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Scientific Opinion on Flavouring Group Evaluation 73, Revision 5 (FGE.73Rev5): consideration of alicyclic alcohols, aldehydes, acids and related esters evaluated by JECFA (59th, 63rd and 86th meeting) and structurally related to substances evaluated in FGE.12Rev5

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

Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 24 flavouring substances assigned to the Flavouring Group Evaluation 73 (FGE.73), using the Procedure as outlined in the Commission Regulation (EC) No 1565/2000. Twenty-three substances have already been considered in FGE.73 and its four revisions ([FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534, 09.615, 05.119, 05.123, 08.034, 08.060, 09.028, 09.536, 05.104, 09.034, 09.712, 09.305, 02.060, 02.091, 09.278, 09.302]). The remaining substance myrtenal [FL-no: 05.106] has been cleared with respect to genotoxicity in FGE.208Rev3 and is considered in this revision 5 of FGE.73. The substances were evaluated through a stepwise approach that integrates information on the structure–activity relationships, intake from current uses, toxicological threshold of concern (TTC), and available data on metabolism and toxicity. The Panel concluded that none of these 24 substances gives rise to safety concerns at their levels of dietary intake, estimated on the basis of the 'Maximised Survey-derived Daily Intake' (MSDI) approach. Besides the safety assessment of the flavouring substances, the specifications for the materials of commerce have also been considered and found adequate for 23 substances. For [FL-no: 09.278], the stereoisomeric composition is not specified. For two substances [FL-no: 09.034, and 09.712], the modified Theoretical Added Maximum Daily Intake (mTAMDI) estimates are above the TTC for their structural class (I). For 17 substances evaluated through the Procedure, no normal and maximum use levels are available. Therefore, for these 19 substances, more detailed data on uses and use levels should be provided in order to refine their exposure assessments and to finalise their safety evaluations.

Keywords: Flavourings, Myrtenal, α,β-unsaturated carbonyls, FGE.73 Rev4, JECFA

Requestor: European Commission

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Correspondence: fip@efsa.europa.eu

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

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1. Introduction

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of myrtenal [FL-no: 05.106], an α,β-unsaturated carbonyl substance that has been evaluated with respect to genotoxicity in FGE.208Rev3 (EFSA FAF Panel, 2019). According to the Mandate and Term of Reference of this FGE, when for a flavouring substance the concern for genotoxicity is ruled out, the European Food Safety Authority (EFSA) proceeds to the full evaluation of this flavouring substance, 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.208Rev3 are cited below.

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

1.1.1. Background of mandate from FGE.208Rev3

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 contains flavouring substances for which the safety evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000[1].

On July 2015, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) adopted an opinion on Flavouring Group Evaluation 208 Revision 1 (FGE.208Rev1): Consideration of genotoxicity data on representatives for 10 alicyclic aldehydes with the α,β-unsaturation in ring/side-chain and precursors from chemical subgroup 2.2 of FGE.19 (EFSA CEF Panel, 2015). This opinion was a revision of the earlier opinion on this group of substances on the basis of additional data.

The Panel concluded that *p*-mentha-1,8-dien-7-al [FL-no: 05.117] is genotoxic *in vivo* and as that substance was regarded as the representative of the group, there is a potential safety concern for the other substances in this group. Following this opinion, the Commission withdrew from the Union List of flavorings the representative substance [FL-no: 05.117][4] with an urgent procedure and also the non-supported substances 2,6,6-trimethyl-1-cyclohexen-1-carboxaldehyde [FL-no: 05.121], myrtenyl formate [FL-no: 09.272], myrtenyl-2-methylbutyrate [FL-no: 09.899] and myrtenyl-3-methylbutyrate [FL-no: 09.900].[5]

Also, following the EFSA opinion of 2015 FGE.208Rev1, the Commission amended the conditions of use of these five substances of this group in another Regulation,[6] pending the evaluation of the additional data.

The applicant submitted individual in vitro studies on the substances myrtenol [FL-no: 02.091], pmentha-1,8-dien-7-ol [FL-no: 02.060], myrtenal [FL-no: 05.106], *p*-mentha-1,8-dien-7-yl acetate [FL-no:09.278] and myrtenyl acetate [FL-no: 09.302]. EFSA evaluated these studies and related scientific data in its Scientific Opinion on Flavouring Group Evaluation 208 Revision 2 (FGE.208Rev2): Consideration of genotoxicity data on alicyclic aldehydes with α,β-unsaturation in ring/side-chain and precursors from chemical subgroup 2.2 of FGE.19. The Panel considered as regards myrtenal [FL-no:

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

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

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

[4] Commission Regulation (EU) 2015/1760 of 1 October 2015 amending Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council as regards removal from the Union list of the flavouring substance p-mentha-1,8-dien-7-al. OJ L 257, 2.10.2015, p. 27–29.

[5] Commission Regulation (EU) 2016/637 of 22 April 2016 amending Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council as regards removal from the Union list of certain flavouring substances. OJ L 108, 23.4.2016, p. 24–27.

[6] Commission Regulation (EU) 2016/1244 of 28 July 2016 amending Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council as regards certain flavouring substances from a group related with an alpha, beta unsaturation structure. OJ L 204, 29.7.2016, p. 7–10.

05.106] assessing in particular the studies on this substance submitted by industry (a bacterial reverse mutation assay, Mc Garry, 2016a, and two micronucleus assays in human peripheral blood lymphocytes, Mc Garry, 2016b and Lloyd, 2017). The Panel concluded that *myrtenal 'did not induce gene mutations in a bacterial reverse mutation assay. The first in vitro micronucleus assay provided was equivocal and had several weaknesses, therefore a repetition of the study was requested. The second study is considered more reliable than the first one, but the result is still not fully adequate to rule out the concern for genotoxicity. In this second study, weak statistically significant increases of the micronuclei frequency were observed at the lowest and highest concentrations (without statistically significant trend) in the absence of S9-mix after long treatment, while after short treatment, there was a statistically significant trend (without statistically significant differences between single concentrations tested and the concurrent control). The Panel considered that the result of this second study was also equivocal and that this was not adequately investigated by the applicant. Therefore, myrtenal cannot be evaluated through the [EFSA] Procedure [for evaluating existing flavouring substances of the program of Regulation 1565/2000], presently'*.

In July 2018 JECFA has assessed myrtenal [FL-no: 05.106] (JECFA no. 980). The substance p-mentha-1,8-dien-7-al [FL-no: 05.117] (JECFA no. 973) was also evaluated by JECFA at this same time. In addition, also other substances included in this FGE were as well evaluated by JECFA at the same time.

1.1.2. Terms of Reference of Mandate from FGE.208Rev3 (M-2018-0137)

The European Commission requests the European Food Safety Authority (EFSA) to evaluate the additional available studies on myrtenal [FL-no: 05.106] and in particular the *in vivo* studies. This substance is part of the FGE.208 (FGE.19 subgroup 2.2).

Depending on the outcome, the Authority is asked to indicate if its current assessment regarding genotoxicity of myrtenal remains or if it can proceed to the full evaluation of this flavouring substance, taking into account the requirements of the Commission Regulation (EC) No 1565/2000[1] and also those of Regulation (EU) No 1334/2008[2].

The Authority is also asked to consider if it is appropriate to revise the section regarding the characterization of the hazard concerning myrtenal and also the quantification of the exposure. The evaluation should be carried out in 6 months.

In case the EFSA Procedure of evaluation of existing flavouring substances can be applied the Authority is asked to deliver its opinion about the application of the Procedure within 9 months from the date of publication of the first opinion mentioned above.

1.2. Interpretation of the Terms of Reference

Myrtenal [FL-no: 05.106] was first allocated to FGE.208Rev3 (EFSA FAF Panel, 2019) for evaluation with respect to genotoxicity. Based on the new genotoxicity data submitted, the Panel concluded that this flavouring substance does not give rise to concern with respect to genotoxicity and can accordingly be evaluated through the Procedure in the present revision of FGE.73 (FGE.73Rev5), in accordance with Commission Regulation (EC) No 1565/2000[1].

Myrtenal 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, 2002a, 2005a, 2018a). For these 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).

1.3. History of evaluation of the substances in FGE.73

FGE.73 includes considerations on alicyclic alcohols, aldehydes, acids and related esters, which have been evaluated by JECFA in a group of 26 flavouring substances at its 59th meeting (JECFA, 2002a,b, 2018a). Ten of the 26 JECFA-evaluated substances are α,β-unsaturated carbonyls, or precursors for that, and they were therefore assessed for their potential genotoxicity concern in FGE.208 [FL-no: 05.117, 02.060, 09.278, 05.121, 05.106, 02.091, 09.302, 09.272], FGE.209 [FL-no: 05.104] and FGE.207 [FL-no: 09.034]. One of the 26 JECFA evaluated substances, santalol (CAS: 115-71-9 or 77-42-9; JECFA nr: 984), was originally included in the Register, but not included in the UL.

In FGE.73, the Panel only considered 15 of the 26 JECFA-evaluated substances and concluded that for nine of these substances, i.e. [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534 and 09.615], additional data were needed (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 of the isomers).

For the remaining 6 of the 15 JECFA-evaluated substances, i.e. [FL-no: 05.119, 05.123, 08.034, 08.060, 09.028 and 09.536], the Panel agreed with the JECFA conclusion 'no safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach.

The first Revision of FGE.73, FGE.73Rev1, included the assessment of one additional candidate substance, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (EFSA CEF Panel, 2012). No toxicity or metabolism data were provided for the substance. Furthermore, EU production volumes were provided for three substances, [FL-no: 02.141, 09.488 and 09.534]. After the publication of FGE.73, the following information was received and included in revision 1: information on the configuration for six substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615] and the composition for one substance [FL-no: 05.112].

The second Revision of FGE.73, FGE.73Rev2, included the assessment of two additional flavouring substances, santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712] (EFSA CEF Panel, 2013a). These two substances have been considered with respect to genotoxicity in FGE.207 (EFSA CEF Panel, 2013b) and the Panel concluded that the data available did rule out the concern for genotoxicity and thus concluded that the substances could be evaluated through the Procedure.

Santalyl phenylacetate [FL-no: 09.712] was evaluated by JECFA at its 59th meeting (JECFA, 2002a,b) together with other phenethyl substances. With the exception of santanyl phenylacetate [FL-no: 09.712], these phenethyl substances were not α,β-unsaturated substances and were considered by EFSA in FGE.53 (EFSA AFC Panel, 2008) with the conclusion 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach. As the phenethyl part of the molecules was considered not to raise concern, the Panel concluded that santalyl phenylacetate [FL-no: 09.712] cleared from genotoxic concern in FGE.207 (EFSA CEF Panel, 2013b), could be included in FGE.73Rev2 (EFSA CEF Panel, 2013a) together with the other santalyl substance (santalyl acetate [FL-no: 09.034]) from FGE.207.

The third revision of FGE.73 (FGE.73Rev3) (EFSA CEF Panel, 2014a) concerned the consideration of one JECFA-evaluated substance β-ionyl acetate [FL-no: 09.305]. β-Ionyl acetate [FL-no: 09.305] was evaluated by JECFA at its 63rd meeting together with other monocyclic and bicyclic secondary alcohols, ketones and related esters (JECFA, 2005a,b). β-ionyl acetate [FL-no: 09.305] may be hydrolysed to β-ionol, which is considered as a precursor for an α,β-unsaturated ketone, and was originally allocated to and evaluated in FGE.213Rev1 (EFSA CEF Panel, 2014b) in which it was considered not to be of concern with respect to genotoxicity. The Panel concluded that the substance could be included in the FGE.73Rev3.

The fourth revision of FGE.73 (FGE.73Rev4) (EFSA CEF Panel, 2017b) concerned the consideration of four JECFA-evaluated substances *p*-mentha-1,8-dien-7-ol [FL-no: 02.060], myrtenol [FL-no: 02.091], *p*-mentha-1,8-dien-7-yl acetate [FL-no: 09.278] and myrtenyl acetate [FL-no: 09.302]. These substances were evaluated in FGE.208Rev2 (EFSA CEF Panel, 2017a) in which they were considered to be of no concern with respect to genotoxicity and they were subsequently evaluated through the procedure in FGE.73Rev4.

The 23 substances that have been considered in the above-mentioned revisions of FGE.73 will not be readdressed in the current revision, unless additional information is provided (e.g. on production volumes, use levels or specifications).

The present revision of FGE.73 (FGE.73Rev5) concerns the consideration on myrtenal [FL-no: 05.106], which was evaluated by JECFA in its 59th and 86th meetings (JECFA, 2002a,b, 2018a). This substance was originally evaluated in FGE.208Rev3 (EFSA FAF Panel, 2019) in which it was considered not to be of concern with respect to genotoxicity. Therefore, myrtenal can be evaluated in the present FGE using the Procedure.

FGE	Adopted by EFSA	Link	No of substances
FGE.73	6 March 2008	http://www.efsa.europa.eu/en/efsajournal/pub/868.htm	15
FGE.73Rev1	22 March 2012	http://www.efsa.europa.eu/en/efsajournal/pub/2638.htm	16
FGE.73Rev2	25 September 2013	http://www.efsa.europa.eu/en/efsajournal/pub/3393.htm	18
FGE.73Rev3	24 September 2014	http://www.efsa.europa.eu/en/efsajournal/pub/3862.htm	19
FGE.73Rev4	19 September 2017	http://www.efsa.europa.eu/en/efsajournal/pub/5010.htm	23
FGE.73Rev5	10 December 2019	http://www.efsa.europa.eu/en/efsajournal/pub/5970.htm	24

FGE: Flavouring Group Evaluation.

2. Data and methodologies

2.1. Data

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

FL-no	Chemical name	Data provided for the current revision 5 of FGE.73	Appendix (Table nr) and relevant section of the opinion	Documentation provided to EFSA
05.106	Myrtenal	Specifications, Use levels (mTAMDI)	Appendix B (Table B.1) Appendix C (Table C.2)	Documentation provided to EFSA n. 3 and 1

FL-no: FLAVIS number; FLAVIS: Flavour Information System; FGE: Flavouring Group Evaluation; mTAMDI: modified Theoretical Added Maximum Daily Intake.

In addition, the following documentation was used:

- EU poundage data for myrtenal (MSDI) (JECFA, 2002a,b,).
- Genotoxicity data evaluated in FGE.208Rev2 (EFSA CEF Panel, 2017a) and FGE.208Rev3 (EFSA FAF Panel, 2019).
- Data evaluated in FGE.73 and its following revisions (EFSA CEF Panel, 2012, 2013a, 2014a, 2017b).
- JECFA specifications for myrtenal [FL-no. 05.106] (JECFA, 2018b).
- 59th and 86th JECFA reports (JECFA, 2002a and JECFA, 2018).

2.2. Methodologies

This opinion was elaborated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing 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 24 flavouring substances [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534, 09.615, 05.119, 05.123, 08.034, 08.060, 09.028, 09.536, 05.104, 09.034, 09.712, 09.305, 02.060, 02.091, 09.278, 09.302 and 05.106] considered in the present opinion FGE.73Rev5 (JECFA, 2002b, 2005b, 2018b).

EFSA considerations

The newly included flavouring substance myrtenal [FL-no: 05.106] (see Table 1) has two chiral centres. According to information provided by EFFA (Documentation provided to EFSA n. 3), the substance is a racemate.

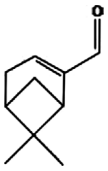
The Panel considered that the available specifications for myrtenal are adequate.

The Panel noted that for flavouring substance *p*-mentha-1,8-dien-7-yl acetate [FL-no: 09.278], the stereoisomeric composition is not specified (see 'EFSA comments' column in Table B.1 – Appendix B).

Therefore, the Panel requests information on the defined composition of the stereoisomeric mixture for this substance.

The most recent specifications data for all 24 substances in FGE.73Rev5 are summarised in Table B.1 – Appendix B. Table 1 below reports the newly added flavouring substance, myrtenal, considered in FGE.73Rev5.

Table 1: Flavouring substance under evaluation in FGE.73Rev5

[FL-no]	UL chemical name	Structural formula	Structural class*
05.106	Myrtenal		Class I

FL-no: FLAVIS number; FLAVIS: Flavour Information System; FGE: Flavouring Group Evaluation.
*: Determined with OECD Toolbox (version 4.3.1 available at https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm).

3.2. Estimation of intake

JECFA status

For the 24 flavouring substances considered in the present opinion FGE.73Rev5 and evaluated through the JECFA Procedure [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534, 09.615, 05.119, 05.123, 08.034, 08.060, 09.028, 09.536, 05.104, 09.034, 09.712, 09.305, 02.060, 02.091, 09.278, 09.302 and 05.106], annual production volumes are available for the EU (JECFA, 2002a, 2005a, 2018a) (see Appendix C, Table C.4).

EFSA considerations

Updated EU production figure for candidate flavouring substance [FL-no: 05.106] has been submitted by industry (Documentation provided to EFSA n. 1). From this information, an MSDI value of 2.2 μg/person per day can be calculated for myrtenal.

For 7 out of the 24 flavouring substances in FGE.73Rev5, i.e. [FL-no: 02.060, 02.091, 05.106, 09.034, 09.278, 09.302 and 09.712], normal and maximum use levels have been submitted by industry (Documentation provided to EFSA n. 1 and EFSA CEF Panel, 2017b) and mTAMDI values can be calculated. The mTAMDI estimated value for the candidate substance [FL-no: 05.106] is 1,700 μg/person per day. For two substances [FL-no: 09.034, and 09.712], the mTAMDI estimates are above the threshold of concern for their structural class (I) and more detailed exposure data are needed to finalise their evaluation.

No normal and maximum use levels have been provided for 17 substances ([FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.289, 09.028, 09.305, 09.488, 09.534, 09.536 and 09.615]) previously considered in FGE.73Rev4.

The MSDI figures and mTAMDI intake estimates for the 24 flavouring substances in FGE.73Rev5 are shown in Appendix C – Table C.4.

3.3. Biological and toxicological data

3.3.1. ADME data

Myrtenal [FL-no: 05.106] was evaluated by JECFA, at its 59th meeting (JECFA, 2002a), within a group of 26 substances that included alicyclic primary alcohols, aldehydes, acids and related esters. According to JECFA, bicyclic compounds, such as myrtenal, could be oxidised to yield the corresponding carboxylic acid. The acid metabolite would be conjugated with glucuronic acid and excreted mainly in the urine. In a minor pathway, the aldehyde can be reduced to the alcohol and excreted as the glucuronic acid conjugate. The endocyclic double-bond could be reduced by the action of gut microbiota. Therefore, JECFA concluded that myrtenal can be anticipated to be metabolised to innocuous products and can be evaluated along the A-side of the Procedure (see Appendix A.1).

FGE.12Rev5 contains flavouring substances with a monocyclic, bicyclic or tricyclic terpenoid moiety, all with a primary oxygenated function, which are structurally related to the substances under

consideration in the present FGE. In FGE.12Rev5 (EFSA CEF Panel, 2014c) there is an extensive description of the possible metabolic routes which would be expected for monocyclic and bicyclic terpenoid aldehydes and alcohols. Particularly for the candidate substance myrtenal [FL-no: 05.106], experimental data are available. Quoting from FGE.12Rev5: 'Six male rabbits received an oral dose of 2,000 mg of 2 ((-)-myrtenal) per animal. In the urine of these animals myrtenol, dihydromyrtenol, myrtenic acid and perillic acid could be detected. Myrtenol and dihydromyrtenol comprised together 99% of the neutral metabolite fraction (5% of the dose). Myrtenic acid represented 76% of the acid metabolites detected in the urine, but the amount of perillic acid was not specified. The total acidic fraction of urinary metabolites comprised 24% of the dose. These results indicate that myrtenal can be metabolised to the corresponding carboxylic acid (myrtenic acid). The presence of perillic acid indicates some cleavage of the strained bicyclic ring. To a lesser extent, the aldehyde can either be reduced to myrtenol, which may be conjugated with glucuronic acid and excreted or it may undergo hydrogenation of the double bond to yield dihydromyrtenol (myrtanol), see Figure 1 which is one of the candidate substances [FL-no: 02.186], shown to be the major neutral metabolite and excreted unchanged with the urine (Ishida et al., 1989). Urine was collected during 3 days post dosing. Only a fairly low part of the administered dose was recovered. Other metabolites were not mentioned' (EFSA CEF Panel, 2014c).

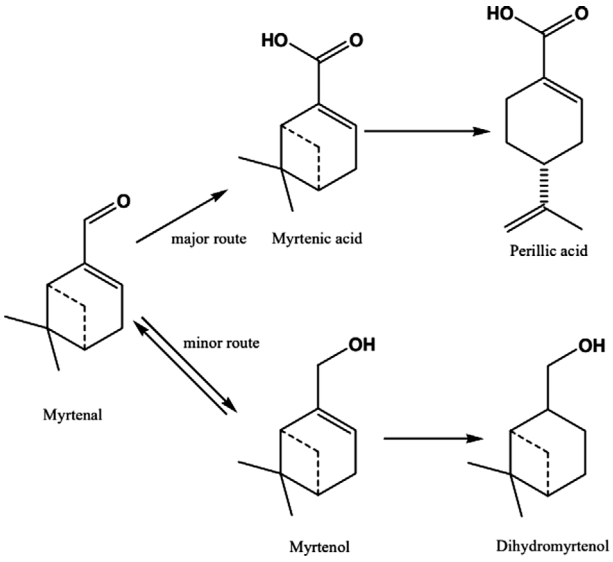


Figure 1: Metabolism of myrtenal in rabbits

In summary, in FGE.12Rev5 it is concluded that in mammals, monocyclic or bicyclic terpenoid primary alcohols and aldehydes are generally oxidised to the corresponding carboxylic acid, conjugated with glucuronic acid and then they are excreted as urinary metabolites. In a minor extent, another possible pathway is the aldehyde reduction to the corresponding alcohol and excreted as the glucuronide (Ishida et al., 1989; Haag and Gould, 1994). If an endocyclic double bond is present, reduction of this double bond may also occur. Further, the cyclohexene derivatives, which may be derived from myrtenal, may also undergo allylic hydroxylation of the ring and then possible oxidation to keto groups or conjugation with glucuronic acid. These polar metabolites would be excreted in the urine.

EFSA considerations

Based on the information provided by JECFA (2002a) and reported in FGE.12Rev5 (EFSA CEF Panel, 2014c), the Panel considers that neither the chemical structure of the candidate substance myrtenal nor its available metabolic data suggest that reactive metabolites could be generated. Therefore, myrtenal would be expected to be absorbed and metabolised to innocuous products, which are excreted. Hence, the Panel agrees with JECFA that myrtenal [FL-no: 05.106] can be evaluated along the A-side of the Procedure (see Appendix A.1).

3.3.2. Genotoxicity data

This revision involves the inclusion of one flavouring substance, myrtenal [FL-no: 05.106] for which in FGE.19 a concern for genotoxicity had been identified based on the presence of a structural alert (i.e. α,β-unsaturated carbonyl substance or precursor for that), precluding its evaluation through the Procedure (see also Appendix A.1). Therefore, this substance was evaluated in FGE.208Rev3 where its genotoxic potential has been assessed and ruled out (EFSA FAF Panel, 2019). Consequently, the safety evaluation through the Procedure can be performed for myrtenal [FL-no: 05.106].

3.3.3. Toxicological data

No subacute, subchronic/chronic toxicity and carcinogenicity studies are available on myrtenal [FL-no: 05.106] or on structurally related supporting substances.

3.4. Application of the Procedure

Application of the Procedure to myrtenal [FL-no: 05.106] from JECFA flavouring group of alicyclic primary alcohols, aldehydes, acids and related esters (JECFA, 2002a, 2018a).

In the 59th and 86th JECFA reports, the candidate substance myrtenal [FL-no: 05.106] was allocated to structural class I using the decision tree approach presented by Cramer et al. (1978).

In 2002, JECFA concluded that myrtenal [FL-no: 05.106] can be anticipated to be metabolised to innocuous products (step 2) and its intake (MSDI) is below the threshold of concern for the structural class I (i.e. 1,800 μg/person per day) (step A3). Therefore, JECFA evaluated myrtenal [FL-no: 05.106] as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

In 2018, JECFA re-evaluated myrtenal [FL-no: 05.106] in its 86th meeting since additional genotoxicity data became available. This new assessment was performed by applying the updated procedure scheme for the safety evaluation of flavouring agents, endorsed by JECFA at the 82nd meeting (JECFA, 2016 and see also Appendix A.2).

In line with the previous evaluation, JECFA confirmed that this flavouring substance would not pose a safety concern at current estimated dietary exposures.

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

EFSA considerations

The FAF Panel agrees with JECFA with respect to the assignment of the candidate flavouring substance [FL-no: 05.106] to Cramer class I. The Panel agrees with the way of the application of the Procedure that has been performed for myrtenal [FL-no: 05.106] at the 59th JECFA meeting (JECFA, 2002a).

The MSDI exposure estimate for myrtenal [FL-no: 05.106] is below the threshold of concern for structural class I (i.e. 1,800 μg/person per day) (see Table C.4 – Appendix C). Therefore the FAF Panel concludes, at step A3 of the Procedure scheme, that myrtenal does not raise a safety concern when used as flavouring substance at the current levels of use, based on the MSDI approach.

In addition, the Panel noted that the revised JECFA Procedure scheme (JECFA, 2016) was applied to myrtenal at its 86th meeting (JECFA, 2018a). This new approach is in line with the modified procedure for evaluation of substances based on the TTC approach, which has been adopted by EFSA Scientific Committee (EFSA Scientific Committee, 2019). However, taking into consideration the requirements set out in Commission Regulation (EC) No 1565/2000, the Panel followed the strategy as specified in the Opinion on a Programme for the Evaluation of Flavouring substances of the Scientific Committee on Food (SCF, 1999) (for details see Appendix A.1).

The stepwise evaluation of myrtenal [FL-no: 05.106] is summarised in Table D.1 - Appendix D.

4. Discussion

This revision 5 of FGE.73 comprises in total 24 flavouring substances, 23 of which have already been considered in FGE. 73 and its revisions. The remaining flavouring substance myrtenal [FL-no: 05.106] has been included in this revision, following an extensive evaluation in FGE.208Rev3 of its genotoxic potential due to the presence of a structural alert for genotoxicity (i.e. α,β-unsaturated carbonyl or precursors for that).

Based on consideration of structural class, metabolism data and the absence of genotoxic potential *in vivo*, and the MSDI exposure estimates, the FAF Panel concludes at step A3 of the Procedure that myrtenal, considered in this revision of FGE.73 (FGE.73Rev5), does not raise a safety concern.

For 7 out of the 24 flavouring substances in FGE.73Rev5, including the candidate substance myrtenal (i.e. [FL-no: 02.060, 02.091, 05.106, 09.034, 09.278, 09.302 and 09.712]), normal and maximum use levels have been submitted by industry and mTAMDI values can be calculated. The mTAMDI estimated value for myrtenal [FL-no: 05.106] is 1,700 μg/person per day. For this substance and for four other substances [FL-no: 02.060, 02.091, 09.278 and 09.302], the mTAMDIs are below the TTC for their structural class I. For two substances [FL-no: 09.034 and 09.712], the mTAMDI estimates are above the threshold of concern for their structural class (I) and more detailed exposure information is needed to finalise their evaluation. For the previously (in FGE.73Rev4) considered 17 substances [FL-no: 02.114, 02.141, 05.104, 05.098, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.028, 09.289, 09.305, 09.488, 09.534, 09.536 and 09.615], no normal or maximum use levels have been provided. For these 17 substances, normal and maximum use levels are needed to calculate the mTAMDI estimates in order to identify those flavouring substances that need more detailed exposure assessment and to finalise the evaluation accordingly. To determine whether the conclusions for the 24 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 23 out of the 24 flavouring substances in this FGE. For substance [FL-no: 09.278], the stereoisomeric composition is not specified.

5. Conclusions

For 24 flavouring substances in FGE.73Rev5, including the newly included substance myrtenal [FL-no: 05.106], the Panel agrees with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach. Besides the safety assessment of the flavouring substances, the specifications for the materials of commerce have also been considered and found adequate for 23 substances. For the remaining substance [FL-no: 09.278], the Panel has reservations as there is incomplete information on the chemical identity (composition of the stereoisomeric composition is lacking). For 19 substances [FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.028, 09.289, 09.034, 09.305, 09.488, 09.534, 09.536, 09.615, 09.712], more detailed data on uses and use levels should be provided in order to finalise their safety evaluations.

6. Recommendations

The Panel recommends the European Commission to consider:

- to request normal and maximum use levels for [FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.289, 09.028, 09.305, 09.488, 09.534, 09.536, 09.615].
- to request more detailed data on uses and use levels for substances [FL-no: 09.034 and 09.712], as their mTAMDI exposure estimates are above the threshold of concern for their structural class I. When these data are received, the assessment for these flavouring substances should be updated accordingly and expanded if necessary (i.e. request of additional toxicity data).
- to request data on the stereoisomeric composition of *p*-Mentha-1,8-dien-7-yl acetate [FL-no:09.278] (see Table B.1 of Appendix B).
- to change the chemical names of [FL-no: 09.289] to reflect the stereochemical configuration and to change the CAS number for [FL-no: 09.302] (see Table B.1 of Appendix B).

Documentation as provided to EFSA

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2) 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.
3) EFFA (European Flavour Association), 2019. EFFA submission of additional information on isomeric composition of myrtenal [FL-no : 05.106].

4) Lloyd M, 2017. Myrtenal: *in vitro* human lymphocyte micronucleus assay. Covance Laboratories Ltd., England. Study no. 8351223. 24 January 2017. Unpublished study report submitted by EFFA to EFSA.
5) Mc Garry S, 2016a. Myrtenal: bacterial reverse mutation assay. Covance Laboratories Ltd., England. Study no. 8332788. 17 February 2016. Unpublished study report submitted by EFFA to EFSA.
6) Mc Garry S, 2016b. Myrtenal: *in vitro* human lymphocyte micronucleus assay. Covance Laboratories Ltd., England. Study no. 8332792. 10 February 2016. Unpublished study report submitted by EFFA to EFSA.

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Abbreviations

ADME	absorption, Distribution, Metabolism, Elimination
BW	body weight
CAS	Chemical Abstract Service

CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFFA	European Flavour and Fragrance Association
FAO	Food and Agriculture Organization of the United Nations
FAF	Panel on Food Additives and Flavourings
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
ID	identity
IR	infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MS	mass spectrometry
MSDI	maximised survey-derived daily intake
mTAMDI	modified Theoretical Added Maximum Daily Intake
NMR	nuclear magnetic resonance
No	number
NOAEL	no observed adverse effect level
(Q)SAR	(quantitative) structure–activity relationship
SCF	Scientific Committee on Food
SPET	single-portion exposure technique
TTC	toxicological thresholds of concern
WHO	World Health Organization

Appendix A – Procedure of the safety evaluation

A.1. EFSA Procedure for the safety evaluation of flavourings

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'.[7]

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

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

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

- Can the flavourings be predicted to be metabolised to innocuous products[8] (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous[9] (step A4)?
- Does a NOAEL exist on the flavourings or on structurally related substances (steps A5 and B4)?

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

[7] The FAF Panel is aware that a Revised Procedure for the Safety Evaluation of Flavouring agents has been agreed by JECFA (2016). Also, the EFSA Scientific Committee has adopted 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.

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

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

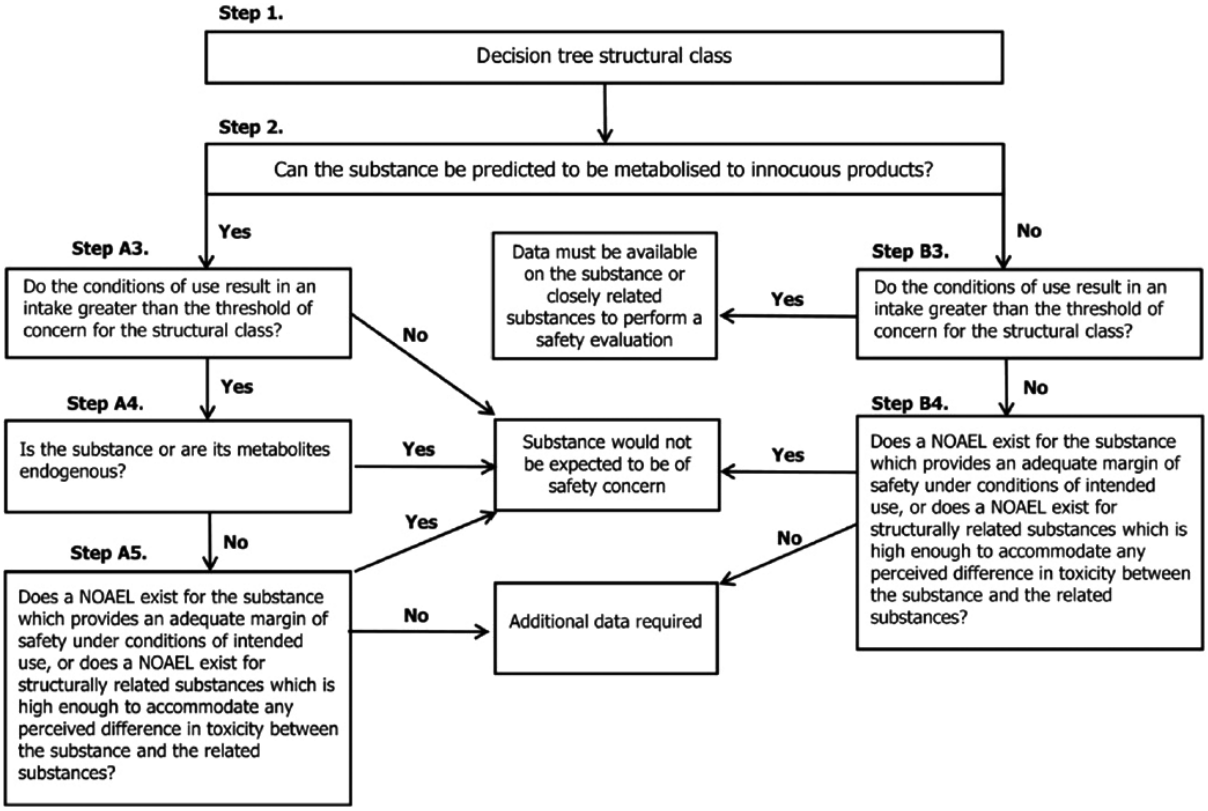


Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances

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

The following issues are of special importance:

a) Intake

In its evaluation, the Panel as a default uses the 'maximised survey-derived daily intake' (MSDI)[10] approach to estimate the per capita intakes of the flavouring substances in Europe.

In its evaluation, JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by JECFA only on the basis of these figures. For substances in the Union List[3] of flavouring substances for which this is the case, the Panel will need European Union (EU) production figures in order to finalise the evaluation.

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

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

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 j.tg/person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents, used at the forty-sixth meeting, should be amended to include the last step on the right-hand side of the original procedure ('Do the conditions of use result in an intake greater than 1.5 j.tg per day?')' (JECFA, 1999).

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

c) Genotoxicity

As reflected in the opinion of SCF (1999), the Panel has in its evaluation focused 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.

A.2. Revised JECFA Procedure for the safety evaluation of flavouring substances (JECFA, 2016)

Based on the recommendations from the joint EFSA/WHO experts workshop (EFSA and WHO, 2016) on how the existing TTC framework may be improved and how to develop a globally harmonized decision-tree for a tiered approach on the application of the TTC in the risk assessment of chemicals, the JECFA Committee proposed a revised Procedure for the safety evaluation of flavouring substances in its 82nd meeting (JECFA, 2016).

In the revised JECFA Procedure scheme an initial question with respect to the genotoxicity potential of the substance is introduced (i.e. if a concern for genotoxicity is identified the Procedure cannot be applied). As a consequence, also step B5 of the old Procedure ('Do the conditions of use result in an intake greater than 1.5 μg/day?') is removed as it was considered of little practical application. Moreover, the Cramer class thresholds as applied would be adequately protective for a non-genotoxic cancer end-point. Another important change is the deletion of the question, at step 2 of the old Procedure, related to the expected metabolites ('Can the substance be predicted to be metabolized to innocuous products?') and therefore to combine the A- and B- side of the old Procedure. The evaluation is then based on the comparison of the highest predicted dietary exposure estimate (based

on MSDI and SPET[11] approach) of the flavouring substance with the corresponding TTC value for its structural class.

The updated JECFA Procedure scheme is reported in the Figure A.2.

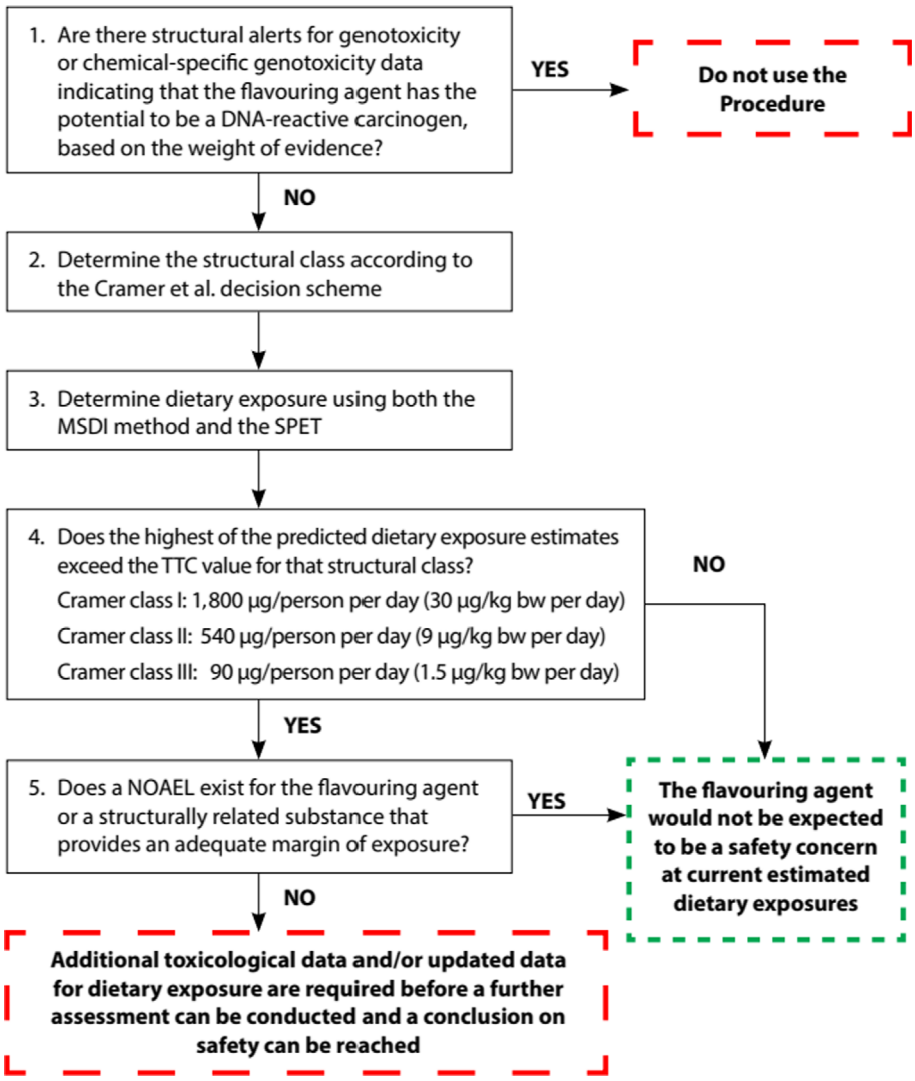


Figure A.2: Revised JECFA Procedure for the safety evaluation of flavouring substances

[11] Single-portion exposure technique.

Appendix B – Specifications

Table B.1: Summary table on specifications data for flavouring substances in FGE.73Rev5

Information included in the EU Union ListRegulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA Comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubilityc[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. Index[f] Spec. gravity[g]**	
02.060 974 2664 2024 536-59-4	*p*-Mentha-1,8-dien-7-ol	b)	Liquid $C_{10}H_{16}O$ 152.24	Slightly soluble Soluble	119 (14 hPa) NMR 96% (racemate)	1.495–1.505 0.956–0.963	
02.091 981 3439 10285 515-00-4	Myrtenol	b)	Liquid $C_{10}H_{16}O$ 152.24	Insoluble Miscible	221 IR NMR 95%	1.490–1.500 0.976–0.983	
02.114 970 3741 1901-38-8	2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol	b)	Liquid $C_{10}H_{18}O$ 154.25	Slightly soluble Miscible	74 (0.8 hPa) NMR 96% (racemate)	1.470–1.478 0.882–0.894 (20°)	
02.141 986 3938 128-50-7	2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol	b)	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Miscible	230 IR NMR 95% (racemate)	1.490–1.500 0.965–0.973	
05.098 971 3178 10347 29548-14-9	*p*-Menth-1-en-9-al	b)	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	95 (13 hPa) NMR 99% (racemate)	1.458–1.466 0.904–0.916 (20°)	
05.104 977 3389 10383 116-26-7	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde	b)	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	70 (1 hPa) NMR 96%	1.525–1.533 0.968–0.980 (20°)	

Information included in the EU Union ListRegulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA Comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubilityc[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. Index[f] Spec. gravity[g]**	
05.106 980 3395 10379 564-94-3	Myrtenal	b)	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	220 NMR 98% (racemate)	1.496–1.507 0.984–0.990	According to the information provided, the substance is a racemate (Documentation provided to EFSA n. 3)
05.112 978 3474 10338 472-66-2	2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde	92%	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Miscible	58 (0.5 hPa) IR NMR 92% SC: β-cyclocitral 2–3%, β-ionone 0.5–1%, methyl β-homocyclogeranate 2–4%, ethyl β-homocyclogeranate 0.6–1%	1.480–1.487 0.873–0.885 (20°)	
05.119 967 3592 10325 4501-58-0	(1*R*) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	b)	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	75 (137 hPa) NMR 99%	1.462–1.469 0.918–0.924	
05.123 968 3645 55253-28-6	(1*R*,2*R*,5*S*) 5-Isopropenyl-2-methylcyclopentane carboxaldehyde	b)	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	80 (14 hPa) IR 95%	1.501–1.508 0.940–0.952 (20°)	
08.034 965 2347 34 5292-21-7	Cyclohexylacetic acid	b)	Solid $C_8H_{14}O_2$ 142.20	Slightly soluble Miscible	242 28–33 NMR 98%	1.459–1.467 1.001–1.009	

Information included in the EU Union ListRegulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA Comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubilityc[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. Index[f] Spec. gravity[g]**	
08.060 961 3531 11911 98-89-5	Cyclohexanecarboxylic acid	b)	Solid $C_7H_{12}O_2$ 128.17	Slightly soluble Miscible	232–233 28–32 IR NMR 98%	1.516–1.520 1.029–1.037	
08.067 976 3731 71298-42-5	1,2,5,6-Tetrahydrocuminic acid	b)	Solid $C_{10}H_{16}O_2$ 168.24	Slightly soluble Soluble	n.a. 61 NMR 95% (racemate)	n.a. n.a.	
09.028 964 2348 218 21722-83-8	2-Cyclohexylethyl acetate	b)	Liquid $C_{10}H_{18}O_2$ 170.25	Insoluble Miscible	211 (996 hPa) NMR 98%	1.442–1.450 0.945–0.948	
09.034 985 3007 224 1323-00-8	Santalyl acetate	b)	Liquid $C_{17}H_{26}O_2$ 262.40	Insoluble Miscible	20.8 (4 hPa) IR 95% (60–65% α- and 30–35% β-form. 80–85% *Z* vs 15–20% *E* (for the α) and 75–80% *Z* vs 20–25% *E* (for the β))	1.485–1.493 0.980–0.986	
09.278 975 3561 10742 15111-96-3	*p*-Mentha-1,8-dien-7-yl acetate	b)	Liquid $C_{12}H_{18}O_2$ 194.27	Insoluble Miscible	218–223 NMR 97%	1.476–1.487 0.972–0.980	Stereoisomeric composition to be specified

Information included in the EU Union ListRegulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA Comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubilityc[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. Index[f] Spec. gravity[g]**	
09.289 969 3657 36789-59-0	α-Campholene acetate	b)	Liquid $C_{12}H_{20}O_2$ 196.29	Insoluble Miscible	96 (7 hPa) IR NMR 98%	1.453–1.460 0.943–0.949	EU Union List name to be changed to (-)-campholenyl acetate or (*S*)-campholenyl acetate (EFSA CEF Panel, 2017b)
09.302 982 3765 10887 1079-01-2	Myrtenyl acetate	b)	Liquid $C_{12}H_{18}O_2$ 194.28	Miscible	134 (49 hPa) IR NMR MS 98% (racemate)	1.470–1.477 0.987–0.996	CAS nr in the Union list to be changed to 35670-93-0 (EFSA CEF Panel, 2017b)
09.305 1409 3844 10702 22030-19-9	β-Lonyl acetate	92%	Liquid $C_{15}H_{24}O_2$ 236.35	Insoluble Soluble	120 (3 hPa) NMR 92% racemate, mainly *E*-isomer: *E*/*Z* ratio about 50–70%/30–50% SC 2–3% acetic acid and 1–2% β-ionol	1.474–1.484 0.934–0.944	
09.488 966 2431 2095 10094-36-7	Ethyl cyclohexanepropionate	b)	Liquid $C_{11}H_{20}O_2$ 184.28	Insoluble Miscible	91 (10 hPa) NMR 98%	1.444–1.452 0.926–0.932	
09.534 963 3544 11916 3289-28-9	Ethyl cyclohexanecarboxylate	b)	Liquid $C_9H_{16}O_2$ 156.22	Insoluble Miscible	82 (16 hPa) IR NMR 99%	1.447–1.454 0.966–0.978 (20°)	

Information included in the EU Union ListRegulation No. (EU) 1334/2008 as amended			Most recent available specifications data[a]				EFSA Comments
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubilityc[c] Solubility in ethanol[d]**	**Boiling point, °C[e] Melting point, °C ID test Assay minimum (isomers distribution/SC)**	**Refrac. Index[f] Spec. gravity[g]**	
09.536 962 3568 11920 4630-82-4	Methyl cyclohexanecarboxylate	b)	Liquid $C_8H_{14}O_2$ 142.19	Insoluble Miscible	183 IR NMR 98%	1.439–1.447 0.990–0.999	
09.615 972 3566 10748 28839-13-6	*p*-Menth-1-en-9-yl acetate	b)	Liquid $C_{12}H_{20}O_2$ 196.28	Insoluble Miscible	228–232 NMR 97% (racemate)	1.441–1.448 0.931–0.937	
09.712 1022 3008 239 1323-75-7	Santalyl phenylacetate	b)	Liquid $C_{23}H_{30}O_2$ 338.49	Insoluble Miscible	328 NMR 98% (60–65% α- and 30–35% β-form. 80-85% *Z* vs 15–20% *E* (for the α) and 75–80% *Z* vs 20–25% *E* (for the β))	1.525–1.576 1.022–1.029	

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; NMR: nuclear magnetic resonance; IR: infrared spectroscopy; SC: secondary components.
(a): JECFA (2002a, 2005a, 2018a), EFSA CEF Panel (2017b) and Documentation provided to EFSA n. 3.
(b): At least 95% unless otherwise specified.
(c): Solubility in water, if not otherwise stated.
(d): Solubility in 95% ethanol, if not otherwise stated.
(e): At 1,013.25 hPa, if not otherwise stated.
(f): At 20°C, if not otherwise stated.
(g): At 25°C, if not otherwise stated.

Appendix C – Exposure estimates

C.1. Normal and Maximum Use Levels

Table C.1: Normal and maximum use levels (mg/kg) of JECFA evaluated flavouring substances in FGE.73Rev5 in food categories listed in Annex III of Reg. (EC) 1565/2000 (Documentation provided to EFSA n. 1 and EFSA CEF Panel, 2013a,b)

FL-no	Normal and Maximum use levels (mg/kg) available for JECFA evaluated substances in FGE.73Rev5																		
	Food Categories (EU Reg 1565/2000)																		
	Normal use levels [(a)] (mg/kg) Maximum use levels (mg/kg)																		
	01.0	**02.0**	**03.0**	**04.1**	**04.2**	**05.0**	**05.3[(b)]**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
02.060	5 10	– –	5 10	5 10	– –	5 25	– –	5 10	8 50	– –	– –	– –	– –	– –	– –	1 5	0.5 1	– –	2 10
02.091	5 10	– –	5 10	– –	– –	5 10	1.1 3.1	5 10	– –	– –	– –	– –	– –	– –	– –	0.5 1	0.5 1	0.1 1	0.1 1
05.106	1 5	8 50	2 10	1 5	1 5	5 20	20 100	1 5	5 20	1 5	1 5	1 5	1 5	5 20	– –	1 5	1 5	1 5	1 5
09.034	7 35	5 25	10 50	7 35	0 0	10 50	10 –	5 25	10 50	2 10	2 10	2 10	2 10	5 25	10 50	5 25	10 50	20 100	5 25
09.278	5 10	0 0	5 10	– –	– –	5 10	0.1 5	5 16	7.2 16	1 3	– –	– –	– –	– –	– –	0.5 2	0.5 2	– –	2 10
09.302	5 10	0 0	5 10	5 10	5 10	5 30	2 30	5 10	2 5	– –	– –	– –	– –	– –	– –	1 4	2.4 4	– –	0 0
09.712	7 35	5 25	10 50	7 35	0 0	10 50	10 –	5 25	10 50	2 10	2 10	2 10	2 10	5 25	10 50	5 25	10 50	20 100	5 25

FL-no: FLAVIS number; FLAVIS: Flavour Information System; JECFA: The Joint FAO/WHO Expert Committee on Food Additives; FGE: Flavouring Group Evaluation.
(a): 'Normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages (Documentation provided to EFSA n. 2).
(b): Additional food category 05.3 (chewing-gum as per Annex II part D of Reg. (EC) 1333/2008) for which EFFA submitted use levels (Documentation provided to EFSA n. 1). These have been considered in the calculation of mTAMDI.

C.2. mTAMDI calculations

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

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

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

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 and reported by the Flavour Industry in the following way (see Table C.4):

- 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 calculations (SCF, 1995)

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

mTAMDI: modified Theoretical Added Maximum Daily Intake.

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

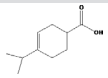
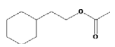
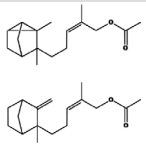
Estimated intakes based on the MSDI approach and the mTAMDI approach						
FL-no	**EU Union List name**	**MSDI[(a)] – EU (μg/capita per day)**	**MSDI[(b)] – USA (μg/capita per day)**	**mTAMDI[(c)] (μg/person per day)**	**Structural class**	**TTC (μg/person per day)**
02.060	*p*-Mentha-1,8-dien-7-ol	0.34	1	1,500	Class I	1,800
02.091	Myrtenol	0.1	0.03	980	Class I	1,800
02.114	2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol	0.012	ND		Class I	1,800
02.141	2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol	33	0.01		Class I	1,800
05.098	*p*-Menth-1-en-9-al	0.12	ND		Class I	1,800
05.106	Myrtenal	2.2	7	1,700	Class I	1,800
05.112	2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde	0.24	2		Class I	1,800
05.119	(1*R*) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	5	ND		Class I	1,800
05.123	(1*R*,2*R*,5*S*) 5-Isopropenyl-2-methylcyclopentanecarboxaldehyde	0.012	ND		Class I	1,800
08.034	Cyclohexylacetic acid	0.12	0.4		Class I	1,800
08.060	Cyclohexanecarboxylic acid	0.061	4		Class I	1,800
08.067	1,2,5,6-Tetrahydrocuminic acid	0.012	ND		Class I	1,800
09.028	2-Cyclohexylethyl acetate	0.97	ND		Class I	1,800
09.034	Santalyl acetate	0.1	0.01	3,900	Class I	1,800
09.278	*p*-Mentha-1,8-dien-7-yl acetate	1.4	0.07	1,300	Class I	1,800
09.289	α-Campholene acetate	0.061	ND		Class I	1,800
09.302	Myrtenyl acetate	0.91	0,04	1,200	Class I	1,800
09.305	β-Lonyl acetate	3.3	9		Class I	1,800
09.488	Ethyl cyclohexanepropionate	0.12	0.1		Class I	1,800
09.534	Ethyl cyclohexanecarboxylate	0.24	0.1		Class I	1,800
09.536	Methyl cyclohexanecarboxylate	0.073	0.01		Class I	1,800
09.615	*p*-Menth-1-en-9-yl acetate	0.85	ND		Class I	1,800
09.712	Santalyl phenylacetate	0.029	1	3,900	Class I	1,800
05.104	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde	3.5	0.07		Class I	1,800

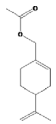
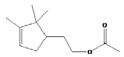
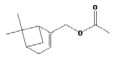
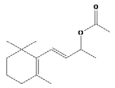
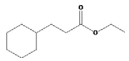
FL-no: FLAVIS number; FLAVIS: Flavour Information System; MSDI: maximised survey-derived daily intake; mTAMDI: modified Theoretical Added Maximum Daily Intake; TTC: toxicological thresholds of concern.
(a): Based on EU production figures from JECFA (2002a,b, 2005a,b).
(b): Based on US production figures from JECFA (2002a,b, 2005a,b).
(c): Based on use levels submitted by industry (Documentation provided to EFSA n.1 and EFSA CEF Panel, 2013a,b).

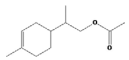
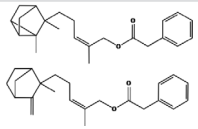
Appendix D – Summary of safety evaluations

Table D.1: Summary of safety evaluations performed by JECFA (2002a, 2005a, 2018a) and EFSA conclusions on flavouring substances in FGE.73 and its revisions

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a]Evaluation procedure path[b]Outcome on the named compound based on the MSDI[c] approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce
02.060 974	*p*-Mentha-1,8-dien-7-ol		Class I A3: Intake below threshold Step 4:[e] No – based on SPET: 1000 No safety concern at current levels of intake	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev4
02.091 981	Myrtenol		Class I A3: Intake below threshold Step 4:[e] No – based on SPET: 1000 No safety concern at current levels of intake	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev4
02.114 970	2-(2,2,3-Trimethylcyclopent-3-enyl) ethan-1-ol		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
02.141 986	2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
05.098 971	*p*-Menth-1-en-9-al		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
05.106 980	Myrtenal		Class I A3: Intake below threshold Step 4[e]: No – based on SPET: 1000 No safety concern at current levels of intake	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev5

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI[c] approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce
05.112 978	2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
05.119 967	(1*R*) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
05.123 968	(1*R*,2*R*,5*S*) 5-Isopropenyl-2-methylcyclopentanecarboxaldehyde		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
08.034 965	Cyclohexylacetic acid		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
08.060 961	Cyclohexanecarboxylic acid		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
08.067 976	1,2,5,6-Tetrahydrocuminic acid		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
09.028 964	2-Cyclohexylethyl acetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
09.034 985	Santalyl acetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev2

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI[c] approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce
09.278 975	*p*-Mentha-1,8-dien-7-yl acetate		Class I A3: Intake below threshold Step 4:[e] No – based on SPET: 1000 No safety concern at current levels of intake	Class I A3: Intake below threshold No safety concern at current levels of intake Not applicable to the material of commerce as pending further information on stereoisomerism (see 'EFSA Comments' Table B.1 Appendix B) Concluded in FGE.73Rev4
09.289 969	α-Campholene acetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Chemical name in the UL should be changed (see 'EFSA Comments' Table B.1 Appendix B) Concluded in FGE.73Rev1
09.302 982	Myrtenyl acetate		Class I A3: Intake below threshold Step 4:[e] No – based on SPET: 1000 No safety concern at current levels of intake	Class I A3: Intake below threshold No safety concern at current levels of intake CAS nr in the UL should be changed (see 'EFSA Comments' Table B.1 Appendix B) Concluded in FGE.73Rev4
09.305 1409	β-Lonyl acetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev3
09.488 966	Ethyl cyclohexanepropionate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
09.534 963	Ethyl cyclohexanecarboxylate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1

FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI[c] approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[d] approach on the named compound and on the material of commerce
09.536 962	Methyl cyclohexanecarboxylate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73
09.615 972	*p*-Menth-1-en-9-yl acetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1
09.712 1022	Santalyl phenylacetate		Class I A3: Intake below threshold	Class I A3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev2
05.104 977	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		Class I B3: Intake below threshold B4: Adequate NOAEL exists	Class I B3: Intake below threshold No safety concern at current levels of intake Concluded in FGE.73Rev1

FGE: Flavouring Group Evaluation; SPET: single-portion exposure technique; MSDI: maximised survey-derived daily intake.
(a): Thresholds of concern: Class I = 1,800 μg/person per day, Class II = 540 μg/person per day, Class III = 90 μg/person per day.
(b): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(c): EU MSDI: Amount added to food as flavour in (kg/year) × 109/(0.1 × population in Europe (= 375 × 106) × 0.6 × 365) = μg/capita per day.
(d): Refer to Appendix C for MSDI values considered by EFSA based on EU production figures submitted by industry (JECFA, 2002a,b, 2005a,b).
(e): Step 4 refers to the revised JECFA Procedure scheme (JECFA, 2016), for further details see also Appendix A.2.