Adopted: 4 July 2024

DOI: 10.2903/j.efsa.2024.8952

efsa JOURNAL

SCIENTIFIC OPINION

Flavouring Group Evaluation 80, Revision 2 (FGE.80Rev2): Consideration of alicyclic, alicyclic-fused and aromatic-fused ring lactones evaluated by the JECFA (61st and 82nd meetings) structurally related to an aromatic lactone evaluated in FGE.27

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Abstract

The EFSA Panel on Food Additives and Flavourings was requested to evaluate 14 flavouring substances assigned to the Flavouring Group Evaluation 80 (FGE.80), using the Procedure as outlined in the Commission Regulation (EC) No 1565/2000. Thirteen substances have already been considered in FGE.80 and its revision and in FGE.96 [FL-no: 10.005, 10.024, 10.025, 10.050, 10.061, 10.069, 10.070, 10.072, 10.169, 13.009, 13.012, 13.161 and 16.055]. The remaining flavouring substance 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one [FL-no: 10.057] has been cleared with respect to genotoxicity in FGE.217Rev3 and it is considered in this revision 2 of FGE.80. The substance [FL-no: 10.057] was evaluated through a stepwise approach that integrates information on the structure–activity relationships, intake from current uses, threshold of toxicological concern (TTC) and available data on metabolism and toxicity. The Panel concluded that [FL-no: 10.057] does not give rise to safety concerns at its levels of dietary intake, when estimated on the basis of the 'Maximised Survey-derived Daily Intake' (MSDI) approach. Besides the safety assessment of the flavouring substance, the specifications for the material of commerce have also been considered and the information provided was complete for [FL-no: 10.057]. However, for the flavouring substance [FL-no: 10.057] in the present revision and for eight substances evaluated in previous revisions, the 'modified Theoretical Added Maximum Daily Intakes' (mTAMDIs) values are above the TTC for their structural class (III). For four substances previously evaluated in FGE.80Rev1 and in FGE.96, use levels are still needed to calculate the mTAMDI estimates. Therefore, in total for 13 flavouring substances, data on uses and use levels should be provided to finalise their safety evaluations. For [FL-no: 10.050, 10.069 and 13.161], information on the composition of stereoisomeric mixtures is needed.

KEYWORDS

FGE.217Rev3, FGE.80Rev2, FGE.96, Flavourings, JECFA, α,β-unsaturated carbonyls and precursors

CONTENTS

1 | INTRODUCTION

The present revision of this Flavouring Group Evaluation (FGE) concerns the inclusion of a gamma-lactone fused to an alicyclic ring, i.e. 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2*(3H)*-one [FL-no: 10.057], which is a precursor for the α,β-unsaturated ketone 3-methyl-6-(1-carboxyethyl)-2-cyclohexen-1-one. The flavouring substance [FL-no: 10.057] has been evaluated with respect to genotoxicity in FGE.217Rev3 (EFSA FAF Panel, 2023). According to the terms of reference of this mandate, once the concern for genotoxicity is ruled out for a flavouring substance, the European Food Safety Authority (EFSA) shall proceed to its full evaluation, taking into account the requirements of the Commission Regulation (EC) No 1565/2000[1] and of Regulation (EU) No 1334/2008.[2] The mandate for FGE.217Rev3 is cited below.

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

The use of flavourings 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.[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.

In December 2018, EFSA FAF Panel adopted the opinion on FGE.217 Revision 2 that includes the flavouring substance 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2*(3H)*-one [FL-no: 10.057] represented by 3,4-dimethyl-5-pentylidenefuran-2(5*H*)-one [FL-no: 10.042] (FGE.217Rev2). For the representative substance 3,4-dimethyl-5-pentylidenefuran-2(5*H*)-one [FL-no: 10.042], the FAF Panel concluded that the potential clastogenicity at the site of contact should be further investigated through an in vivo comet assay in duodenum. [FL-no: 10.042] is also aneugenic in vitro and for such substances, there was no agreed follow-up strategy to finalise their safety assessment. Therefore, the Panel concluded that the substance [FL-no: 10.042] and the other eight represented substances [FL-no: 10.034, 10.036, 10.043, 10.046, 10.054, 10.057, 10.060 and 10.170] could not be evaluated through the Procedure.

Following that evaluation there was an indication that the applicants were no longer interested to support the evaluation of the representative substance [FL-no: 10.042] and the other 8 substances, including [FL-no: 10.057]. Therefore, these substances were flagged for deletion from the Union List. However, early in 2021 the company Takasago indicated that they would support the evaluation of the substance [FL-no: 10.057]. Since the representative substance is no longer supported, in September 2021, they provided the relevant data for the substance [FL-no: 10.057].

Terms of Reference

The European Commission requests the European Food Safety Authority (EFSA) to evaluate the new information submitted and, depending on the outcome, proceed to the full evaluation of the substance 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2*(3H)*-one [FL-no: 10.057] in accordance with Commission Regulation (EC) No 1565/2000.

In case the genotoxic potential cannot be ruled out, EFSA is asked to estimate the exposure.

1.2 | Interpretation of the Terms of Reference

The flavouring substance [FL-no: 10.057] was first allocated to FGE.217Rev3 (EFSA FAF Panel, 2023) for evaluation with respect to genotoxicity. Based on new genotoxicity data submitted, in FGE.217Rev3, 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.80 (FGE.80Rev2), in accordance with Commission Regulation (EC) No 1565/2000.

The above-mentioned flavouring substance belongs 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, 2004). Other substances in this group have already been considered by EFSA in FGE.80 (EFSA, 2008a), FGE.80Rev1 (EFSA CEF Panel, 2009a) and FGE.96 (EFSA CEF Panel, 2011). For substances already evaluated by JECFA, a full evaluation is not required, but EFSA should consider whether the JECFA evaluation 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]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 of the European Parliament and of the Council. 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.

2 | DATA AND METHODOLOGIES

2.1 | Data

The present opinion is based on the data presented in Table 1. Additional information was provided by the industry during the risk assessment process on 22 March 2024 (Documentation provided to EFSA No. 2) and on 15 May 2024 (Documentation provided to EFSA No. 3) in response to requests from EFSA sent on 23 October 2023 and on 19 April 2024, respectively.

TABLE 1 Data considered in the current revision 2 of FGE.80 (FGE.80Rev2).

FL-no	Chemical name	Data provided for the current revision 2 of FGE.80	Appendix (table no.) and relevant section of the opinion	Documentation provided to EFSA/reference
10.005	3-Propylidenephthalide	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
10.024	3-Butylidenephthalide	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
10.025	3-Butylphthalide	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
10.050	Hexahydro-3,6-dimethyl-2(3*H*)-benzofuranone	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
10.057	3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one	Specifications, EU poundage data (MSDI), use levels, toxicity data	Appendix B (Table B.1); Appendix C (Tables C.1 and C.4); Appendix D (Table D.1); Sections 3.1, 3.2 and 3.3	Documentation provided to EFSA no.1, 2, 3; Food and Drug Research Laboratories, 1985
10.072	Dimethyl-3,6-benzo-2(3*H*)-furanone	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
13.009	3,4-Dihydrocoumarin	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
13.012	6-Methylcoumarin	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
13.161	Octahydrocoumarin	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014
16.055	(R)-(+)-Sclareolide	Use levels	Appendix C (Tables C.1 and C.4); Section 3.2	DG SANCO, 2014

In addition, the following assessments were considered for the evaluation:

- JECFA specifications for the candidate flavouring substance [FL-no: 10.057] (JECFA, 2016b).
- 82nd JECFA report (JECFA, 2016a) and 82nd JECFA toxicology monograph (JECFA, 2017).
- Genotoxicity data evaluated in FGE.217Rev3 (EFSA FAF Panel, 2023).
- EFSA scientific opinion on FGE.80 (EFSA, 2008a).
- EFSA scientific opinion on FGE.27 (EFSA, 2008b).
- EFSA scientific opinion on FGE.80Rev1 (EFSA CEF Panel, 2009a).
- EFSA scientific opinion on FGE.96 (EFSA CEF Panel, 2011).

2.1.1 | History of the evaluation of the substances in Flavouring group evaluation 80

The JECFA evaluated a group of 16 flavouring substances consisting of alicyclic, alicyclic-fused and aromatic-fused ring lactones (JECFA, 2004). One of the JECFA evaluated substances was not in the Register (dihydro-5-((Z,Z)octa-2,5-dienyl)-2(3*H*)-furanone) (JECFA-no: 1160) and therefore not considered by EFSA.

Four substances [FL-no: 10.034, 10.036, 10.169, 13.012] are precursors for *α,β*-unsaturated ketones and aldehydes and were allocated to FGE.217 for the evaluation of genotoxicity.

Therefore, in FGE.80 (EFSA, 2008a), the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) considered 11 JECFA evaluated substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.061, 10.069, 10.070, 10.072, 13.009, 13.161 and 16.055]. The AFC Panel considered that these substances are structurally related to the one aromatic lactone evaluated by EFSA in the FGE.27 (phthalide [FL-no: 10.056]). Furthermore, the JECFA evaluation is supported by a group of lactones evaluated in FGE.10 as well as by alicyclic secondary and tertiary alcohols in FGE.09 and FGE.18, respectively.

Regarding specifications, the AFC Panel considered that information was lacking about the stereoisomerism for six substances [FL-no: 10.050, 10.061, 10.069, 10.070, 10.072 and 13.161].

MSDI values for the EU could not be calculated for [FL-no: 10.061, 10.069, 10.070, 10.050, 10.072 and 13.161].

For one substance [FL-no: 10.072], the AFC Panel did not agree with the JECFA that an adequate NOAEL is available and, accordingly, the AFC Panel requested additional data for [FL-no: 10.072].

In FGE.80Rev1 (EFSA CEF Panel, 2009a), 13 substances were considered because 6-methylcoumarin [FL-no: 13.012] and 5,6,7,7-alpha-tetrahydro-4,4,7alpha-trimethyl-2-(4*H*)-benzofuranone [FL-no: 10.169] were included.

6-Methylcoumarin [FL-no: 13.012] was evaluated for genotoxicity in FGE.217 (subgroup 4.1 in FGE.19), where the CEF Panel (EFSA CEF Panel, 2009b) concluded that [FL-no: 13.012] is not considered genotoxic and can therefore be evaluated through the Procedure in FGE.80Rev1.

The substance [FL-no: 10.169] was not evaluated in FGE.80 because it was considered a precursor for an α,β-unsaturated ketone, which would need to be evaluated for genotoxicity first. However, the CEF Panel recognised that, upon hydrolysis, a tertiary alcohol would be formed, and therefore, the substance would not be of concern with respect to genotoxicity. Therefore, [FL-no: 10.169] was allocated to FGE.80Rev1 for evaluation through the procedure.

In FGE.80Rev1, the CEF Panel considered the available specifications adequate for six substances [FL-no: 10.005, 10.024, 10.025, 13.009, 13.012 and 16.055].

For seven substances [FL-no: 10.050, 10.061, 10.069, 10.070, 10.072, 10.169 and 13.161], information on stereoisomerism was not available or incomplete.

For six substances [FL-no: 10.050, 10.061, 10.069, 10.070, 10.072 and 13.161], MSDI values for EU were not available. For all the 13 substances, information on uses and use levels were not available to calculate mTAMDI.

In 2010, additional information on specifications (EFFA, 2010a) and on MSDI (EFFA, 2010b) was provided by industry for the substances [FL-no: 10.050, 10.061, 10.069, 10.070, 10.072 and 13.161] and evaluated in FGE.96 (EFSA CEF Panel, 2011). For five substances [FL-no: 10.050, 10.061, 10.069, 10.070 and 13.161], the CEF Panel concluded at step A3 of the Procedure that these substances would be of no safety concern at their estimated level of intake based on the MSDI approach. The substance [FL-no: 10.072] was evaluated via the B-side of the procedure. The CEF Panel considered the NOAEL of 5.42 mg/kg body weight (bw) per day (one dose level tested) for the structurally related substance 3-propylidenephthalide [FL-no: 10.005] as derived from a 90-day toxicity study (Posternak et al., 1969) and concluded that [FL-no: 10.072] is of no safety concern at the estimated level of intake based on the MSDI approach (EFSA CEF Panel, 2011).

In FGE.96, the CEF Panel reported that for [FL-no: 10.050 and 13.161] industry (EFFA, 2010a) informed that the commercial products are mixtures of stereoisomers, but no information on the ratio of the stereoisomers was given. The CEF Panel concluded that the composition of stereoisomeric mixtures has to be specified.

In 2010, industry provided also information on stereoisomerism for the substance [FL-no: 10.169] (EFFA, 2010a). The CEF Panel already concluded in FGE.80Rev1 (EFSA CEF Panel, 2009a) that this substance is of no safety concern, based on the MSDI approach. Therefore, the new information on stereoisomerism (EFFA, 2010a) was not considered in FGE.96, but included in the EU list.

In 2014, industry provided use levels data for nine substances from FGE.80Rev1 [FL-no: 10.005, 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161 and 16.055] (DG SANCO, 2014), which are included in the present revision 2 of FGE.80 (see Section 3.2 and Appendix C).

The present opinion deals with the evaluation of one flavouring substance 3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one [FL-no: 10.057]. This substance has been evaluated by JECFA as JECFA no. 2223 in its 82nd meeting (JECFA, 2016a, 2016b, 2017). This substance was evaluated by EFSA in FGE.217Rev3 (EFSA FAF Panel, 2023), where it was concluded that the concern for genotoxicity for [FL-no: 10.057] could be ruled out. Therefore, it can be evaluated through the procedure for which purpose it has now been added to this revision 2 of FGE.80.

Together with the 13 substances that were already considered in FGE.80Rev1, the current revision comprises 14 substances. The 13 flavouring substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.061, 10.069, 10.070, 10.072, 10.169, 13.009, 13.012, 13.161 and 16.055], for which the evaluation was finalised in FGE.80Rev1 and in FGE.96, will not be further discussed except for the inclusion of use levels data for nine substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161 and 16.055]. For the sake of completion, the information for all the 14 substances is maintained in the various tables in this revision 2 of FGE.80.

The remaining two JECFA evaluated substances [FL-no: 10.034 and 10.036], which were allocated to FGE.217 for evaluation of genotoxicity will not be considered further because these have been removed from the Union List[4] as explained in FGE.217Rev3 (EFSA FAF Panel, 2023).

FGE	Adopted by EFSA	Link	No. of substances
FGE.80	1 April 2008	https://www.efsa.europa.eu/en/efsajournal/pub/919	11
FGE.80Rev1	17 June 2009	https://www.efsa.europa.eu/en/efsajournal/pub/1169	13
FGE.80Rev2	4 July 2024	https://www.efsa.europa.eu/en/efsajournal/pub/8952	14

[4]Commission Regulation (EU) 2022/1466 of 5 September 2022 amending Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council as regards the removal of certain flavouring substances from the Union list. OJ L 231, 6.9.2022, p. 32–35.

2.2 | Methodologies

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

2.2.1 | Procedure for the safety evaluation of flavouring substances

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

2.2.2 | Approach used for the calculation of exposure

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

3 | ASSESSMENT

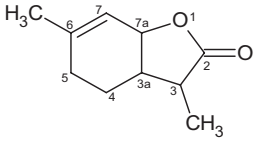
3.1 | Specifications

The JECFA specifications are available for all 14 flavouring substances in FGE.80Rev2 [FL-no: 10.005, 10.024, 10.025, 10.050, 10.057, 10.061, 10.069, 10.070, 10.072, 10.169, 13.009, 13.012, 13.161 and 16.055] (JECFA, 2004, 2016b).

EFSA considerations

Table 2 shows the chemical structure of the candidate substance which is considered in this revision of FGE.80 (FGE.80Rev2).

TABLE 2 Flavouring substance under evaluation in FGE.80Rev2.

FL-no JECFA-no	Chemical structure	Chemical name	Structural class[5]
10.057 2223		3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one	Class III

The information on the stereochemistry of the flavouring substance [FL-no: 10.057] reported by JECFA (2016b) is as follows: (3a*S*,7a*R*): 81%–84%, (3a*R*,7a*S*): 16%–19%.

Considering that the flavouring substance contains three asymmetric centres (3, 3a, 7a), EFSA requested the applicant to provide stereochemical information that includes the missing data on the configuration at position 3. In response, the applicant provided the following information on the flavouring substance currently on the market: (3*S*, 3a*S*, 7a*R*): 22%–25%, (3*S*, 3a*R*, 7a*S*): 22–25%, (3*S*, 3a*S*, 7a*S*): 0%–1%, (3*S*, 3a*R*, 7a*R*): 0%–1%, (3*R*, 3a*S*, 7a*R*): 22%–25%, (3*R*, 3a*R*, 7a*S*): 22%–25%, (3*R*, 3a*S*, 7a*S*): 0%–1%, (3*R*, 3a*R*, 7a*R*): 0%–1%.

The sum of all (3R) and the sum of all (3S) stereoisomers both amount to 50% (i.e. racemic mixture). The proportions of the stereoisomers of the flavouring substance possessing (3a*S*,7a*R*)- and (3a*R*,7a*S*)-configuration, respectively, amount to 44%–50% each (Documentation provided to EFSA no. 2 and 3).

With this information, the data required for the specifications of this flavouring substance are complete. However, in line with the applicant, the Panel noted that, according to this information, the proportions of the stereoisomers of the flavouring substance possessing (3a*S*,7a*R*)- and (3a*R*,7a*S*)-configuration deviate from the specification reported by JECFA (2016b).

For the substances [FL-no: 10.050, 10.069 and 13.161], industry (EFFA, 2010a) informed that the commercial products are mixtures of stereoisomers, but the information provided on stereoisomers was incomplete. The composition of stereoisomeric mixtures (diastereoisomers/enantiomers) has to be specified. For the remaining 10 substances, in this FGE, the specifications are complete.

The most recent specifications data for the substances evaluated in FGE.80 and its revisions are summarised in Table B.1 – Appendix B.

[5]According to OECD (Q)SAR Toolbox (version 4.6).

3.2 | Estimation of intake

JECFA status

For the flavouring substance [FL-no: 10.057], evaluated through the JECFA Procedure, intake data are available for the EU (JECFA, 2017). Dietary exposure was estimated using the maximised survey-derived intake (MSDI) method and the single-portion exposure technique (SPET).

According to JECFA, the substance [FL-no: 10.057] has been reported to occur as a natural component of orange and grapefruit juice and fresh apples (JECFA, 2017).

EFSA considerations

An updated EU production figure for the newly included flavouring substance [FL-no: 10.057] has been submitted by industry (Documentation provided to EFSA no. 1). The MSDI value is 0.012 μg/capita per day (see Table C.4 – Appendix C).

For the flavouring substance [FL-no: 10.057], normal and maximum use levels have been submitted (Documentation provided to EFSA no. 2) and an mTAMDI intake value was calculated based on the normal use levels (see Appendix C.2). The mTAMDI intake estimate of 1708 μg/person per day is above the threshold of toxicological concern (TTC) for structural class III (90 μg/person per day). For [FL-no: 10.057], more reliable data on use levels should be provided in order to refine the exposure assessment and to finalise its safety evaluation.

In FGE.80Rev1, the CEF Panel considered that for all 13 substances evaluated through the Procedure use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise their evaluation. After the publication of FGE.80Rev1, industry provided use levels for nine substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161 and 16.055] (DG SANCO, 2014). No normal and maximum use levels were provided for four flavouring substances [FL-no: 10.061, 10.069, 10.070 and 10.169], previously considered in FGE.80Rev1.

The MSDI figures and mTAMDI intake estimates for the flavouring substances in FGE.80Rev2 are shown in Table C.4 – Appendix C.

Natural occurrence

Information on natural occurrence was reported by JECFA (2017) and provided by industry (Documentation provided the EFSA no.1). This information is not considered in this evaluation, but is included in Appendix C.3.

3.3 | Biological and toxicological data

3.3.1 | ADME data

The candidate substance [FL-no: 10.057] was evaluated by JECFA, in its 82nd meeting, within the group of alicyclic, alicyclic-fused and aromatic-fused ring lactones (JECFA, 2017).

JECFA (2017) reported that '*The metabolic pathways applicable to lactones fused to alicyclic rings (e.g. No. 2223) include excretion as the open-chain hydroxycarboxylic acid derivative, hydroxylation of ring alkyl substituents producing polar metabolites that may be excreted, or oxidative degradation of the carboxylic acid side-chain to yield polar alicyclic or aromatic carboxylic acids that are excreted unchanged or in conjugated form*.' This statement follows from a more detailed description of these molecules by JECFA (JECFA, 2004). JECFA concluded that the substance can be predicted to be metabolised to innocuous products.

EFSA considerations

For the supporting flavouring substance phthalide [FL-no: 10.056], the CEF Panel concluded in FGE.27 (EFSA, 2008b) that this substance:

> *'is expected to be hydrolysed to the corresponding benzoic acid derivative, 2-hydroxymethyl benzoic acid, before absorption or upon entering systemic circulation. 2-Hydroxymethyl benzoic acid is anticipated to be further metabolised by conjugation to glycine and excreted in the urine as the major pathway. As minor pathways it is likely that the hydroxymethyl group can be conjugated with glucuronic acid, followed by excretion, or that the hydroxymethyl group will be further metabolised to a carboxylic acid group yielding phthalic acid. As a further minor pathway phthalide might be hydroxylated at the benzene ring. Overall, it is concluded that phthalide is metabolised to innocuous products.'*

Following these considerations, the FAF Panel agreed with the JECFA that [FL-no: 10.057] can be anticipated to be metabolised to innocuous substances.

3.3.2 | Genotoxicity data

The present revision of FGE.80 includes the evaluation of the flavouring substance [FL-no: 10.057], a precursor for an α,β-unsaturated ketone, which is a structural alert for genotoxicity (Eder et al., 1990; EFSA, 2008c). Because of this, the genotoxic potential of [FL-no: 10.057] has been assessed in FGE.217 and its revision 3 (FGE.217Rev3), where the concern was ruled out (EFSA FAF Panel, 2023). Therefore, the safety evaluation through the Procedure can be performed for the flavouring substance [FL-no: 10.057].

3.3.3 | Toxicological data

For the candidate substance [FL-no: 10.057], a subchronic toxicity study in rats for the structurally related substance dehydromenthofurolactone (Food and Drug Research Laboratories, 1985) was considered by JECFA (JECFA, 2017) and submitted by industry (Documentation provided to EFSA no. 2).

3.3.3.1 | *Acute toxicity study*

JECFA reported that '*an oral median lethal dose (LD50) value in rats of greater than 2000 mg/kg bw has been reported for one of the additional flavouring agents in this group, 2-(2-hydroxy-4-methyl-3-cyclohexenyl)propionic acid gamma-lactone (No. 2223).*' JECFA considered these data consistent with the low acute toxicity of other members of the group of alicyclic, alicyclic-fused and aromatic-fused ring lactones.

Acute toxicity studies were not provided to EFSA. The Panel considered that, for [FL-no: 10.057], the acute toxicity does not raise a concern, based on the data described in the JECFA evaluation (JECFA, 2017).

3.3.3.2 | *Repeated dose toxicity study*

For the evaluation of wine lactone (2-(2-hydroxy-4-methyl-3-cyclohexenyl)propionic acid gamma lactone [FL-no: 10.057]), JECFA (JECFA, 2016a, 2017) considered a 90-day dietary toxicity study on the structurally related dehydromenthofurolactone (former [FL-no: 10.034]). The NOAEL from this study was 1 mg/kg bw per day. The same 90-day toxicity study (Food and Drug Research Laboratories, 1985) was provided by industry for the present evaluation of [FL-no: 10.057].

Dehydromenthofurolactone was administered to male and female Sprague Dawley rats (20/sex) for 13 weeks via diets. The concentrations in feed were adjusted weekly to provide intended dose levels of 0, 1, 10 or 100 mg/kg bw. Actual mean dose levels calculated over the duration of the study were 0/0, 0.94/0.98, 9.5/10.0 or 95.3/99.7 mg/kg bw per day for male and female rats (M/F), respectively (see Table D.1 – Appendix D). Body weight changes, food consumption, haematological, clinical chemistry parameters, absolute and relative weights of five organs, and macroscopic and microscopic changes (5/sex, control and highest dose) were assessed. Also, urinalysis was undertaken.

Rats in the high-dose group had statistically significant lower body weight (13 and 18% for males and females, respectively) compared to controls. Food consumption of the high-dosed animals was also reduced for the majority of the study duration. At terminal sacrifice, in male rats, higher relative liver (mid- and high-dose groups) and testes (high dose group) weights were observed. In females, at the highest dose tested, higher relative liver, kidney, brain and ovaries weights were observed; however, this was attributed to the lowered body weights. In both sexes, a statistically significant increase in the incidence of hyperkeratosis and epithelial thickening (in the absence of basal cells proliferation) of the oesophagus was observed at the mid and high dose tested. Also a statistically significant increase in the incidence of hyperkeratosis of the squamous epithelium of the forestomach was observed in both sexes of the high dose group, which was considered to be the result of direct epithelial irritation caused by continuous consumption of diet with the test substance.

The Panel noted that the study had some shortcomings, e.g. purity of test substance was not specified and ophthalmological examination and functional observations were not performed. In addition, organ weight measurements were only performed for a few organs. The Panel considered that despite the limitations of the toxicity data available, the NOAEL of 1 mg/kg bw per day (which is based on the oesophageal and gastric lesions), from the study on dehydromenthofurolactone, can be used for the calculation of a margin of exposure (MOE) for the structurally related substance [FL-no: 10.057].

3.4 | Application of the procedure

Application of the Procedure to one substance from JECFA flavouring group of alicyclic, alicyclic-fused and aromatic-fused ring lactones' (JECFA, 2016a, 2017).

In the 82nd JECFA meeting report, the flavouring substance [FL-no: 10.057] was allocated to structural class III, according to the decision tree approach presented by Cramer et al. (1978).

JECFA considered that the flavouring substance [FL-no: 10.057] can be anticipated to be metabolised to innocuous products, and accordingly, it should be evaluated along the A-side of the Procedure scheme. JECFA estimated the dietary intake, based on the single portion exposure technique (SPET). The estimated exposure was 300 μg/person per day, which was above the TTC for structural class III (90 μg/person per day) (step A3). At step A4, JECFA considered that metabolites of [FL-no: 10.057] are not endogenous; therefore, the evaluation proceeded to step A5. For [FL-no: 10.057], the NOAEL of 1 mg/kg bw per day for the structurally related substance dehydromenthofurolactone (JECFA No. 1163) obtained from a 90-day toxicity study in rats (Food and Drug Research Laboratories, 1985) provided an adequate margin of exposure of 200 in relation to the highest estimated dietary exposure to [FL-no: 10.057] (SPET = 300 μg/person per day or 5 μg/kg bw per day) when used as a flavouring agent. Therefore, JECFA concluded that the substance [FL-no: 10.057] would pose no safety concern at its estimated exposure, based on the SPET approach.

EFSA considerations

The FAF Panel agreed with JECFA with respect to the allocation of the candidate flavouring substance in structural class III. The Panel agreed with the way of the application of the Procedure that has been performed by JECFA for the flavouring substance [FL-no: 10.057], but the Panel applied the MSDI approach[6] (see Appendices A and C). The MSDI exposure estimate for [FL-no: 10.057] (0.012 μg/capita per day) is below the TTC for structural class III (i.e. 90 μg/person per day) (see Table C.4 – Appendix C). Therefore, the FAF Panel concluded, at step A3 of the Procedure scheme, that [FL-no: 10.057] does not raise a safety concern when used as flavouring substance at the current levels of use, when based on the MSDI approach.

For the 13 flavouring substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.061, 10.069, 10.070, 10.072, 10.169, 13.009, 13.012, 13.161 and 16.055] considered in the previous revision of this FGE, FGE.80Rev1, data on uses and use levels were not available. In 2014, these data (DG SANCO, 2014) were provided for nine substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161 and 16.055], which are included in the present revision. Uses and use levels data are also available for [FL-no: 10.057] (Documentation provided to EFSA no. 2). These 10 substances, for which data on uses and use levels are available, were all classified as structural class III. The resulting mTAMDI is below the corresponding TTC (90 μg/person per day) for [FL-no: 10.005], and above the TTC for nine substances [FL-no: 10.024, 10.025, 10.050, 10.057, 10.072, 13.009, 13.012, 13.161 and 16.055]. For these nine substances, more detailed and reliable data on uses and use levels should be provided in order to refine the exposure assessment and to finalise their safety evaluation.

The JECFA safety evaluations and EFSA conclusions on the 14 flavouring substances are summarised in Table E.1 – Appendix E.

4 | DISCUSSION

This revision 2 of FGE.80 comprises in total 14 JECFA-evaluated flavouring substances, 13 of which have already been considered in FGE.80, FGE.80Rev1 and FGE.96. The remaining substance [FL-no: 10.057] has been included in this revision, following its evaluation by JECFA in 2017. In FGE.217Rev3 (EFSA FAF Panel, 2023), the FAF Panel ruled out a concern for genotoxicity on the basis of newly submitted genotoxicity studies, which were needed due to the presence of a structural alert for genotoxicity (i.e. the substance is a precursor for the α,β-unsaturated ketone 3-methyl-6-(1-carboxyethyl)-2-cyclo hexen-1-one).

The FAF Panel evaluated the flavouring substance [FL-no: 10.057] through the Procedure and concluded at step A3 of the Procedure scheme, that [FL-no: 10.057] does not raise a safety concern when used as flavouring substance at the current levels of use, based on the MSDI approach.

For the flavouring substance [FL-no: 10.057], normal and maximum use levels have been provided. The mTAMDI intake estimate for this substance is above the TTC for its structural class (III). Therefore, for [FL-no: 10.057], more detailed and reliable data on uses and use levels should be provided in order to refine the exposure assessment and to finalise its safety evaluation.

Use levels data were provided for nine flavouring substances from FGE.80Rev1 (all classified as structural class III) which were also considered in the present revision. The calculated mTAMDI is below the corresponding TTC (90 μg/person per day) for [FL-no: 10.005], and above the TTC for eight substances [FL-no: 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161 and 16.055]. For these eight substances, more detailed and reliable data on uses and use levels should be provided in order to refine the exposure assessment and to finalise their safety evaluation.

Data on uses and use levels are needed for [FL-no: 10.061, 10.069, 10.070 and 10.169] in order to calculate mTAMDI.

For the substances [FL-no: 10.050, 10.069 and 13.161], industry informed (see EFFA, 2010a) that the commercial products are mixtures of stereoisomers, but the information provided on stereoisomers was incomplete. The composition of stereoisomeric mixtures (diastereoisomers/enantiomers) has to be specified. For the remaining 10 substances, in this FGE and for [FL-no: 10.057], the specifications are complete.

[6]For historical reasons and to maintain methodological consistency with other FGEs and with Regulation (EC) 1565/2000.

5 | CONCLUSIONS

For the flavouring substance [FL-no: 10.057] in FGE.80Rev2, the Panel agreed with JECFA conclusions 'No safety concern at estimated levels of intake as flavouring substances' when based on the MSDI approach. For 13 substances [FL-no: 10.024, 10.025, 10.050, 10.057, 10.061, 10.069, 10.070, 10.072, 10.169, 13.009, 13.012, 13.161 and 16.055], data on uses and use levels are needed to finalise their safety evaluation.

6 | RECOMMENDATION

The Panel recommends the European Commission to consider:

- to request normal and maximum use levels for [FL-no: 10.061, 10.069, 10.070 and 10.169] to calculate the mTAMDI estimates in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation accordingly.
- to request more detailed and reliable data on uses and use levels for [FL-no: 10.024, 10.025, 10.050, 10.057, 10.072, 13.009, 13.012, 13.161 and 16.055], as the mTAMDI exposure estimates are above the TTC for their structural class III. When the above data are received, the assessment for these flavouring substances should be updated accordingly and expanded if necessary (i.e. request of additional toxicology data).
- To request information on the composition of stereoisomeric mixtures (diastereoisomers/enantiomers) for [FL-no: 10.050, 10.069 and 13.161].

7 | DOCUMENTATION PROVIDED TO EFSA

1. Addendum of Additional Data Relevant to the Flavouring Group Evaluation of the FGE.217 of Chemical Group 3 (Annex I of 1565/2000/EC), Heterocyclic α,β-unsaturated aldehydes, ketones and related substances with the α,β-conjugation in the ring or in the side chain, Lactones Used as Flavouring Substances. Submitted by Takasago International Corporation.
2. Additional information received on 22 March 2024, submitted by Takasago International Corporation in response to a request from EFSA (23 October 2023).
3. Additional information received on 15 May 2024, submitted by Takasago International Corporation in response to a request from EFSA (19 April 2024).
4. Food and Drug Research Laboratories, 1985. 90-day dietary toxicity study of SRA 84–11 in Sprague-Dawley rats (preliminary summary report). FDRL study no. 8326. August 1985. Submitted by Takasago International Corporation.
5. DG SANCO (Directorate General for Health and Consumer Affairs), 2014. Information from DG SANCO concerning a list of use levels for 123 JECFA evaluated substances allocated to structural class III. 16.09.2014.
6. EFFA (European Flavour Association), 2002. Letter from EFFA to Danish Veterinary and Food Administration. Dated 31 October 2002. Re.: Second group of questions. FLAVIS/8.26.
7. EFFA (European Flavour Association), 2010a. EFFA Letters to EFSA for clarification of specifications and isomerism for which data were requested in published FGEs.
8. EFFA (European Flavour Association), 2010b. European production volumes for selected flavouring substances (footnote 8 substances). Private communication from EFFA to DG SANCO. February 2010.

ABBREVIATIONS

AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFFA	European Flavour Association
FAF	Panel on Food Additives and Flavourings
FEMA	Flavour and Extract Manufacturer 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
MOE	Margin of exposure
MS	Mass spectra
MSDI	Maximised Survey-derived Daily Intake
NOAEL	No-observed-adverse-effect-level
NMR	Nuclear Magnetic Resonance

No	Number
OECD	Organisation for Economic Co-operation and Development
(Q)SAR	(Quantitative) structure–activity relationship
SCF	Scientific Committee on Food
SPET	Single-Portion Exposure Technique
TTC	Threshold of Toxicological Concern
WHO	World Health Organisation

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2023-00296

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REFERENCES

Cramer, G. M., Ford, R. A., & Hall, R. L. (1978). Estimation of toxic hazard – A decision tree approach. *Food and Cosmetics Toxicology*, *16*, 255–276.

Eder, E., Hoffman, C., Bastian, H., Deininger, C., & Scheckenbach, S. (1990). Molecular mechanisms of DNA damage initiated by alpha, beta-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity. *Environmental Health Perspectives*, *88*, 99–106. https://doi.org/10.1289/ehp.908899

EFSA (European Food Safety Authority). (2008a). Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from Commission on Flavouring Group Evaluation 80 (FGE.80) consideration of alicyclic, alicyclic-fused and aromatic-fused ring lactones evaluated by JECFA (61st meeting) structurally related to a aromatic lactone evaluated by EFSA in FGE.27. *EFSA Journal*, *6*(12), 919. https://doi.org/10.2903/j.efsa.2008.919

EFSA (European Food Safety Authority). (2008b). Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from Commission on FGE.27: One aromatic lactone from chemical group 11. *EFSA Journal*, *6*(9), 806. https://doi.org/10.2903/j.efsa.2008.806

EFSA (European Food Safety Authority). (2008c). Minutes of the 26th Plenary meeting of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food, held in Parma on 27–29 November 2007.

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2009a). Flavouring Group Evaluation 80, Revision 1 (FGE.80Rev1): Consideration of alicyclic, alicyclic-fused and aromatic-fused ring lactones evaluated by JECFA (61st meeting) structurally related to a aromatic lactone evaluated by EFSA in FGE.27 (2008). *EFSA Journal*, *7*(9), 1169. https://doi.org/10.2903/j.efsa.2009.1169

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2009b). Flavouring Group Evaluation 217: Alpha, beta-unsaturated ketones and precursors from chemical subgroup 4.1 of FGE.19: Lactones. *EFSA Journal*, *7*(4), 1068. https://doi.org/10.2903/j.efsa.2009.1068

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2011). Scientific Opinion on Flavouring group evaluation 96 (FGE.96): Consideration of 88 flavouring substances considered by EFSA for which EU production volumes / anticipated production volumes have been submitted on request by DG SANCO. Addendum to FGE. 51, 52, 53, 54, 56, 58, 61, 62, 63, 64, 68, 69, 70, 71, 73, 76, 77, 79, 80, 83, 84, 85 and 87. *EFSA Journal*, *9*(12), 1924. https://doi.org/10.2903/j.efsa.2011.1924

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings). (2023). Scientific Opinion on the flavouring Group Evaluation 217 Revision 3 (FGE.217Rev3): consideration of genotoxic potential for α,β-unsaturated ketones and precursors from chemical subgroup 4.1 of FGE.19: lactones. *EFSA Journal*, *21*(4), 7967. https://doi.org/10.2903/j.efsa.2023.7967

EFSA Scientific Committee. (2009). Guidance of the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles. *EFSA Journal*, *7*(7), 1051. https://doi.org/10.2903/j.efsa.2009.1051

EFSA Scientific Committee. (2019). Guidance on the use of the threshold of toxicological concern approach in food safety assessment. *EFSA Journal*, *17*(6), 5708. https://doi.org/10.2903/j.efsa.2019.5708

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (1995). Evaluation of certain food additives and contaminants. Forty-fourth meeting of the joint FAO/WHO expert committee on food additives. WHO technical report series, no. 859. Geneva.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (1996). Toxicological evaluation of certain food additives. The forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives and contaminants.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (1997). Evaluation of certain food additives and contaminants. Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 6-15 February 1996. WHO Technical Report Series, no. 868. Geneva.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (1999). Evaluation of certain food additives and contaminants. Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. Rome, 17-26 June 1997. WHO Technical Report Series, no. 884. Geneva.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2004). Safety evaluation of certain food additives and contaminants. Sixty-first meeting of the joint FAO/WHO expert committee on food additives, WHO food additives series: 52. IPCS, WHO, Geneva.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2006). Sixty-seventh meeting Rome, 20–29 June 2006, Summary and Conclusions. Issued 7 July 2006.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2016a). Evaluation of certain food additives. Eighty-second report of the joint FAO/WHO expert committee on food additives, WHO technical report series: 1000. WHO, Geneva.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2016b). *Compendium of food additive specifications. Joint FAO/WHO Expert Committee on Food Additives eighty-second meeting*.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2017). Safety evaluation of certain food additives. Eighty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series, No. 73. WHO, Geneva.

Posternak, J. M., Linder, A., & Vodoz, C. A. (1969). Summaries of toxicological data. Toxicological tests on flavouring matters. *Food and Cosmetics Toxicology*, *7*, 405–407.

SCF (Scientific Committee for Food). (1995). First annual report on chemically defined flavouring substances. May 1995, 2nd draft prepared by the SCF Working Group on Flavouring Substances (Submitted by the SCF Secretariat, 17 May 1995). CS/FLAV/FL/140-Rev.2. . Annex 6 to Document III/5611/95, European Commission, Directorate-General III, Industry.

SCF (Scientific Committee on Food). (1999). Opinion on a programme for the evaluation of flavouring substances (expressed on 2 December 1999). SCF/CS/FLAV/TASK/11 Final 6/12/1999. Annex I the minutes of the 119th Plenary meeting. European Commission, Health & Consumer Protection Directorate-General.

How to cite this article: EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Castle, L., Andreassen, M., Aquilina, G., Bastos, M., Boon, P., Fallico, B., Fitzgerald, R., Frutos Fernandez, M. J., Grasl-Kraupp, B., Gundert-Remy, U., Gürtler, R., Houdeau, E., Kurek, M., Louro, H., Morales, P., Passamonti, S., Benigni, R., Degen, G., … Mennes, W. (2024). Flavouring Group Evaluation 80, Revision 2 (FGE.80Rev2): Consideration of alicyclic, alicyclic-fused and aromatic-fused ring lactones evaluated by the JECFA (61st and 82nd meetings) structurally related to an aromatic lactone evaluated in FGE.27. *EFSA Journal*, *22*(8), e8952. https://doi.org/10.2903/j.efsa.2024.8952

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'.[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 thresholds of toxicological 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 (Figure A.1).

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

[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).

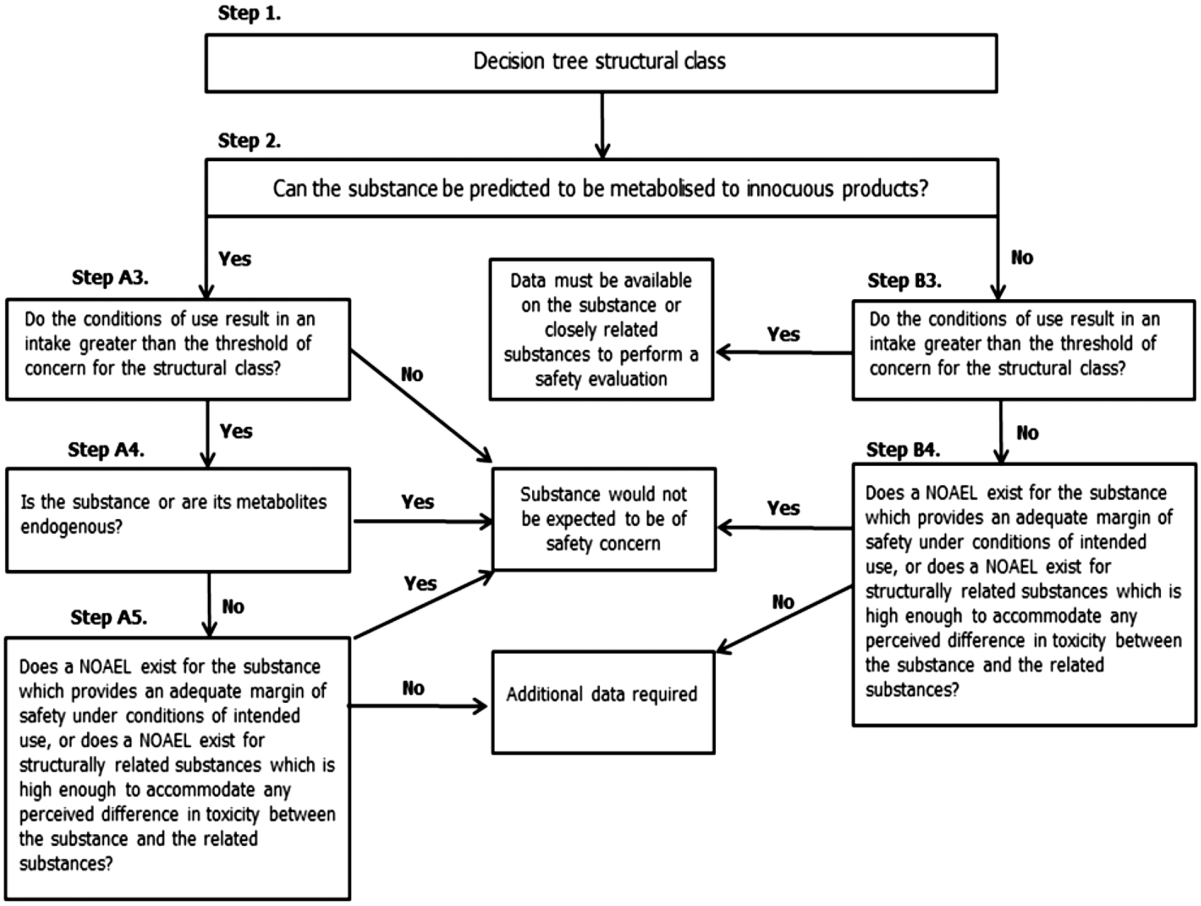


FIGURE A.1 Procedure for the safety evaluation of chemically defined flavouring substances.

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, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The considerations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance:

a. *Intake*

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

In its evaluation, JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by JECFA only on the basis of these figures. For substances in the Union List of flavouring substances[11] for which this is the case, the Panel will need European Union (EU) production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use levels reported by the industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach. It is noted that JECFA, at its 65th meeting, 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) × 10^9/(0.1 × population in Europe (= 375 × 10^6) × 0.6 × 365) = μg/capita per day.

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

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/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 P anel 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 Flavouring Group Evaluation (FGE).

APPENDIX B

Specifications

TABLE B.1 Summary table on specifications data for flavouring substances in FGE.80Rev2 (for chemical structures, see Appendix E).

Information included in the EU Union list Regulation (EC) No 1334/2008 as amended			Most recent available specifications data[a]				
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point,°C[e] Melting point,°C ID test Assay minimum (isomers distribution and secondary components)**	**Refrac. Index[f] Spec. gravity[g]**	**EFSA Comments**
10.005 1168 2952 494 17369-59-4	3-Propylidenephthalide	[b]	Liquid $C_{11}H_{10}O_2$ 174.20	Insoluble Soluble	169–171 (17 hPa) – NMR 96%	1.557–1.562 1.127–1.132	
10.024 1170 3333 10083 551-08-6	3-Butylidenephthalide	[b]	Liquid $C_{12}H_{12}O_2$ 188.23	Insoluble Soluble	114–116 (0.07 hPa) – NMR 99%	1.554–1.559 1.098–1.103	
10.025 1169 3334 10084 6066-49-5	3-Butylphthalide	[b]	Liquid $C_{12}H_{14}O_2$ 190.24	Slightly soluble Soluble	113 (0.3 hPa) – IR NMR 97% Racemate	1.524–1.529 1.068–1.074	
10.050 1161 4032 – 92015-65-1	Hexahydro-3,6-dimethyl-2(3*H*)-benzofuranone	[b]	Liquid $C_{10}H_{16}O_2$ 168.24	Soluble Soluble	274–276 (17 hPa) – IR NMR 99.4% Mixture of optical isomers (diastereoisomers) (EFFA, 2010a)	1.464–1.470 1.016–1.022 (20°)	Stereoisomeric composition (diastereoisomers/ enantiomers) to be specified
10.057 2223 4140 – 57743-63-2	3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one	[b]	Liquid $C_{10}H_{14}O_2$ 166.10	Practically insoluble or insoluble Freely soluble	231–232 13 MS IR NMR > 95% (mixture of isomers) Isomeric composition: (3*S*, 3a*S*, 7a*R*): 22–25%, (3*S*, 3a*R*, 7a*S*): 22–25%, (3*S*, 3a*S*, 7a*S*): 0%–1% (3*S*, 3a*R*, 7a*R*): 0%–1% (3*R*, 3a*S*, 7a*R*): 22–25%, (3*R*, 3a*R*, 7a*S*): 22%–25%, (3*R*, 3a*S*, 7a*S*): 0%–1% (3*R*, 3a*R*, 7a*R*): 0%–1%	1.490–1.496 1.065–1.071	

TABLE B.1 (Continued)

Information included in the EU Union list Regulation (EC) No 1334/2008 as amended			Most recent available specifications data[a]				
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point,°C[e] Melting point,°C ID test Assay minimum (isomers distribution and secondary components)**	**Refrac. Index[f] Spec. gravity[g]**	**EFSA Comments**
10.061 1159 3937 – 70851-61-5	cis-5-Hexenyldihydro-5-methylfuran-2(3*H*)-one	[b]	Liquid $C_{11}H_{18}O_2$ 182.26	Insoluble Soluble	150 (8 hPa) – IR NMR 97 % Racemate of (Z)-isomer (EFFA, 2010a)	1.463–1.468 0.960–0.967	
10.069 1158 3999 – 67663-01-8	3-Methyl gamma-decalactone	At least 94% (sum of cis and trans isomers); secondary component 1%–2% heptan-1-ol	Liquid $C_{11}H_{20}O_2$ 184.28	Insoluble Soluble	110–115 (5 hPa) - NMR 94% Composition: *cis*-3-methyl-gamma-decalactone (40–54 %), *trans*-3-methyl-gamma-decalactone (40–54 %) and heptan-1-ol (1–2 %) (EFFA, 2010a)	1.446–1.452 0.938–0.944	No information on the enantiomeric compositions of the *cis* and *trans* diastereoisomers has been provided
10.070 1157 4051 – 1073-11-6	4-Methyl-5-hexen-1,4-olide	[b]	Liquid $C_7H_{10}O_2$ 126.15	Insoluble Soluble	219 – IR NMR 97 % Racemate (EFFA, 2010a)	1.457–1.462 1.015–1.025 (20°)	
10.072 1167 3863 – 65817-24-5	Dimethyl-3,6-benzo-2(3*H*)-furanone	[b]	Liquid $C_{10}H_{10}O_2$ 162.19	Insoluble Soluble	64 (0.1 hPa) – IR NMR 98% Racemate (EFFA, 2010a)	1.518–1.524 1.099–1.104	
10.169 1164 1020 – 15356-74-8	5,6,7,7alpha-Tetrahydro-4,4,7alpha-trimethyl-2-(4*H*)-benzofuranone	At least 90%; secondary components 3%–5% 2,9-dimethyl 3,8-decanedione, 3%–5% 4-hydroxy-5,6-oxo- beta-ionone	Liquid $C_{11}H_{16}O_2$ 180.25	Insoluble Soluble	90 – NMR 90% Racemate (EFFA, 2010a)	1.499–1.505 1.051–1.058	

(Continues)

TABLE B.1 (Continued)

Information included in the EU Union list Regulation (EC) No 1334/2008 as amended			Most recent available specifications data[a]				
FL-no JECFA-no FEMA no CoE no CAS no	**Chemical name**	**Purity of the named compound**	**Phys. form Mol. formula Mol. weight**	**Solubility[c] Solubility in ethanol[d]**	**Boiling point,°C[e] Melting point,°C ID test Assay minimum (isomers distribution and secondary components)**	**Refrac. Index[f] Spec. gravity[g]**	**EFSA Comments**
13.009 1171 2381 535 119-84-6	3,4-Dihydrocoumarin	[b]	Liquid $C_9H_8O_2$ 148.16	Slightly soluble Soluble	272 – IR 99%	1.555–1.559 1.186–1.192	
13.012 1172 2699 579 92-48-8	6-Methylcoumarin	[b]	Solid $C_{10}H_8O_2$ 160.17	Insoluble Soluble	– 73–79 IR 99%	– –	
13.161 1166 3791 – 4430-31-3	Octahydrocoumarin	[b]	Liquid $C_9H_{14}O_2$ 154.21	Insoluble Soluble	293–298 – NMR 99% Mixture of optical isomers (diastereoisomers) (EFFA, 2010a)	1.489–1.493 1.090–1.096	Stereoisomeric composition (diastereoisomers/ enantiomers) to be specified
16.055 1165 3794 – 564-20-5	(R)-(+)-Sclareolide	[b]	Solid $C_{16}H_{26}O_2$ 250.38	Insoluble Slightly soluble	– 124.4 IR NMR 98%	– –	

Abbreviations: CoE, Council of Europe; CAS, Chemical Abstract Service; FEMA, Flavor and Extract Manufacturers Association; FL-No, FLAVIS number; JECFA, The Joint FAO/WHO Expert Committee on Food Additives; ID, identity; IR, infrared spectroscopy; MS, mass spectrometry; NMR, nuclear magnetic resonance.

[a]JECFA (2004, 2016b), EFSA CEF Panel (2009a, 2011) and Documentation provided to EFSA no. 1 and 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 1013.25 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

For the flavouring substance [FL-no: 10.057], use levels were provided by industry (Documentation provided to EFSA no. 2) for the different food categories reported in Annex III of Regulation (EC) 1565/2000.[1] After the publication of FGE.80Rev1, industry provided data on uses and use levels for the substances [FL-no: 10.005, 10.024, 10.025, 10.050, 10.072, 13.009, 13.012, 13.161, 16.055] (DG SANCO, 2014) for the different food categories reported in Annex III of Regulation (EC) 1565/2000[1]. These data are included in the present revision, FGE.80Rev2, and used for the calculation of mTAMDI (Tables C.1 and C.4).

TABLE C.1 Normal and maximum use levels (mg/kg) for 10 out of 14 flavouring substances evaluated in FGE.80Rev2 (DG SANCO, 2014; Documentation provided to EFSA no. 2).

	Food categories																		
	Normal use[a] levels (mg/kg) Maximum use levels (mg/kg)																		
FL-no	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
10.005	0.001 0.01	–	–	–	–	0.03 0.05	–	–	–	0.04 0.09	–	–	–	0.24 0.74	–	0.0005 –	–	0.01 0.27	–
10.024	0.3 0.22	–	–	–	–	–	–	0.09 0.37	0.11 0.37	0.07 0.16	–	–	–	0.33 3.3	–	0.25 0.5	0.0002 –	0.02 0.09	–
10.025	0.31 1.5	0.5 1	–	–	–	1 5	–	–	2.1 9	0.04 0.1	–	–	–	4.5 70	–	0.015 0.05	–	–	–
10.050	0.6 2	–	–	0.6 2	–	1.3 10	–	–	3 9	–	–	–	–	–	–	–	–	–	–
10.057	7 35	5 25	7 35	7 35	7 35	10 50	1 10	2 10	1 5	2 10	2 10	–	5 25	5 25	–	0.5 5	2 10	10 50	5 25
10.072	1.2 7	–	–	–	–	1.3 6	–	–	1.4 3	–	–	–	–	–	–	1.8 5	–	–	–
13.009	0.27 12	0.08 180	– 300	–	0.38 1.6	2.1 250	–	0.011 1.6	2.5 43	–	–	–	–	–	–	4 2000	0.01 0.07	0.27 1.1	–
13.012	0.5 460	–	–	–	–	0.5 1400	–	0.25 1.7	2 1900	–	–	–	–	–	–	1.9 120	–	–	–
13.161	– –	–	1 –	–	0.5 –	0.5 –	–	–	1.5 –	–	–	–	–	1 –	–	1 –	–	–	–
16.055	1 4	1 10	1 3	1 2	1 2	1 3	–	1 3	2 3	1 4	1 2	–	1 3	1 3	–	1 5	1 5	2 4	–

Abbreviation: FL-No, FLAVIS number; '–' no value for normal or maximum use level was provided.

[a]'Normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages (EFFA, 2002).

[b]Additional food category 05.3 (chewing gum as per Annex II part D of Reg. (EC) 1333/2008) for which industry submitted use levels (Documentation provided to EFSA no. 2). These data were considered in the calculation of mTAMDI.

C.2 | mTAMDI CALCULATIONS

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

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

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

The mTAMDI calculations are based on the normal use levels reported by industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 and reported by the Flavour Industry in the following way (see Table C.3):

- Beverages (SCF, 1995) correspond to food 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		

TABLE C.4 Estimated intakes based on the MSDI approach and the mTAMDI approach (DG SANCO, 2014; EFFA, 2010a; Documentation provided to EFSA no.1 and 2).

FL-no	EU Union list chemical name	MSDI – EU (μg/*capita*/day)	mTAMDI	Structural class	TTC (μg/person/day)
10.005	3-propylidenephthalide	17	11	Class III	90
10.024	3-butylidenephthalide	8.6	128	Class III	90
10.025	3-butylphthalide	0.49	402	Class III	90
10.050	hexahydro-3,6-dimethyl-2(3*H*)-benzofuranone	8	435	Class III	90
10.057	3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one	0.012	1708	Class III	90
10.061	cis-5-hexenyldihydro-5-methylfuran-2(3*H*)-one	100	n.a.	Class I	1800
10.069	3-methyl gamma-decalactone	4.5	n.a.	Class I	1800
10.070	4-methyl-5-hexen-1,4-olide	2.2	n.a.	Class I	1800
10.072	dimethyl-3,6-benzo-2(3*H*)-furanone	0.84	805	Class III	90
10.169	5,6,7,7alpha- Tetrahydro-4,4,7alpha-trimethyl-2-(4*H*)-benzofuranone	0.12	n.a.	Class III	90
13.009	3,4-dihydrocoumarin	1200	1692	Class III	90
13.012	6-methylcoumarin	250	896	Class III	90
13.161	octahydrocoumarin	1.3	558	Class III	90
16.055	(R)-(+)-sclareolide	1.1	698	Class III	90

Abbreviations: FL-No, FLAVIS number; MSDI, maximised survey-derived daily intake; mTAMDI, modified theoretical added maximum daily intake; n.a., not available.

C.3 | NATURAL OCCURRENCE

JECFA status (JECFA, 2017).

The flavouring substance [FL-no: 10.057] has been reported to occur as a natural component of orange and grapefruit juice and fresh apples.

Information provided by industry (Documentation provided to EFSA no. 1)

The candidate chemical [FL-no: 10.057] has been reported to occur in foods: fresh apple, citrus fruits, sherry and wine.

APPENDIX D

Summary of toxicity data evaluated in FGE.80Rev2

TABLE D.1 Summary of toxicity data evaluated by the Panel in FGE.80Rev2 and by JECFA at the 73rd meeting (JECFA, 2016a, 2017).

Chemical name [FL-no]	Species; Sex No/group	Route	Doses (mg/kg bw per day)	Duration (days)	NOAEL (mg/kg bw per day)	Reference	Comments
Dehydromenthofurolactone [FL-no: 10.034]	Sprague Dawley Rats M, F 20	Diet	0.94, 9.5, 95.3 (M) 0.98, 10.0, 99.7 (F)	90	1	Food and Drug Research Laboratories, 1985	The study had some shortcomings, e.g. purity of test substance was not specified and ophthalmological examination and functional observations were not performed. In addition, organ weight measurements were only performed for a few organs. NOAEL of 1 mg/kg bw per day is based on the oesophageal and gastric lesions

Abbreviations: F, Female; FL-No, FLAVIS number; M, Male.

APPENDIX E

Summary of safety evaluations

TABLE E.1 Summary of safety evaluations performed by JECFA (JECFA, 2004, 2016a, 2017) and EFSA conclusions on flavouring substances in FGE.80 and its revisions and in FGE.96.

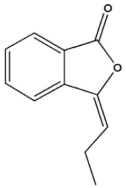
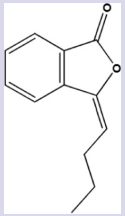
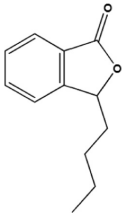
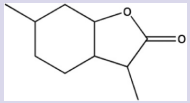
FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[c] approach on the named compound and on the material of commerce
10.005 1168	3- Propylidenephthalide		Class III B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80
10.024 1170	3-Butylidenephthalide		Class III B3: Intake below threshold B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80
10.025 1169	3-Butylphthalide		Class III B3: Intake below threshold, B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80
10.050 1161	Hexahydro-3,6-dimethyl-2(3*H*)-benzofuranone		Class III A3: intake below threshold No safety concern	No safety concern at the estimated level of intake Stereoisomeric composition (diastereoisomers/enantiomers) to be specified. Concluded in FGE.96

TABLE E.1 (Continued)

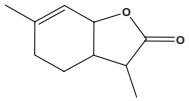
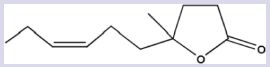
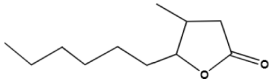
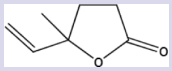
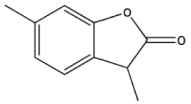
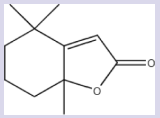
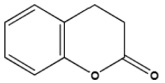
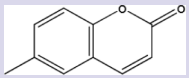
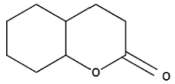
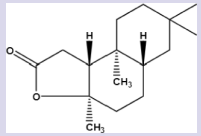
FL-no JECFA-no	EU Union List chemical name	Structural formula	JECFA conclusions Class[a] Evaluation procedure path[b] Outcome on the named compound based on the MSDI approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[c] approach on the named compound and on the material of commerce
10.057 2223	3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one		Class III A3: intake above threshold (based on SPET 300 µg/person per day) A4: metabolites are not endogenous A5: Adequate NOAEL exists No safety concern	A3: intake below threshold (based on MSDI 0.012 µg/capita per day) No safety concern at the estimated level of intake Concluded in FGE.80Rev2
10.061 1159	cis-5-Hexenyldihydro-5-methylfuran-2(3*H*)-one		Class I A3: intake below threshold No safety concern	No safety concern at the estimated level of intake Concluded in FGE.96
10.069 1158	3-Methyl gamma-decalactone		Class I A3: intake below threshold No safety concern	No safety concern at the estimated level of intake No information on the enantiomeric compositions of the *cis* and *trans* diastereoisomers has been provided Concluded in FGE.96
10.070 1157	4-Methyl-5-hexen-1,4-olide		Class I A3: intake below threshold No safety concern	No safety concern at the estimated level of intake Concluded in FGE.96
10.072 1167	Dimethyl-3,6-benzo-2(3*H*)-furanone		Class III B3: Intake below threshold B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake Concluded in FGE.96
10.169 1164	5,6,7,7alpha-Tetrahydro-4,4,7alpha-trimethyl-2-(4*H*)-benzofuranone		Class III A3: intake below threshold No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80Rev1
13.009 1171	3,4-Dihydrocoumarin		Class III B3: Intake above threshold B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80
13.012 1172	6-Methylcoumarin		Class III B3: Intake above threshold B4: Adequate NOAEL exists No safety concern	No safety concern at the estimated level of intake. Concluded in FGE.80Rev1

TABLE E.1 (Continued)

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 approach	EFSA conclusion Procedural path if different from JECFA, Conclusion based on the MSDI[c] approach on the named compound and on the material of commerce
13.161 1166	Octahydrocoumarin		Class III A3: intake below threshold No safety concern	No safety concern at the estimated level of intake. Stereoisomeric composition (diastereoisomers/enantiomers) to be specified. Concluded in FGE.96
16.055 1165	(R)-(+)-Sclareolide		Class III A3: intake below threshold No safety concern	No safety concern at the estimated level of intake Concluded in FGE.80

[a]Thresholds of concern: Class I = 1800 μg/person per day, Class II = 540 μg/person per day, Class III = 90 μg/person per day.

[b]Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.

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