Scientific Opinion on Flavouring Group Evaluation 70, Revision 1 (FGE.70Rev1): consideration of aliphatic, linear, \(\alpha,\beta\)-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, if required, additional toxicological data.

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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 of flavourings is regulated under Regulation (EC) No 1334/2008\(^2\) of the European Parliament and Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of Article 9(a) of this Regulation, an evaluation and approval are required for flavouring substances.

The Union list of flavourings and source materials was established by Commission Implementing Regulation (EC) No 872/2012\(^3\). The list includes a number of flavouring substances for which the safety evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000\(^1\).

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

Additional data were submitted in February and June 2013 by Industry related to one representative substance of subgroup 1.1.1, hex-2(trans)-enal [FL-no: 05.073] and two other substances of the group. On 21 May 2014 the EFSA CEF Panel adopted an opinion on this Flavouring Group Evaluation 200 (FGE.200). The Panel confirmed the need for an in vivo Comet assay performed in duodenum and liver for hex-2(trans)-enal [FL-no: 05.073]. For the two representative substances of subgroup 1.1.1 (nona-2(trans), 6(cis)-dienal [FL-no: 05.058] and oct-2-enal [FL-no: 05.060]), a combined in vivo Comet assay and micronucleus assay would be required and 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 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. The list contains flavouring substances for which the scientific evaluation should be completed taking into account Commission Regulation (EC) No 1565/2000.

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 and of Regulation (EU) No 1334/2008. 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, \[\alpha,\beta\]-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\text{-octadien-1-ol and } (E,Z)-2,6\text{-nonadien-1-ol acetate (JECFA-no: 1180 and 1188). Seventeen substances are } \alpha,\beta\text{-unsaturated aldehydes, or precursors, and they were considered by the Panel to be of concern for genotoxicity and were considered together with other } \alpha,\beta\text{-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 (mMTAMDI) 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\text{-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).

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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 C.1 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, 0.140, 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 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 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: 08.085, 09.371 and 09.639], considered in the previous version of this FGE (FGE.70), the Panel noted that 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 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).

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, 05.125, 05.173, 09.194, 09.260, 09.300, 09.573, 09.840 and 09.947], 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, 05.057, 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.70 Rev1 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-\(\alpha,\beta\)-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-\(\alpha,\beta\)-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-\(\alpha,\beta\)-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-\(\alpha,\beta\)-unsaturated substances and these substances were evaluated via the A-side. Moreover, the sixteen 2,4-\(\alpha,\beta\)-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. \(\alpha,\beta\)-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(\(\text{trans}\)),4(\(\text{trans}\))-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, \(\alpha,\beta\)-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 09.947] 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 mTAMDI values 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 mTAMDI 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)

References

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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
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’.

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 innocuous9 products (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous9 (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.

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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).
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) 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 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, estimated the per capita intake of certain substances.

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**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.

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a) **Intake**

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

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10 EU MSDI: Amount added to food as flavour in (kg/year) × 10^9/(0.1 × population in Europe (= 375 × 10^9) × 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

| FL-no | JECFA-no | FEMA no | CoE no | CAS no | Chemical name | Purity of the named compound | Phys. form | 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 | C₉H₁₆O | 140.23 | Insoluble | Soluble | 196 | – | IR NMR | 95% not less than 92% (2E,6Z), 3-5% (2E,6E) < 3% (2Z,6Z) and (2Z,6E) | 1.463–1.465 | 0.860–0.880 | The chemical name in the UL should be changed to deca-(2E,4E)-dien-1-ol, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10) |
| 02.139 | 1189 | 3911 | 11748 | 18409-21-7 | Deca-2,4-dien-1-ol | (b) | Liquid | C₁₀H₁₈O | 154.25 | Insoluble | Soluble | 112 (13 hPa) | – | IR NMR MS | 95% (sum of isomers) 92–95% (2E,4E); 2–5% (2E,4Z); 2–5% (2Z,4E); 0–2% (2Z,4Z) | 1.485–1.495 | 0.861–0.871 | The chemical name in the UL should be changed to deca-(2E,4E)-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 | C₇H₁₂O | 112.17 | Freely soluble | – | 80 (19 hPa) | – | MS | 95% 90–98% (2E,4E); 2–10% (2E,4Z); 2–10% (2Z,4E); 0–2% (2Z,4Z) | 1.487–1.493 | The chemical name in the UL should be changed to Hepta-(2E,4E)-di-en-1-ol, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10) |
| 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 | Assay minimum | ID test | isomers distribution/SC(h) | Refrac. index(f) | Spec. gravity(g) | EFSA Comments |
|-------|----------|---------|-------|-------|---------------|-----------------------------|------------|-------------|-------------|--------------|-------------------------|-------------------|-----------------|----------------|---------|-----------------------------|---------------|-----------------|---------------|
| 02.162| 1174 | 3922 | 111-28-4 | | Hexa-2,4-dien-1-ol | (b) | Solid | C\textsubscript{6}H\textsubscript{10}O | 98.16 | Insoluble | Soluble | – | 24.33 | IR NMR MS | 95% | 95% or greater (2E,4E), up to 5% of (2E,4Z), < 3% (2Z,4E) and (2Z,4Z) | – | – |  |
| 02.188| 1183 | 3951 | 11802 | 62488-56-6 | Nona-2,4-dien-1-ol | | Liquid | C\textsubscript{9}H\textsubscript{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-(trans),4-(trans)-dienal | (b) | Liquid | C\textsubscript{6}H\textsubscript{12}O | 96.13 | Slightly soluble | Soluble | 64 (20 hPa) | MS | 97% | SC: (2-5%) hexa-(2E,4Z)-dienal, (1%) hexa-(2Z,4Z)-dienal, (1%) hexa-(2Z,4E)-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-(trans),6(cis)-dienal | | Liquid | C\textsubscript{9}H\textsubscript{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**

| FL-no | JECFA-no | Chemical name | Purity of the named compound | Phys. form | Solubility | Solubility in ethanol | Boiling point, °C<sup>(e)</sup> | Melting point, °C | Assay minimum | Refrac. index<sup>(f)</sup> | Spec. gravity<sup>(g)</sup> | EFSA Comments |
|-------|----------|---------------|------------------------------|------------|------------|------------------------|------------------|----------------|----------------|----------------|----------------|----------------|
| 05.064| 1198     | Trideca-2    | At least 71%; secondary     | Liquid     | Insoluble  | Soluble                | 138 (0.4 hPa)    | –              | NMR MS        | 1.472–1.478    | 0.801–0.809     | The chemical name in the UL should be changed to Hepta-(2E,4E)-dienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10) |
|       | 3638     | (trans),4    | components 14% 4-cis-7-cis- | C<sub>13</sub>H<sub>20</sub>O | 192.30     |                        | –                | –              | –             | 1.522–1.525    | 0.850–0.870     |                                            |
|       | 685      | trienal      | tridecadienol; 6% 3-cis-7-cis- |            |            |                        | –                | –              | –             |                |                  |                                            |
|       | 13552-96-0|              | tridecadienol; 5% 2-trans-7- |            |            |                        | –                | –              | –             |                |                  |                                            |
|       |          |              | cis-tridecadienial; 3% 2-    |            |            |                        | –                | –              | –             |                |                  |                                            |
|       |          |              | trans-4-trans-7-cis-         |            |            |                        | –                | –              | –             |                |                  |                                            |
|       |          |              | tridecatrienial               |            |            |                        | –                | –              | –             |                |                  |                                            |
| 05.071| 1185     | Nona-2,4-     | At least 89%; secondary     | Liquid     | Insoluble  | Soluble                | 97 (13 hPa)      | –              | IR MS         | 1.522–1.525    | 0.850–0.870     |                                            |
|       | 3212     | dienal       | components 5-6% 2,4-nonadien | C<sub>9</sub>H<sub>14</sub>O | 138.21     |                        | –                | –              | –             |                |                  |                                            |
|       | 732      |              | 1-ol and 1-2% 2-nonen-1-ol    |            |            |                        | –                | –              | –             |                |                  |                                            |
|       | 6750-03-4|              |                             |            |            |                        | –                | –              | –             |                |                  |                                            |
| 05.084| 1179     | Hepta-2,4-    | At least 92%; Secondary     | Liquid     | Insoluble  | Soluble                | 84 (1 hPa)       | –              | IR MS         | 1.478–1.480    | 0.822–0.828     |                                            |
|       | 3164     | dienal       | components 2-4% (E,Z)-2,4-   | C<sub>7</sub>H<sub>10</sub>O | 110.16     |                        | –                | –              | –             |                |                  |                                            |
|       | 729      |              | heptadienal and 2-4% 2,4-    |            |            |                        | –                | –              | –             |                |                  |                                            |
|       | 4313-03-5|              | heptadienoic acid            |            |            |                        | –                | –              | –             |                |                  |                                            |

(a) Most recent available specifications data
(b) EFSA Comments

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| FL-no | JECFA-no | Chemical name | Purity of the named compound | Phys. form | Mol. formula | Mol. weight | Solubility(c) | Refrac. index(f) | Spec. gravity(g) | EFSA Comments |
|-------|----------|---------------|-----------------------------|------------|--------------|-------------|---------------|-----------------|-----------------|----------------|
| 05.101 1173 3217 11695 764-40-9 | Penta-2,4-dienal | Liquid | C₅H₆O | 82.13 | n.a. | Soluble | 60 (91 hPa) | – | NMR MS | 0.801–0.809 | |
| 05.108 1195 3422 10385 13162-46-4 | Undeca-2,4-dienal | Liquid | C₁₁H₁₈O | 166.26 | Insoluble | Soluble | 129 (17 hPa) | – | NMR MS | 0.896–0.906 | |
| 05.111 1182 3466 10371 56767-18-1 | Octa-2( trans),6(trans)-dienal | Liquid | C₈H₁₂O | 124.19 | Insoluble | Soluble | 97-99 (5 hPa) | – | IR NMR | 0.835–0.841 | |
| 05.120 1197 3637 21662-13-5 | Dodeca-2,6-dienal | Liquid | C₁₂H₂₀O | 180.28 | Insoluble | Soluble | 130 (7 hPa) | – | NMR | 0.987–0.993 | The chemical name in the UL should be changed to Dodeca-(2E,6Z)-dienal, in accordance with the CAS nr and the most recent specifications on stereoismeric composition (Documentation provided to EFSA nr.10) |
| FL-no | JECFA-no | Chemical name | Purity of the named compound | Phys. form | Mol. formula | Mol. weight | Solubility(a) | Solubility in ethanol(b) | Boiling point, °C(e) | Melting point, °C | ID test | Assay minimum isomers distribution/(c) | Refrac. index(f) | Spec. gravity(g) | EFSA Comments |
|-------|----------|---------------|-----------------------------|------------|--------------|-------------|---------------|------------------------|-------------------|----------------|----------|--------------------------------------|---------------|----------------|----------------|
| 05.125 | 1196 | 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% (2E,4E); 0.1–9% (2E,4Z); 0.1–9% (2Z,4E); 0–2% (2Z,4Z) | 1.470–1.476 | 0.983–0.989 | The chemical name in the UL should be changed to Dodeca-(2E,4E)-dienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr: 10) |
| 05.127 | 1181 | Octa-2(trans),4(trans)-dienal | (b) | Liquid | C_{8}H_{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 | Deca-2(trans),4(trans)-dienal | At least 89%, Secondary components (3-4%) mixture of (2Z,4Z), (2Z,4E) and (2E,4Z) - 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% (2E,4Z); < 1% (2Z,4E); < 0.5% (2Z,4E); < 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 | 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%) (6E,4E,7Z) (5–6%) (2E,4Z,7Z); (10–11%) (2E,4E,7E) | 1.538–1.544 | 0.898–0.905 | |
### Information included in the EU Union List
Regulation No. (EU) 1334/2008 as amended

| FL-no | JECFA-no | CAS no | Chemical name | Purity of the named compound | Phys. form | Mol. formula | Mol. weight | Solubility | Solubility in ethanol | Boiling point, °C | Melting point, °C | Assay minimum | Assay ID test | Refrac. index | Spec. gravity | EFSA Comments |
|-------|----------|--------|---------------|-----------------------------|------------|--------------|-------------|------------|----------------------|----------------|----------------|---------------|---------------|--------------|--------------|---------------|
| 05.172 | 1187     | 3766   | Nona-2 (trans),6 (trans)-dienal | Liquid | C₉H₁₄O | 138.21 | Insoluble | Soluble | 88 (14 hPa) | – | NMR 97% | – | – | 1.439–1.445 | 0.856–0.864 | The chemical name in the UL should be changed to Nona-(2E,4E,6E)-trienal, in accordance with the CAS nr and the most recent specifications on stereoisomeric composition (Documentation provided to EFSA nr.10) |
| 05.173 | 1785     | 4187   | Nona-2,4,6-trienal | Liquid | C₉H₁₄O | 136.19 | Freely soluble | Soluble | 194 | – | MS 95% (sum of isomers) > 95% (2E,4E,6E); < 5% other isomers; 0–1% (2Z,4Z,6Z) | – | – | 1.550–1.556 | 0.867–0.873 | This flavouring substance is also called sorbic acid and corresponds to food additive (E-200) |
| 08.085 | 1176     | 3921   | (E,E)-Hexa-2,4-dienoic acid | Solid | C₆H₈O₂ | 112.13 | Slightly soluble | Soluble | – | 132–135 IR NMR 99% | – | – | – | – | This purity and content of the secondary components should be clarified |
| 09.194 | 1178     | 2459   | 635 2396-84-1 | Ethyl (E,E)-hexa-2,4-dienoic acid | Liquid | C₈H₁₂O₂ | 140.18 | Slightly soluble | Soluble | 195–196 | – | IR MS 98% | – | – | 1.491–1.498 | 0.936–0.939 | The purity and content of the secondary components should be clarified |
| 09.260 | 1192     | 3148   | 10574 3025-30-7 | Ethyl (E,Z)-deca-2,4-dienoate | Liquid | C₁₂H₂₀O₂ | 196.29 | Insoluble | – | 120 (9 hPa) | – | NMR 90% SC: (E,E)-ethyl 2,4-decadienoate | – | – | 1.480–1.486 | 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

| FL-no | JECFA-no | CAS no | Chemical name | Purity of the named compound | Phys. form | Mol. formula | Mol. weight | Solubility | Solubility in ethanol(a) | Boiling point, °C(e) | Melting point, °C | Assay minimum | Refrac. index(f) | Spec. gravity(g) | EFSA Comments |
|-------|----------|--------|---------------|-----------------------------|------------|--------------|-------------|------------|------------------------|------------------|----------------|----------------|---------------|---------------|--------------|----------------|
| 09.300| 1177     | 3714   | Methyl (E,E)-hexa-2,4-dienoic acid | Liquid | C<sub>7</sub>H<sub>10</sub>O<sub>2</sub> | 126.16     | Slightly soluble | Soluble | 180 – IR NMR 99% | 1.501–1.505 | 0.933–0.938 | CAS nr in Union List does not specify stereoisomeric composition. Composition of stereoisomeric mixture to be specified |
| 09.371| 1193     | 3832   | Ethyl deca-2,4,7-trienoate | Liquid | C<sub>12</sub>H<sub>18</sub>O<sub>2</sub> | 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 |
| 09.573| 1780     | 10675  | Hexa-2,4-dienyl acetate | Liquid | C<sub>10</sub>H<sub>20</sub>O<sub>2</sub> | 140.18     | Freely soluble | | | 1.470–1.476 | 0.908–0.914 |
| 09.639| 1191     | 3859   | Methyl (E,Z)-deca-2,4-dienoate | At least 93%; secondary component 2–5% (E,E) methyl 2,4-decadienoate | Liquid | C<sub>11</sub>H<sub>18</sub>O<sub>2</sub> | 182.26 | Insoluble | Soluble | 67 (1 hPa) – IR NMR 93% (Material in commerce is min. 93% pure (2E,4Z)-isomer. Min. Purity > 95% (sum of isomers: other isomer mainly (2E,4E)-isomer) | 1.488–1.494 | 0.917–0.923 |
| 09.840| 1194     | 3648   | Propyl 2,4-decadienoate | Liquid | C<sub>13</sub>H<sub>22</sub>O<sub>2</sub> | 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

| 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 |
|-------|----------|---------|--------|--------|---------------|-----------------------------|------------|--------------|-------------|---------------|---------------------------|-------------------|-----------------|---------|------------------------------------------|-----------------|-----------------|--------------|
| 09.947 | 1188     | 3952    |    |        | (E,Z)-2,6-Nonadienyl acetate | Liquid | C₁₁H₁₈O₂ | 182.26 | Sparingly soluble | Soluble | 231 | - | IR NMR MS 95% | 1.448-1.458 | 0.905-0.907 |          |
|       | 68555-65-7 |        |    |        |                                |                |           |              |              |               |                          |                   |                 |          |

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  | 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   | 0.05   | –      | –      | 0.02   | 0.44   | 0.17   | 0.25   | –      | –      | –      | –      | –      | 0.01   | –      | 0.15   | 0.19   | 0.02   | –     |
| 02.139 | 0.3    | 0.05   | 0.03   | 1.04   | 0.54   | 0.63   | –      | –      | –      | –      | –      | –      | –      | –      | –      | 0.53   | 0.48   | 0.03   | –     |
| 02.153 | 3      | 2      | 30     | –      | 50     | 25     | 5      | 1      | 1      | –      | –      | –      | 2      | 0      | 0      | 2      | 0      | 5     | 2     |
| 02.162 | 0.5    | 1      | –      | 0.5    | 0.5    | –      | –      | –      | –      | –      | –      | –      | –      | 1      | 1      | 0.2    | 0.1    | 0.5    | –     |
| 02.188 | 0.5    | 1      | 5      | 1      | 1      | 2      | 0.2    | 3      | 1      | –      | –      | –      | –      | 2      | –      | 0.5    | 1      | 1      | 0.5   |
| 05.057 | 3      | 10     | 5      | 1      | 1      | 1      | 1      | 1      | –      | –      | –      | –      | –      | 10     | –      | 2      | 5      | 5      | 2.5   |
| 05.058 | 5.7    | 1.5    | 14.25  | 2.98   | –      | 5.03   | 14.46  | 4.8    | 8      | 0.9    | 0.9    | 0.9    | 2      | –      | 2      | 1      | 2.5    | 0.9   |
| 05.064 | 0.001  | 1      | –      | –      | –      | –      | –      | –      | 0.001  | 0.001  | 0.001  | 0.001  | 0.001  | –      | –      | –      | 0.05   | –     |
| 05.071 | 0.5    | 0.5    | 0.01   | –      | 0.01   | 1      | 0.01   | 1      | 3      | 2      | 2      | 0.01   | 0.01   | 3      | –      | 0.05   | 0.02   | 3      | 0.01  |
| 05.084 | 5      | 5      | 0.01   | –      | 0.01   | 1      | 0.01   | 1      | 3      | 2      | 2      | 0.01   | 0.01   | 3      | –      | 0.05   | 0.02   | 3      | 0.01  |
| 05.101 | 0.2    | 0.2    | –      | –      | –      | 0.2    | 0.2    | 1      | 0.2    | –      | –      | 0.2    | 0.2    | –      | –      | 0.2    | 0.2    | –      | 0.2   |
| 05.108 | 0.1    | 0.5    | 0.01   | –      | 0.01   | 1      | 0.01   | 1      | 3      | 0.5    | 0.5    | 0.5    | 0.01   | 0.01   | 0.3    | –      | 0.01   | 0.02   | 0.5    | 0.01  |
| 05.111 | 5.7    | 1.5    | 0.9    | –      | 5      | 5.5    | 4.8    | 8      | 0.9    | 0.9    | 0.9    | 2      | –      | 2      | 1      | 2.5    | 0.9   |
| FL-no | Food Categories | Normal use levels (mg/kg)<sup>(a)</sup> | 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          | 1.5          | 0.9          | –          | 5          | –          | 4.8          | 8          | –          | 0.9          | 0.9          | 0.9          | 2          | –          | 2          | 1          | 2.5          | 0.9          |
|        | 12          | 14.25        | 2.98         | –          | 5.03        | –          | 11.55       | 19.07       | –          | 2.98         | 2.98         | 2.98         | 5          | –          | 4.43        | 2          | 4.5          | 2.98         |
| 05.125 | 0.01        | 0.5          | 0.01         | –          | 0.01        | 0.05       | 0.05        | 0.9         | 0.9         | 0.9          | 2          | –          | 2          | 1          | 0.9          | 0.01        | 0.01        | 2.98         |
|        | 1           | 5            | 1            | –          | 1           | 1          | 1         | 3          | 3          | 3            | 1          | 1          | –          | 1          | 1           | –          | 1           | 1            |
| 05.127 | 0.01        | –            | 0.3          | –          | –           | 5.5        | 0.2        | 0.5        | 0.5         | –            | –          | –          | –          | 0.5        | –          | 0.25        | –          | 0.051        | 0.5          |
|        | 1           | –            | 1            | –          | 1           | 10         | 2          | 2          | 2           | –            | –          | –          | 2          | 3          | 1           | –          | 1            | 2            |
| 05.140 | 0.5         | 0.5          | 0.5          | –          | 1           | 1          | 1          | 2          | 0.5         | 0.01         | 2.5        | 1          | 7.5        | 10         | –          | 1          | 1           | 20           | 1.5          |
|        | 1.5         | 5            | 1.5          | –          | 5           | 5          | 5          | 5          | 10          | 3            | 1          | 7.5        | 10         | –          | 1          | 1           | 20           | 1.5          |
| 05.141 | 0           | 0.05         | 0            | 0.001      | 0           | 0.01       | 1          | 0.05       | 0.05        | 0.05         | 0.05        | 1          | 1          | 1          | 0.01        | –          | 0           | 0            | 0.05         | 0.05         |
|        | 1           | 1            | 1            | 0.3        | 1           | 1          | 1          | 1          | 1           | 1            | 1          | 1          | 1          | 1           | 1           | 1           | 1            |
| 05.172 | 5.7         | 1.5          | 2.98         | 5.03       | 14.46       | 11.55      | 8          | 0.9        | 0.9         | 0.9          | 2          | –          | 2          | 1          | 2           | 1.5          | 2.5          | 0.9          |
|        | 12          | 14.25        | 2.98         | –          | 5.03        | 14.46      | 11.55      | 19.07      | 2.98        | 2.98         | 2.98        | 2.98        | 2.98        | 5          | –          | 4.43         | 2           | 4.5          | 2.98         |
| 05.173 | 3           | 2            | 3            | 3           | 4          | 2          | 5          | 1          | 1           | –            | –          | 5          | 3          | 2          | –          | 3           | 3            |
|        | 15          | 10           | 15           | –          | 15          | 20         | 10         | 25         | 5           | 5            | –          | –          | 25         | 10         | –          | 15           | 15           |
| 09.573 | 5           | –            | 4            | 5           | 5          | 2          | 5          | –          | –            | –            | –          | –          | –          | –          | 2           | –          | 2           | 4            | 5            | 3            |
|        | 25          | –            | 20           | –          | 25          | 25         | 10         | 25         | –            | –            | –          | –          | –          | –          | 10          | –           | 20          | 20           | 25           | 25           |
| 09.947 | 5.7         | 1.5          | 0.9          | –          | 5           | 5.5        | 4.8        | 8          | 0.9         | 0.9          | 0.9        | 0.9        | 2          | –          | 2           | 1           | 2.5          | 0.9          |
|        | 12          | 14.25        | 2.98         | 5.03       | 14.46       | 11.55      | 19.07      | 2.98       | 2.98        | 2.98         | 2.98        | 2.98        | 5          | –          | 4.43         | 2           | 4.5          | 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 usage’ is defined as the average of reported usages and ‘maximum usage’ 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 favourable 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 favourable 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)

| Key | Food category | Distribution of the seven SCF food categories |
|-----|---------------|-----------------------------------------------|
| 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<sup>(a)</sup> (µg/capita per day) | MSDI US<sup>(b)</sup> (µg/capita per day) | mTAMDI<sup>(c)</sup> (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        | 1,800                            |
| 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                               | 1,800                            | Class I        | 1,800                            |
| 09.194 | Ethyl (E,E)-hexa-2,4-dienoic acid | 50              | 3                               | 1,800                            | Class I        | 1,800                            |
| 09.260 | Ethyl (E,Z)-deca-2,4-dienoate| 29                              | 3                               | 1,800                            | Class I        | 1,800                            |
| 09.300 | Methyl (E,E)-hexa-2,4-dienoic acid | 0.097 | ND                             | 1,800                            | Class I        | 1,800                            |
| 09.371 | Ethyl deca-2,4,7-trienoate  | 0.024                           | 0.4                             | 1,800                            | Class I        | 1,800                            |
| 09.639 | Methyl (E,Z)-deca-2,4-dienoate| 0.097                           | 1                               | 1,800                            | Class I        | 1,800                            |
| 09.840 | Propyl 2,4-decadienoate     | 0.77                            | ND                              | 1,800                            | Class I        | 1,800                            |
| 09.947 | (E,Z)-2,6-Nonadienyl acetate | 0.012                          | 2,000                           | 1,800                            | 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                            |
| 05.573 | 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).
### 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 | EU Union List chemical name | Structural formula | JECFA conclusions | EFSA conclusions |
|-------|-----------------------------|-------------------|-------------------|-----------------|
|       |                             |                   | Class(a) Evaluation procedure path(b) Outcome on the named compound based on the MSDI(c) approach | Procedural path if different from JECFA, Conclusion based on the MSDI(d) approach on the named compound and on the material of commerce |
| 02.049 | Nona-2,6-dien-1-ol | ![Structural formula](image) | 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 | Deca-2,4-dien-1-ol | ![Structural formula](image) | 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 | Hexa-2,4-dien-1-ol | ![Structural formula](image) | 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 | Nona-2,4-dien-1-ol | ![Structural formula](image) | 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 | Hexa-2(trans),4(trans)-dienal | ![Structural formula](image) | 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 | EU Union List chemical name | Structural formula | JECFA conclusions | EFSA conclusions |
|-------|-----------------------------|--------------------|-------------------|-----------------|
| 05.058 1186 | Nona-2(trans),6(cis)-dienal | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 |
| 05.101 1173 | Penta-2,4-dienal | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | EU Union List chemical name | Structural formula | JECFA conclusions | EFSA conclusions |
|-------|-----------------------------|--------------------|------------------|-----------------|
| 05.111 1182 | Octa-2(trans),6(trans)-dienal | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | EFSA conclusions |
|-------|----------|-----------------------------|--------------------|-------------------|----------------|
| 08.085 | 1176 | (E,E)-Hexa-2,4-dienoic acid | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | ![Structural formula](image) | 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 | EFSA conclusions |
|-------|----------|----------------------------|-------------------|-------------------|-----------------|
|       |          |                            |                   | Class (a)        | Procedural path if different from JECFA, Conclusion based on the MSDI (d) approach on the named compound and on the material of commerce |
|       |          |                            |                   | Evaluation procedure path (b) | on the named compound based on the MSDI (c) approach | |
|       |          |                            |                   | Outcome on the named compound based on the MSDI (c) approach | |
| 09.840 | 1194     | Propyl 2,4-decadienoate    | ![Propyl 2,4-decadienoate](image) | Class I A3: Intake below threshold | 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 |
|        |          |                            |                   | | 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 | ![E,Z)-2,6-Nonadienyl acetate](image) | Class I A3: Intake below threshold | Class I A3: Intake below threshold |
|        |          |                            |                   | No safety concern at the estimated level of intake | No safety concern at the estimated level of intake |
|        |          |                            |                   | | Concluded in FGE.70Rev1 |
| 02.153 | 1784     | Hepta-2,4-dien-1-ol        | ![Hepta-2,4-dien-1-ol](image) | Class I B3: Intake below threshold, B4: Adequate NOAEL exists | Class I A3: Intake below threshold |
|        |          |                            |                   | No safety concern at 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 |
| 05.141 | 1786     | Deca-2,4,7-trienal         | ![Deca-2,4,7-trienal](image) | Class I B3: Intake below threshold, B4: Adequate NOAEL exists | Class I A3: Intake below threshold |
|        |          |                            |                   | No safety concern at the estimated level of intake | No safety concern at the estimated level of intake |
|        |          |                            |                   | | Concluded in FGE.70Rev1 |
| 05.173 | 1785     | Nona-2,4,6-trienal         | ![Nona-2,4,6-trienal](image) | Class I B3: Intake below threshold, B4: Adequate NOAEL exists | Class I A3: Intake below threshold |
|        |          |                            |                   | No safety concern at the estimated level of intake | 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 | EU Union List chemical name | Structural formula | JECFA conclusions | EFSA conclusions |
|---|---|---|---|---|
| 09.573 1780 | Hexa-2,4-dienyl acetate | ![Structural formula](image) | 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) × 10⁷/(0.1 × population in Europe (≈ 375 × 10⁶) × 0.6 × 365) = µg/capita per day.  
(d): Refer to Appendix C for MSDI values considered by EFSA based on EU production figures submitted by Industry (Documentation provided to EFSA n. 1; 3 and 6).
### 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] | 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 | | | | |
| 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.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 (mg/kg bw per day) | 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.