01 1	0.5 2	– –	0.03 1	0.1 1	0.5 3	0.01 1
05.101	0.2 1	– –	0.2 1	– –	– –	0.2 1	0.2 1	1	0.2 1	– –	– –	– –	0.2 1	– –	0.2 1	0.2 1	– –	0.2 1
05.108	0.1 1	0.5 5	0.01 1	– –	0.01 1	0.1 1	0.3 1	0.5 5	0.5 3	0.5 3	0.01 1	0.01 1	0.3 1	– –	0.01 1	0.02 1	0.5 3	0.01 1
05.111	5.7 12	1.5 14.25	0.9 2.98	– –	5 5.03	5.5 14.46	4.8 11.55	8 19.07	0.9 2.98	0.9 2.98	0.9 2.98	0.9 2.98	2 5	– –	2 4.43	1 2	2.5 4.5	0.9 2.98

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**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
05.120	5.7 12	1.5 14.25	0.9 2.98	– –	5 5.03	– –	4.8 11.55	8 19.07	– –	0.9 2.98	0.9 2.98	0.9 2.98	2 5	– –	2 4.43	1 2	2.5 4.5	0.9 2.98
05.125	0.01 1	0.5 5	0.01 1	– –	0.01 1	0.05 1	0.05 1	0.5 3	0.5 3	0.5 3	0.01 1	1	0.05 1	– –	0.01 1	0.01 1	0.5 3	0.01 1
05.127	0.01 1	– –	0.3 1	– –	– –	5.5 10	0.2 5	0.5 2	0.5 2	– –	– –	– –	0.5 2	– –	0.25 3	– –	0.051 1	0.5 2
05.140	0.5 1.5	0.5 5	0.5 1.5	– –	1 5	1 5	1 5	1 5	2 10	0.5 3	0.01 1	2.5 7.5	3 10	– –	0.2 1	0.06 1	5 20	0.5 1.5
05.141	0 1	0.05 1	0 1	0.001 0.3	0 1	0.01 1	1	0.05 1	0.05 1	0.05 1	1	1	0.01 1	– –	0 1	0 1	0.05 1	0.05 1
05.172	5.7 12	1.5 14.25	0.9 2.98	– –	5 5.03	5.5 14.46	4.8 11.55	8 19.07	0.9 2.98	0.9 2.98	0.9 2.98	0.9 2.98	2 5	– –	2 4.43	1 2	2.5 4.5	0.9 2.98
05.173	3 15	2 10	3 15	– –	3 15	4 20	2 10	5 25	1 5	1 5	– –	– –	5 25	3	2 10	– –	3 15	3 15
09.573	5 25	– –	4 20	– –	5 25	5 25	2 10	5 25	– –	– –	– –	– –	2 10	– –	2 20	4 20	5 25	3 25
09.947	5.7 12	1.5 14.25	0.9 2.98	– –	5 5.03	5.5 14.46	4.8 11.55	8 19.07	0.9 2.98	0.9 2.98	0.9 2.98	0.9 2.98	2 5	– –	2 4.43	1 2	2.5 4.5	0.9 2.98

FGE: Flavouring Group Evaluation; FL-no: FLAVIS number; FLAVIS: Flavour Information System; JECFA: The Joint FAO/WHO Expert Committee on Food Additives.
(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. 11)

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 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 calculation (SCF, 1995)

	Food categories according to Commission Regulation 1565/2000	Distribution of the seven SCF food categories		
Key	**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; MSDI: maximised survey-derived daily intake.

MSDI and mTAMDI values for 22 of the 29 flavouring substances in FGE.70Rev1, for which industry has provided use and use levels, are presented in the table below.

Table C.4: Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Union List chemical name	MSDI EU[(a)] (μg/capita per day)	MSDI US[(b)] (μg/capita per day)	mTAMDI[(c)] (μg/person per day)	Structural class	Threshold of concern (μg/person per day)
02.049	Nona-2,6-dien-1-ol	9.1	1	120	Class I	1,800
02.139	Deca-2,4-dien-1-ol	0.0012	26	640	Class I	1,800

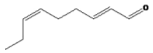
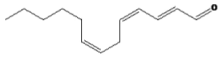
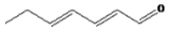
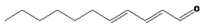
FL-no	EU Union List chemical name	MSDI EU[(a)] (μg/capita per day)	MSDI US[(b)] (μg/capita per day)	mTAMDI[(c)] (μg/person per day)	Structural class	Threshold of concern (μg/person per day)
02.162	Hexa-2,4-dien-1-ol	0.0012	0.4	500	Class I	1,800
02.188	Nona-2,4-dien-1-ol	0.0012	26	700	Class I	1,800
05.057	Hexa-2(*trans*),4(*trans*)-dienal	0.51	0.1	1,800	Class I	1,800
05.058	Nona-2(*trans*),6(*cis*)-dienal	16	24	2,000	Class I	1,800
05.064	Trideca-2(*trans*),4(*cis*),7(*cis*)-trienal	0.18	0.009	1.2	Class I	1,800
05.071	Nona-2,4-dienal	0.94	0.7	560	Class I	1,800
05.084	Hepta-2,4-dienal	2.2	23	710	Class I	1,800
05.101	Penta-2,4-dienal	0.0012	0.2	100	Class I	1,800
05.108	Undeca-2,4-dienal	2.8	0.4	89	Class I	1,800
05.111	Octa-2(*trans*),6(*trans*)-dienal	0.012	0.007	2,000	Class I	1,800
05.120	Dodeca-2,6-dienal	0.012	0.009	1,800	Class I	1,800
05.125	Dodeca-2,4-dienal	0.095	0.1	82	Class I	1,800
05.127	Octa-2(*trans*),4(*trans*)-dienal	0.65	0.007	420	Class I	1800
05.140	Deca-2(*trans*),4(*trans*)-dienal	62	70	560	Class I	1,800
05.172	Nona-2(*trans*),6(*trans*)-dienal	6.5	0.007	2,000	Class I	1,800
08.085	(*E,E*)-Hexa-2,4-dienoic acid	61	6		Class I	1,800
09.194	Ethyl (*E,E*)-hexa-2,4-dienoic acid	50	3		Class I	1,800
09.260	Ethyl (*E,Z*)-deca-2,4-dienoate	29	3		Class I	1,800
09.300	Methyl (*E,E*)-hexa-2,4-dienoic acid	0.097	ND		Class I	1,800
09.371	Ethyl deca-2,4,7-trienoate	0.024	0.4		Class I	1,800
09.639	Methyl (*E,Z*)-deca-2,4-dienoate	0.097	1		Class I	1,800
09.840	Propyl 2,4-decadienoate	0.77	ND		Class I	1,800
09.947	(*E,Z*)-2,6-Nonadienyl acetate	0.012		2,000	Class I	1,800
02.153	Hepta-2,4-dien-1-ol	0.0012	0.01	1,600	Class I	1,800
05.141	Deca-2,4,7-trienal	0.088	0.01	8.1	Class I	1,800
05.173	Nona-2,4,6-trienal	0.0012	ND	1,700	Class I	1,800
09.573	Hexa-2,4-dienyl acetate	0.0012	0.01	1,700	Class I	1,800

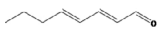
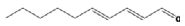
MSDI: maximised survey-derived daily intake; mTAMDI: modified Theoretical Added Maximum Daily Intake.
(a): Based on EU production figures from JECFA and submitted by industry (JECFA 2004a and Documentation provided to EFSA n. 1; 3 and 6).
(b): Based on US production figures from JECFA (2004a, 2008a).
(c): Based on use levels submitted by industry (Documentation provided to EFSA n. 2 and 3).

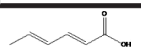
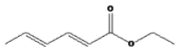
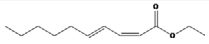
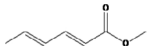
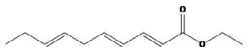
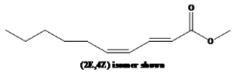
Appendix D – Summary of safety evaluations

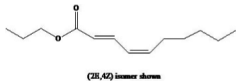
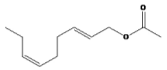
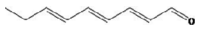
Table D.1: Summary of Safety Evaluations performed by JECFA (2004a, 2007, 2008b) and EFSA conclusions on flavouring substances in FGE.70 and FGE.70Rev1

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
02.049 1184	Nona-2,6-dien-1-ol		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
02.139 1189	Deca-2,4-dien-1-ol		Class I B3: Intake below threshold, B4: adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Chemical name in the UL to be changed (see 'EFSA comments' Appendix A– Table B.1) Concluded in FGE.70Rev1
02.162 1174	Hexa-2,4-dien-1-ol		Class I B3: Intake below threshold, B4: adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
02.188 1183	Nona-2,4-dien-1-ol		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.057 1175	Hexa-2(*trans*),4(*trans*)-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1

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
05.058 1186	Nona-2(*trans*),6(*cis*)-dienal		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.064 1198	Trideca-2(*trans*),4(*cis*),7(*cis*)-trienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.071 1185	Nona-2,4-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.084 1179	Hepta-2,4-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Chemical name in the UL should be changed (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1
05.101 1173	Penta-2,4-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.108 1195	Undeca-2,4-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1

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
05.111 1182	Octa-2(*trans*),6(*trans*)-dienal		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.120 1197	Dodeca-2,6-dienal		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	No safety concern at the estimated level of intake Chemical name in the UL should be changed (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1
05.125 1196	Dodeca-2,4-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Chemical name in the UL should be changed (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1
05.127 1181	Octa-2(*trans*),4(*trans*)-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.140 1190	Deca-2(*trans*),4(*trans*)-dienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake The minimum purity assay should be updated (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1
05.172 1187	Nona-2(*trans*),6(*trans*)-dienal		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1

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
08.085 1176	(*E,E*)-Hexa-2,4-dienoic acid		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
09.194 1178	Ethyl (*E,E*)-hexa-2,4-dienoic acid		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70
09.260 1192	Ethyl (*E,Z*)-deca-2,4-dienoate		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Not applicable to the material of commerce as pending further information on purity and content of secondary components (see 'EFSA comments' Table B.1 Appendix A) Concluded in FGE.70
09.300 1177	Methyl (*E,E*)-hexa-2,4-dienoic acid		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70
09.371 1193	Ethyl deca-2,4,7-trienoate		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Not applicable to the material of commerce as pending further information on stereoisomerism (see 'EFSA comments' Table B.1 Appendix A) Concluded in FGE.70Rev1
09.639 1191	Methyl (*E,Z*)-deca-2,4-dienoate		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1

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
09.840 1194	Propyl 2,4-decadienoate		Class I A3: Intake below threshold No safety concern based on the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Not applicable to the material of commerce as pending further information on stereoisomerism (see 'EFSA comments' Table B.1 Appendix A) Concluded in FGE.70
09.947 1188	(*E,Z*)-2,6-Nonadienyl acetate		Class I A3: Intake below threshold No safety concern at the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
02.153 1784	Hepta-2,4-dien-1-ol		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern at the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Chemical name in the UL should be changed (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1
05.141 1786	Deca-2,4,7-trienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern at the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1
05.173 1785	Nona-2,4,6-trienal		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern at the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Chemical name in the UL to be changed (see 'EFSA comments' Appendix A – Table B.1) Concluded in FGE.70Rev1

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
09.573 1780	Hexa-2,4-dienyl acetate		Class I B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern at the estimated level of intake	Class I A3: Intake below threshold No safety concern at the estimated level of intake Concluded in FGE.70Rev1

JECFA: The Joint FAO/WHO Expert Committee on Food Additives; FGE: Flavouring Group Evaluation; MSDI: The Joint FAO/WHO Expert Committee on Food Additives; NOAEL: No observed adverse effect level; UL: EU Union List.

(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. 1; 3 and 6).

Appendix E – Repeated dose toxicity and carcinogenicity studies

Table E.1: Toxicity studies considered in FGE.70Rev1 as summarised by JECFA (2004b).

EU Union List Name [FL-no]	Species; Sex No./Group	Route	Dose levels (mg/kg bw per day)	Duration	NO(A)EL (mg/kg bw per day)	Reference	EFSA Comments
2-*trans*-6-*cis*-Dodecadienal [FL-no:05.120] 2-*trans*-4-*cis*-7-*cis*-Tridecatrienal [FL-no:05.064]	Rats; Male, Female 6/sex per group	Diet (microencapsulated in maltodextrin)	0 (maltodextrin), [FL-no:05.120]: up to 1.93 and 2.06 for males and females, respectively [FL-no:05.064]: up to 30.9 and 33 males and females, respectively	4 weeks	[FL-no:05.120]: 2.06 [FL-no:05.064]: 33	Edwards (1973)	This study of short duration on the mixture is not suitable for the evaluation of flavouring substances
Hexa-2(*trans*),4(*trans*)-dienal [05.057]	F344/N rats; male and female, 10/sex per group	Gavage	0, 7.5, 15, 30, 60 and 120	14 weeks	15 for male rats 60 for female rats	NTP (2003)	Based on the magnitude of the observed effect (body weight changes), the Panel considered the NOAEL in rats in this study to be 60 mg/kg bw per day
	B6C3F1 mice male and female, 10/sex per group	Gavage	0, 7.5, 15, 30, 60 and 120		30 for male mice		JECFA did not derive a NOEL for female mice owing to the increased relative liver weights observed at all doses. However, the Panel noted that there was no indication of histopathological or clinical changes at all doses
Deca-2(*trans*),4(*trans*)-dienal [FL-no: 05.140]	Rats; Male, Female 10/sex per group	Gavage	0, 50, 100, 200, 400 and 800 in corn oil (dosing volume: 5 ml/kg)	14 weeks	100	NTP (2011)	The study has actually been performed during 1996/1997
	Mice; Male, Female 10/sex per group	Gavage	0, 50, 100, 200, 400 and 800 in corn oil (dosing volume: 10 ml/kg)		100		

bw: body weight; NOAEL: no observed adverse effect level; JECFA: The Joint FAO/WHO Expert Committee on Food Additives.

Table E.2: Reproductive toxicity study on [FL-no: 08.085] (i.e. sorbic acid) considered by the FAF Panel in scientific opinion on the follow-up of the re-evaluation of sorbic acid (E200) and potassium sorbate (E202) as food additives (EFSA FAF Panel, 2019)

EU Union List Name [FL-no]	Species; Sex No./Group	Route	Dose levels (mg/kg bw per day)	Duration	BMDL (BMR set to 5% producing a lower bound)	Reference	Comments
(*E,E*)-Hexa-2,4-dienoic acid [FL-no: 08.085] (sorbic acid)	CD/Crl:CD rats cohorts 1A and 1B (reproductive toxicity) 25 animals/sex per group in the F0-generation; 20 animals/sex per group to cohort F1A and F1B	Diet	0, 1,000, 2,000 and 4,000 mg sorbic acid/kg bw per day	Extended one-generation	1110 mg sorbic acid/kg body weight (bw) per day	Documentation provided to EFSA n. 1 in EFSA FAF Panel (2019)	

bw: body weight; BMR: benchmark response.

Table E.3: Carcinogenicity Studies considered by the Panel in FGE.203 (EFSA CEF Panel, 2009b)

EU Union List Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	Results	Reference	Comments
Hexa-2 (*trans*),4 (*trans*)-dienal [05.057]	Rats; Male, Female 50/sex per group	Gavage in corn oil	0 (controls), 22.5, 45 or 90 mg/kg bw per day, five times per week	105 weeks	Males: Positive trend in increased squamous cell papillomas of the forestomach. One squamous cell carcinoma of the forestomach was seen in the mid-dose group and two in the high-dose group. Females: Positive trend in increased squamous cell papillomas of the forestomach. No carcinomas were seen	NTP (2003)	Males: The carcinomas of the forestomach were preceded by epithelial hyperplasia and papillomas Females: Squamous cell papillomas and epithelial hyperplasia were increased at the two highest doses
	Mice; Male, Female 50/sex per group	Gavage in corn oil	0 (controls), 30, 60 or 120 mg/kg bw per day, five times per week	105 weeks	Males and females: Increased incidences of squamous cell papillomas and carcinomas of the forestomach in the high-dose groups. Squamous cell carcinoma of the tongue observed in two mice of the high-dose group)	NTP, (2003)	The carcinomas of the forestomach were preceded by epithelial hyperplasia and squamous cell papillomas

bw: body weight.