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SCIENTIFIC OPINION

Flavouring Group Evaluation 82 Revision 2 (FGE.82Rev2): Consideration of epoxides evaluated by JECFA

EFSA Panel on Food Additives and Flavourings (FAF) | Laurence Castle | Monica Andreassen | Gabriele Aquilina | Maria Bastos | Polly Boon | Biagio Fallico | Rex FitzGerald | María José Frutos Fernández | Bettina Grasl-Kraupp | Ursula Gundert-Remy | Rainer Gürtler | Eric Houdeau | Marcin Kurek | Henriqueta Louro | Patricia Morales | Sabina Passamonti | Gisela Degen | Karl-Heinz Engel | Maria Carfí | Ana Criado | Borana Dino | Carla Martino

Correspondence: Ask a Question

The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts.

Abstract

The Panel on Food Additives and Flavourings (FAF) of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No. 1565/2000. The present consideration concerns a group of five epoxides evaluated by JECFA at the 65th meeting. This revision of FGE.82 is made due to new information on stereoisomeric composition, toxicity studies, uses and use levels for beta-ionone epoxide [FL-no: 07.170]. In addition, new data on uses and use levels for the substances [FL-no: 16.015, 16.018, 16.040 and 16.043] have been provided and considered for the estimation of exposure (modified theoretical added maximum daily intake (mTAMDI) approach). The Panel considered that the information on the stereochemical composition of [FL-no: 07.170] is sufficient. The Panel did not agree with the application of the Procedure for the epoxides as performed by JECFA, because in the absence of experimental data, the extent of detoxification of these epoxides remains uncertain. Therefore, [FL-no: 07.170] was assessed via the B-side of the Procedure. In the 90-day toxicity study on [FL-no: 07.170], substance-related findings were observed in adrenal glands of male rats. Based on this observation, the Panel identified a no observed adverse effect level (NOAEL) of 39 mg/kg bw per day and concluded that for [FL-no: 07.170] there is 'no safety concern at estimated levels of intake as flavouring substance', when based on the maximised survey-derived daily intake (MSDI) approach. Based on new information on uses and use levels for [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043], the mTAMDI exposure estimates are above the toxicological threshold of concern (TTC) for their structural class III. The Panel concluded that more reliable data on uses and use levels would be needed for these five substances.

KEYWORDS

epoxides, FGE.82, flavourings, JECFA

CONTENTS

Abstract 1
1. Introduction 3
1.1. Background and Terms of Reference as provided by the requestor 3
1.1.1. Background 3
1.1.2. Terms of Reference 3
1.2. Interpretation of the Terms of Reference 3
1.3. History of the evaluation and presentation of the substances in the present FGE 3
2. Data and Methodologies 5
2.1. Data 5
2.2. Methodologies 6
3. Assessment 6
3.1. Specifications 6
3.2. Estimation of intake 7
3.3. Biological and toxicological data 7
3.3.1. ADME data 7
3.3.2. Genotoxicity studies 8
3.3.3. Toxicity studies 9
3.4. Application of the procedure 10
3.4.1. Application of the procedure by JECFA 10
3.4.2. EFSA considerations 10
4. Discussion 11
5. Conclusions 11
6. Recommendation 11
Documentation as provided to EFSA 12
Abbreviations 12
Acknowledgements 12
Requestor 12
Question number 12
Copyright for non-EFSA content 13
Panel members 13
Legal notice 13
References 13
Appendix A 15
Appendix B 18
Appendix C 20
Appendix D 24
Appendix E 25

1 | INTRODUCTION

The present revision of FGE.82 (FGE.82Rev2) is made due to newly submitted data for beta-ionone epoxide [FL-no: 07.170]: information on stereoisomeric composition, toxicity studies, uses and use levels. In addition, new information on uses and use levels has been provided for the substances [FL-no: 16.015, 16.018, 16.040 and 16.043] and considered for the estimation of exposure (modified Theoretical Added Maximum Daily Intake (mTAMDI) approach).

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

1.1.1 | Background

The use of flavourings in food is regulated under Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008[1] 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.[2] The list includes flavouring substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000.[3]

In the scientific opinion on Flavouring group evaluation 82 revision 1 (FGE.82Rev1) adopted on 21 May 2014, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and processing Aids (CEF) concluded that the evaluation of beta-ionone epoxide [FL-no: 07.170] cannot be finalised because a NOAEL from a 90-day study is not available and information on its stereoisomeric composition are missing.

In March 2025, the European Flavour Association submitted to the Commission the missing data.

1.1.2 | Terms of Reference

The European Commission requests the European Food Safety Authority (EFSA) to evaluate this new information and to proceed to the full evaluation of the flavouring substance [FL-no: 07.170], in accordance with Commission Regulation (EC) No 1565/2000.[3]

1.2 | Interpretation of the Terms of Reference

In addition to assess the new data submitted for [FL-no: 07.170], new information on uses and use levels provided for the substances [FL-no: 16.015, 16.018, 16.040 and 16.043] (Documentation provided to EFSA No. 3) are considered in the present revision to estimate the exposure based on the mTAMDI approach.

1.3 | History of the evaluation and presentation of the substances in the present FGE

FGE.82

At its 65th meeting, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of nine flavouring substances belonging to the class of epoxides (JECFA, 2006a, 2006b). One substance evaluated by JECFA, *trans*-carvone-5,6-oxide (JECFA no. 1572), was not included in the EU Register[4] at the time of EFSA's assessment and was therefore not evaluated further by EFSA, while the other eight substances [FL-no: 07.170, 16.015, 16.018, 16.043, 16.040, 16.044, 16.051, 16.071] were included in the EU Register and therefore considered by EFSA.

Owing to the presence of an α, β-unsaturated carbonyl moiety, which constitutes a structural alert for genotoxicity, three substances from this group, two α, β-unsaturated ketones (β-ionone epoxide [FL-no: 07.170] and piperitenone oxide [FL-no: 16.044]) and one α, β-unsaturated aldehyde (4,5-epoxydec-2(trans)-enal [FL-no: 16.071]), were assessed separately

[1]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, pp. 34–50.

[2]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, pp. 1–161.

[3]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, pp. 8–16.

[4]Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996. OJ L 84, 27.3.1999, pp. 1–215.

for their genotoxic potential within dedicated EFSA genotoxicity flavouring group evaluations (FGE.210Rev1, FGE.213 and FGE.226Rev1, respectively).

Piperitenone oxide [FL-no: 16.044] was evaluated in FGE.213, where the CEF Panel requested additional genotoxicity data (EFSA, 2009a). Industry informed that [FL-no: 16.044] was no longer of interest for use as a flavouring substance in Europe, and no further data were submitted (Documentation provided to EFSA No. 2). Therefore, the substance [FL-no: 16.044] was not included in the Union List.[2]

4,5-Epoxydec-2(trans)-enal [FL-no: 16.071] was evaluated in FGE.226Rev1, where the CEF Panel concluded that [FL-no: 16.071] does raise a safety concern with respect to genotoxicity and, therefore, it was not evaluated according to the Procedure (which is described in Appendix A) (EFSA CEF Panel, 2017).

The remaining epoxide flavouring substances, i.e. ethyl methylphenylglycidate [FL-no: 16.015], ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018], ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate [FL-no: 16.040], β-caryophyllene epoxide [FL-no: 16.043] and epoxy oxophorone [FL-no: 16.051], were evaluated by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC Panel) in FGE.82 (EFSA, 2009b).

Among these five substances, adequate specifications, including complete purity criteria and identity tests, were available only for β-caryophyllene epoxide [FL-no: 16.043]. Information on stereoisomeric composition was lacking for [FL-no: 16.015, 16.018, 16.040 and 16.051], and data on solubility in water and ethanol were missing for ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018].

The AFC Panel considered that epoxy oxophorone [FL-no: 16.051] should not be evaluated through the Procedure because of concerns regarding genotoxicity and concluded that adequate genotoxicity data would be required.

For ethyl methylphenylglycidate [FL-no: 16.015] and ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018], the AFC Panel considered that the available in vitro and in vivo studies indicated a genotoxic potential. However, for ethyl methylphenylglycidate [FL-no: 16.015], a carcinogenicity study allowed derivation of a no observed adverse effect level (NOAEL) of 0.1% in the diet (35 mg/kg bw per day for males and 60 mg/kg bw per day for females). The AFC Panel considered that the negative outcome of this carcinogenicity study overruled the positive genotoxicity findings for ethyl methylphenylglycidate [FL-no: 16.015] and also for the structurally related substances ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018] and ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate [FL-no: 16.040].[5]

For ethyl methylphenylglycidate [FL-no: 16.015], ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018], ethyl 2,3-epoxy-3-methyl-3-ptolylpropionate [FL-no: 16.040] and beta-caryophyllene epoxide [FL-no: 16.043], the AFC Panel concluded that the available data do not preclude their evaluation through the Procedure.

Accordingly, ethyl methylphenylglycidate [FL-no: 16.015], ethyl 3-phenyl-2,3-epoxypropionate [FL-no: 16.018], ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate [FL-no: 16.040] and β-caryophyllene epoxide [FL-no: 16.043] were evaluated through the Procedure. Contrary to JECFA, the AFC Panel considered that these substances could not be predicted to be metabolised to innocuous products and therefore these substances were evaluated via the B-side of the Procedure. For β-caryophyllene epoxide [FL-no: 16.043], no toxicity studies were available from which a NOAEL could be identified (see Appendix A) for the substance or for structurally related substances and additional toxicity data were therefore required.

For the four substances evaluated through the B-side of the Procedure, the AFC Panel expressed reservations due to missing information on stereoisomerism for three substances [FL-no: 16.015, 16.018, 16.040] and the need for additional toxicity data for one substance [FL-no: 16.043]. In addition, for these substances [FL-no: 16.015, 16.018, 16.040 and 16.043], use levels would be required to calculate the mTAMDIs in order to identify those flavouring substances that need a more refined exposure assessment and to finalise their evaluation.

FGE.82Rev1

After the publication of FGE.82, industry informed that epoxy oxophorone [FL-no: 16.051] is no longer of interest for use as flavouring substance in Europe (Documentation provided to EFSA No. 2), and therefore the data requested by the AFC Panel in FGE.82 were not provided. Accordingly, this substance [FL-no: 16.051] was not included in the Union List.[2]

The α, β-unsaturated epoxide, beta-ionone epoxide [FL-no: 07.170] was evaluated in FGE.210Rev1 (EFSA CEF Panel, 2014b), where the substance was considered not to be of concern with respect to genotoxicity. Beta-ionone epoxide [FL-no: 07.170] was therefore included in FGE.82Rev1 (EFSA CEF Panel, 2014a) to complete the evaluation through the Procedure.

Therefore, in FGE.82Rev1, the CEF Panel considered five flavouring substances evaluated by JECFA [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043].

New information on missing stereoisomeric composition for [FL-no: 16.015, 16.018 and 16.040] was provided (Documentation provided to EFSA No. 6) and considered in FGE.82Rev1. The CEF Panel considered that adequate specifications including complete purity criteria and identity tests were available for four JECFA-evaluated substances [FL-no: 16.015, 16.018, 16.040 and 16.043], but for [FL-no: 07.170] information on stereoisomeric composition was not adequate.

[5]The FAF Panel is aware that the opinion of the AFC Panel was adopted in 2009, before the EFSA Scientific Committee (SC) guidance on genotoxicity (EFSA Scientific Committee, 2011) was published and that the conclusions drawn by the AFC Panel on the substances [FL-no: 16.015, 16.018, 16.040] are not in line with the EFSA SC guidance from 2011, where it is stated that 'clear evidence of genotoxicity in somatic cells in vivo should be considered an adverse effect *per se*, since genotoxicity is also implicated in degenerative diseases other than cancer'. However, since the mandate of the present opinion is related to [FL-no: 07.170], this issue is not further considered in this revision of FGE.82 (FGE.82Rev2).

Additional toxicity data (a 14-day dose range-finding study and a 90-day dietary study) were provided for beta-caryophyllene epoxide [FL-no: 16.043]. Based on the NOAEL derived from the 90-day study and the estimated exposure, the CEF Panel considered that the margin of safety[6] when used as a flavouring substance was adequate.

The CEF Panel considered that four of the five substances [FL-no: 16.015, 16.018, 16.040 and 16.043] evaluated via the B-side of the Procedure scheme were of no safety concern at the estimated levels of intake, when based on the MSDI approach.

The evaluation of beta-ionone epoxide [FL-no: 07.170] could not be finalised because a 90-day study was not available.

For [FL-no: 07.170 and 16.043] data on use levels were provided and considered in FGE.82Rev1.

For the other three substances [FL-no: 16.015, 16.018 and 16.040] use levels would be required to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise their evaluation.

Table 1 provides a compilation of the three opinions on FGE.82.

TABLE 1 References to the opinions on FGE.82.

FGE	Reference	Substances[a]
FGE.82	EFSA (2009b)	5
FGE.82Rev1	EFSA CEF Panel (2014a)	5
FGE.82Rev2	Current opinion	5

[a]Substances considered in: FGE.82: [FL-no: 16.015, 16.018, 16.040, 16.043 and 16.051]; FGE.82Rev1: [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043]; FGE.82Rev2: [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043].

A summary of the history of the evaluation of the substances in FGE.82 and revisions is presented in Figure 1.

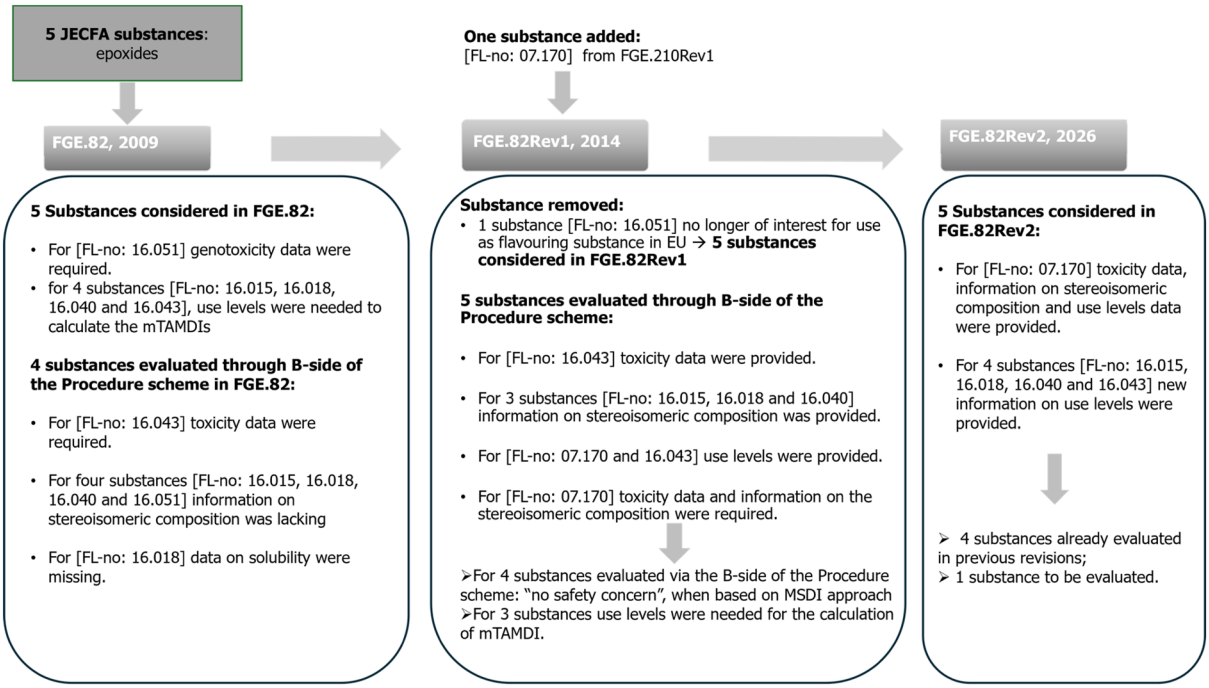


FIGURE 1 Summary of the history of evaluation of the substances in FGE.82 and revisions.

2 | DATA AND METHODOLOGIES

2.1 | Data

In the present revision (FGE.82Rev2) the following data were considered:

– a 14-day dietary toxicity/palatability study, a 90-day toxicity study in rats, information on stereoisomeric composition and updated information on uses and use levels for beta-ionone epoxide [FL-no: 07.170] (Documentation provided to EFSA No. 1, 7 and 8).

[6]'Margin of safety' was used by the CEF Panel. Now the term has been replaced by 'margin of exposure' (EFSA Scientific Committee, 2025).

– new information on uses and use levels for four substances [FL-no: 16.015, 16.018, 16.040 and 16.043] has been provided (Documentation provided to EFSA No. 3).

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, 2009c) and following the relevant existing Guidelines from the EFSA Scientific Committee. As requested in the EC mandate, the assessment strategy applied is in line with the evaluation programme of flavouring substances, as laid down in Commission Regulation (EC) No 1565/2000,[3] which is based on the Opinion on a Programme for the Evaluation of Flavouring substances of the Scientific Committee on Food (SCF, 1999).

The approach for safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000,[3] named the 'Procedure', is described in Appendix A.

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

The present revision of FGE.82 (FGE.82Rev2) addresses the evaluation of β-ionone epoxide [FL-no: 07.170] for which a 14-day dietary toxicity/palatability study, a 90-day toxicity study, updated information on uses and use levels and data on stereoisomerism have been provided (Documentation provided to EFSA No. 1, 7 and 8).

After the publication of FGE.82Rev1 in 2014, new information on uses and use levels has been provided for four substances [FL-no: 16.015, 16.018, 16.040 and 16.043] (Documentation provided to EFSA No. 3). Accordingly, the corresponding mTAMDI estimates for these four substances are included in the present opinion.

Therefore, FGE.82Rev2 includes five substances, of which four were already considered in FGE.82Rev1 as of no safety concern when based on the MSDI approach. For the sake of completeness, information on specifications, intake and evaluation status of all five substances, being already available in previous assessments, is presented in the respective Appendices B, C and E.

3.1 | Specifications

JECFA status

JECFA specifications are available for all five substances [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043] (JECFA, 2005). All these five substances have one or more chiral centres.

For β-caryophyllene epoxide [FL-no: 16.043], JECFA 'revised the melting point to 55–63°C and the assay minimum to 95% (sum of isomers) from data on eight lots of commercial product. Specifications for the isomeric compositions were also established: 84%–89% 1*R*,4*R*,6*R*,10*S* (CAS No. 1139-30-6), 7%–9% 1*R*,4*R*,6*S*,10*S* (CAS No. 60594-22-1), 0.3–2% 1*R*,4*S*,6*S*,10*S* (CAS No. 103475-43-0) and 1%–2% humulene-1,2-epoxide (CAS No. 19888-34-7) (JECFA, 2020).

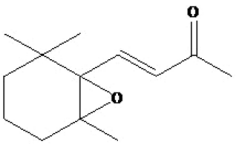
EFSA considerations

The chemical name, structure and structural class (Cramer et al., 1978) of the flavouring substance [FL-no: 07.170] considered in FGE.82Rev2 are reported in Table 2.

Specifications including complete purity criteria and identity are available for four substances [FL-no: 16.015, 16.018, 16.040 and 16.043]. Information about the stereoisomerism for one substance [FL-no: 07.170] has been provided. According to the information provided by industry, beta-ionone epoxide [FL-no: 07.170] is a racemic mixture of 50%–70% (*E*)- and 30%–50% (*Z*)-isomers (Documentation provided to EFSA No. 1). Since [FL-no: 07.170] has two chiral centres with two configurations each, it may occur as a mixture of four stereoisomers.

Specifications for all five substances in FGE.82Rev2 are summarised in Appendix B, Table B.1, based on data reported in FGE.82Rev1, information considered by JECFA (JECFA, 2020) and the additional information provided for [FL-no: 07.170] (Documentation provided to EFSA No. 1). The available specifications are considered adequate for all five substances.

TABLE 2 Chemical name, structure and structural class (Cramer et al., 1978) of the flavouring substance under evaluation in FGE.82Rev2.

FL-no JECFA no	Structural formula[b]	Chemical name	Structural class[a]
07.170 1571		beta-Ionone epoxide	III

Abbreviations: FL-no, FLAVIS number; JECFA, The Joint FAO/WHO Expert Committee on Food Additives; JECFA no, JECFA number.
[a]Determined with OECD Toolbox (version 4.8 available at https://qsartoolbox.org/).
[b]Only the (*E*) isomer is shown.

3.2 | Estimation of intake

JECFA status

For all five substances evaluated through the JECFA Procedure, production volume data in the EU were available and allowed the calculation of MSDI values (JECFA, 2006a, 2006b). Since beta-ionone epoxide [FL-no: 07.170] was proposed for use as a flavouring substance, an anticipated volume of production was available to JECFA at that time. The conclusions of JECFA on the safety of [FL-no: 07.170] were conditional pending the submission of actual poundage data (JECFA, 2006a, 2006b). The actual production volume for [FL-no: 07.170] was subsequently submitted and considered by JECFA at the 69th meeting (JECFA, 2009). Based on this new information, JECFA confirmed the assessment of [FL-no: 07.170] as of no safety concern (JECFA, 2009).

EFSA considerations

EU production volumes are available for all substances [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043].

Information on uses and use levels has been provided for each of the five substances (Documentation provided to EFSA No. 1 and 3) and considered in the present revision, FGE.82Rev2 (see Table C.1, Appendix C).

The MSDI figures and mTAMDI intake estimates for the flavouring substances in FGE.82Rev2 are shown in Table C.4, Appendix C.

Natural occurrence

Data on natural occurrence were reported by JECFA (2006a, 2006b) for [FL-no: 07.170] (JECFA no. 1571) and [FL-no: 16.043] (JECFA no. 1575) and were also provided by industry for [FL-no: 07.170] (Documentation provided to EFSA No.1). This information is included in Appendix C.

3.3 | Biological and toxicological data

3.3.1 | ADME data

JECFA status

JECFA (2006a, 2006b) considered that epoxides are 'readily and adequately' detoxified in animals via two pathways, hydrolysis in the gastrointestinal tract or in other tissues resulting in diols, or via reaction of epoxides with glutathione, and concluded that 'all the flavouring agents in this group can be predicted to be metabolised to innocuous products'. Therefore, the substances were evaluated via the A-side of the Procedure.

EFSA considerations

The Panel considered that beta-ionone epoxide as well as the other epoxides in this FGE can be metabolised to non-toxic products. However, in the absence of experimental data, the extent to which these epoxides are detoxified remains uncertain. For this reason, the Panel cannot confirm that the flavouring substances in this group can be predicted to be completely metabolised to innocuous products. Therefore, these substances are evaluated through the Procedure via the B-side (Appendix A) as in the previous opinions on FGE.82 (EFSA, 2009b; EFSA CEF Panel, 2014a).

3.3.2 | Genotoxicity studies

JECFA status

JECFA (2006a) assessed the genotoxicity of this group of epoxides (including [FL-no: 07.170] based on genotoxicity studies available for [FL-no: 16.015, 16.018 and 16.043]):

'The genotoxic potential of glycidate and alicyclic epoxides was studied in several standard assays in bacteria and mammalian cells in vitro. In the Ames assay for reverse mutation, both caryophyllene oxide[7] and ethyl methylphenylglycidate[8] gave unequivocally negative results with and without metabolic activation in a series of standard *S*. Typhimurium tester strains. Ethyl 3-phenylglycidate[9] gave positive results only in *S*. Typhimurium strains TA100 and TA98 and mainly in the presence of metabolic activation; however, a digest of ethyl 3-phenylglycidate had no mutagenic potential in *S*. Typhimurium TA100 and TA98 with or without metabolic activation. Negative results were reported with cis-methyl epoxycinnamate, a structurally related glycidic ester, in the standard battery of *S*. Typhimurium tester strains, but trans-methyl epoxycinnamate was mutagenic in TA1535, TA1537, TA1538 and TA100, only in the absence of metabolic activation. Cyclopentane and cyclohexane oxide induced reverse mutation in *S*. Typhimurium strains TA1535 and TA100. Although cycloaliphatic epoxides of larger ring size were generally less mutagenic than the smaller-ring epoxides, marked cytotoxicity was seen. Uniformly negative results were obtained in the SOS Chromotest in *E. coli*. Although clastogenic activity was reported in mammalian cell lines with most glycidate and alicyclic epoxides, increased sister chromatid exchange frequencies were observed with ethyl methylphenylglycidate only in the absence of metabolic activation. Likewise, chromosomal aberrations were reported in Chinese hamster ovary cells incubated with ethyl methylphenylglycidate or cyclohexane oxide, but the results with ethyl methylphenylglycidate were equivocal when S9 activation was incorporated into the assay. No unscheduled DNA synthesis was found with a series of epoxyalkanes and alicyclic epoxides.

In vivo, ethyl methylphenylglycidate had slight potential to induce sex-linked recessive lethal mutations in Drosophila, but ethyl 3-phenylglycidate showed no activity. Ethyl 3-phenylglycidate and ethyl methylphenylglycidate did not induce micronucleus formation in mice given single intraperitoneal doses.

Epoxides are naturally occurring substances that are also added to food as flavouring agents. The principal epoxide used in this way is ethyl methylphenylglycidate. Studies on the metabolism of glycidate and alicyclic (including terpene) epoxides indicate that these compounds are readily and adequately detoxicated in animals via two pathways, GSH conjugation and hydrolysis in the gastrointestinal tract or other tissues, followed by glucuronic acid or sulphate conjugation in the liver. Although glycidate and alicyclic epoxides had some genotoxic potential in standard assays in vitro, the results of assays for genotoxicity in mammals in vivo were negative. Furthermore, a number of long-term studies with dietary administration provided no evidence of carcinogenic potential. Several long-term studies with repeated doses of ethyl methylphenylglycidate showed no carcinogenicity even at intake levels that were orders of magnitude higher than the intake of epoxides added as flavouring agents. The NOEL in the 2-year bioassay of ethyl methylphenylglycidate was 35 mg/kg bw per day. This intake level is > 1100 times the daily per capita intake ('eaters only') of 0.031 mg/kg bw per day from use of ethyl methylphenylglycidate as a flavouring agent.'

JECFA (2006a) concluded that: 'The known pathways of metabolic detoxication, the lack of evidence of carcinogenicity in long-term feeding studies and the lack of genotoxic potential in vivo indicate that it is unlikely that epoxides pose a significant genotoxic risk to humans under the conditions of their use as flavouring agents'.

EFSA considerations

The genotoxic potential of [FL-no: 07.170], an α, β-unsaturated epoxide, was assessed in FGE.210Rev1 (EFSA CEF Panel, 2014b) where the concern was ruled out.

In FGE.210Rev1 (EFSA CEF Panel, 2014b), the CEF Panel assessed in vitro genotoxicity studies for [FL-no: 07.170]: 'beta-Ionone epoxide did not induce any significant increase in bacterial mutation when evaluated in five different *S*. Typhimurium strains and an *E. coli* strain, either in the presence or absence of S9 metabolic activation in two independent studies. Beta-Ionone epoxide also did not increase mutation frequencies when tested in a *tk* mutation assay using mouse lymphoma cells either in the presence or absence of S9 metabolic activation. No *in vitro* assay for chromosomal aberration is available, but the mouse lymphoma assay is a test that is able to detect the chemical potential to induce structural chromosomal aberrations. The lack of an *in vitro* micronucleus assay is not consistent with the current EFSA guideline (EFSA Scientific Committee, 2011), it is however consistent with the genotoxicity test strategy for substances belonging to subgroups of FGE.19 (EFSA, 2008) applicable at the time when the scientific opinion on FGE.210 was adopted (EFSA, 2009d). The Panel concluded that the data submitted for beta-ionone epoxide are sufficient in the light of data available for structurally related substances'. (EFSA CEF Panel, 2014b).

In FGE.210Rev1, the CEF Panel concluded that based on the experimental data on the representative substances alpha-ionone [FL-no: 07.007] and beta-ionone epoxide [FL-no: 07.170], the concern with respect to genotoxicity could be ruled out.

[7][FL-no: 16.043].
[8][FL-no: 16.015].
[9][FL-no: 16.018].

Therefore, for the flavouring substance [FL-no: 07.170] the safety evaluation through the Procedure can be performed.

3.3.3 | Toxicity studies

JECFA status

Toxicological data for the flavouring substance [FL-no: 07.170] were not considered by JECFA, because JECFA concluded on the safety of this substance at step A3 of the Procedure (JECFA, 2006a, 2006b).

EFSA considerations

Since [FL-no: 07.170] is evaluated via the B-side of the Procedure, the CEF Panel requested toxicity data for this substance in FGE.82Rev1 (EFSA CEF Panel, 2014a). The new data provided are described below and summarised in Appendix D.

Toxicity studies on beta-ionone epoxide [FL-no: 07.170]
14-day dose range-finding study

A 14-day dose range-finding study (Documentation provided to EFSA No. 7) was performed with beta-ionone epoxide (purity 95.6%) to support dose selection for the subsequent 90-day oral toxicity study. The study was not GLP compliant.

Four groups of seven to 8 weeks old CRL Sprague–Dawley® CD® IGS rats (5/sex/group) were fed with a diet containing beta-ionone epoxide at concentrations of 0, 1200, 2400 and 4800 mg/kg that would correspond to intended doses of 0, 100, 200 and 400 mg/kg bw per day for 14 days. The study authors calculated the mean nominal overall daily intake to be 0, 106, 214 and 419 mg/kg bw per day for males and 0, 103, 211 and 421 mg/kg bw per day for females.

To evaluate the stability of beta-ionone epoxide in diet, samples of the diet were collected on days 0, 4, 7 and 10. Due to marked variability of analytical results, the nominal overall intake could not be confirmed. The test substance was considered stable over the course of the study under the conditions of storage, but stability in the diet could not be assessed due to large variability in the measured concentrations.

No mortality occurred and no test substance-related clinical observations were observed. A statistically significant lower body weight ($p < 0.05$) was observed in females of the low dose group compared to controls on day 7. At the low dose, females had significantly lower ($p < 0.01$) mean body weight gain on days 0–7 compared to controls. A slight, but statistically significant decrease in food consumption was observed in males at the highest dose on days 0–3, and in females at the low and mid dose on days 3–7 and 10–14.

All animals in the study were subjected to gross necropsy; there were no macroscopic alterations in any of the rats.

The study authors concluded that treatment with beta-ionone epoxide was well tolerated at doses up to 400 mg/kg bw per day (the highest dose tested).

90-day toxicity study

Beta-ionone epoxide (purity 95.6%) was tested in a 90-day repeated dose toxicity study in rats (Documentation provided to EFSA No. 8) according to OECD TG 408 (OECD, 1998) and in compliance with GLP. Four groups of seven to 8 weeks old CRL Sprague–Dawley® CD® IGS rats (10/sex/group) were fed a diet containing beta-ionone epoxide aimed to provide doses of 0, 20, 40 or 80 mg/kg bw per day. Based on food consumption data (collected throughout the study), the actual mean doses were 0, 19, 39 and 77 mg/kg bw per day for males and 0, 20, 39 and 78 mg/kg bw per day for females. Stability of the test substance in the diet was confirmed by analysis, and variability of test substance concentrations in the diet was considered to be within an acceptable margin of variation. The study authors reported that selection of dose levels was based on the 14-day palatability/toxicity study. However, the highest tolerated dose of 400 mg/kg bw per day in the 14-day study was not tested in the 90-day study. In the respective publication of this study (Lu et al., 2021), the authors justified that the dose range selected for the 90-day study was limited by test substance availability as the annual production volume for this substance is low.

No mortality occurred and no test substance-related clinical signs were observed. No effects on ophthalmological parameters, body weights and food consumption were observed.

No changes in organ weights or organ weights relative to terminal body and brain weights were observed in male rats fed a diet with beta-ionone epoxide. In the females of the high dose group, a significant increase in absolute liver weight, liver-to-body weight ratio ($p < 0.05$) and liver-to-brain weight ratio was observed. Without any correlating hepatic histopathological findings, these increases are interpreted to be non-adverse.

Haematology, clinical chemistry and urine analysis were carried out in blood and urine samples collected on days 51 and 86 from all animals. Blood samples were also collected prior to necropsy for coagulation determinations on day 94/95.

The Panel noted some statistically significant changes in clinical parameters (prothrombin time, absolute large unstained cell count, absolute reticulocyte count, aspartate aminotransferase, bilirubin, calcium, chloride); however, these were considered non-adverse as they were within historical control ranges, showed no biological significance, were not supported by corresponding histopathological findings and/or were not dose-related.

Oestrus cycle was also evaluated in all groups on 6–7 and 12–13 weeks. The mean cycle length and the number of cycles were not altered at any dose.

No alterations on spermatozoid motility, epididymal sperm count, homogenisation-resistant sperm count or percent abnormal sperm were observed.

Macroscopic findings include a small right adrenal gland in one male of the mid-dose group and a kidney cyst in one male of the high dose group, which had no microscopic correlation in both cases. Uterus was noted as fluid-filled at necroscopy in 8/10, 3/10, 6/10 and 4/10 females of the control group and of the low-, mid- and high dose, respectively. Fluid-filled uteri usually corresponded microscopically to luminal dilation of the uterus that was attributable by the study authors to variations in the oestrus cycle. Additionally, one female of the control group presented agenesis of the left ovary, noted macroscopically and microscopically, which was considered by the study authors to be not related to administration of beta-ionone epoxide.

There were treatment-related adrenal gland findings in 8/10 males of the high dose group. The adrenal glands exhibited minimal to moderate diffuse cortical vacuolation, which was limited to the zona fasciculata. The vacuoles were clear, variably sized and discrete. An increased incidence and severity of diffuse cortical vacuolation was observed in 8 high-dose males (5 rats with minimal severity, 1 mild, 2 moderate) when compared to controls (3/10 males, minimal severity). Although this alteration was considered to be test substance-related, the study authors concluded that it was not adverse due to its non-degenerative nature (Documentation provided to EFSA No. 8).

The Panel considered that vacuolation of the zona fasciculata has been described as a background finding in rats (McInnes, 2012). However, it could also be the result of chemically-induced impairment of steroid synthesis leading to lipid accumulation (Brändli-Baiocco et al., 2018). Despite the lack of degenerative changes (i.e. degeneration/necrosis), the Panel considered the adrenal findings, at the high dose, as adverse based on the severity (moderate) that is above the threshold of concern (i.e. minimal to mild). In the absence of data from functional assays demonstrating the preserved functionality of adrenal cortex this concern could not be dismissed.

Thus, based on the substance-related findings observed in adrenal glands of males of the high dose group that were considered adverse, the Panel identified the (actual) dose of 39 mg/kg bw per day as the NOAEL in this study.

3.4 | Application of the procedure

3.4.1 | Application of the procedure by JECFA

According to JECFA (JECFA, 2006a, 2006b) all five substances belong to structural class III, using the decision tree approach presented by Cramer et al. (1978).

JECFA considered that all five substances can be predicted to be metabolised to innocuous products (step 2 of the Procedure), so they were evaluated along the A-side of the Procedure.

For three substances [FL-no: 07.170, 16.040 and 16.043], the estimated intakes performed by JECFA were below the toxicological threshold of concern (TTC) (90 μg/person per day) for structural class III (step A3 of the Procedure).

For two substances [FL-no: 16.015 and 16.018], the estimated intakes were above the TTC for structural class III, and they do not occur endogenously in humans (step A4 of the Procedure). Therefore, the evaluation proceeded to step A5, where a long-term study (Dunnington et al., 1981) for ethyl methylphenylglycidate [FL-no: 16.015] was considered by JECFA. From this study, a NOAEL of 35 mg/kg bw per day was derived, which provides a margin of safety of more than 8000 for [FL-no: 16.015] and more than 17,000 times the estimated intake of the related substance, [FL-no: 16.018]. In conclusion, JECFA evaluated all five substances to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The summary evaluations by JECFA of the five epoxides are presented in Appendix E.

3.4.2 | EFSA considerations

In FGE.82Rev1 (EFSA CEF Panel, 2014a), the CEF Panel did not agree with the application of the Procedure for the epoxides as performed by JECFA (see Section 3.3.1). The five substances [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043] were evaluated via the B-side of the Procedure scheme (Appendix A).

Taking into account the absorption, distribution, metabolism, excretion (ADME) considerations (Section 3.3.1), the Panel agreed with the CEF Panel and assessed [FL-no: 07.170] via the B-side of the Procedure scheme (Appendix A):

Step 1. The Panel agreed with JECFA with respect to the allocation of the candidate flavouring substance [FL-no: 07.170] in structural class III.

Step 2. The Panel did not agree with JECFA that [FL-no: 07.170] can be predicted to be completely metabolised to innocuous products. Therefore, the evaluation was performed via the B-side of the Procedure.

Step B3. The estimated MSDI value of 0.4 μg/capita per day, calculated by the Panel, is below the TTC for class III (Table C.4, Appendix C).

Step B4. Based on a NOAEL of 39 mg/kg bw per day identified from a 90-day toxicity study on [FL-no: 07.170] (see Section 3.3.3) and the estimated MSDI value, an adequate margin of exposure of almost 6 million is calculated.[10]

Thus, the Panel concluded that beta-ionone epoxide [FL-no: 07.170] is of no safety concern when based on the MSDI approach.

In addition, industry provided updated use levels for [FL-no: 07.170], resulting in an estimation of mTAMDI of 840 μg/person per day (Appendix C). Industry also provided new information on uses and use levels for the other structural class III substances [FL-no: 16.015, 16.018, 16.040 and 16.043] included in FGE82, allowing the estimation of the mTAMDI for each substance of 710, 630, 880 and 1200 μg/person per day, respectively. All mTAMDI values are above the TTC for structural class III substances of 90 μg/person per day.

Therefore, the Panel concluded that more reliable data on uses and use levels are needed for [FL-no: 07.170, 16.015, 16.018, 16.040 and 16.043]. When these data become available, the assessment for these flavouring substances may be updated accordingly and expanded if necessary (e.g. request of additional toxicity data).

4 | DISCUSSION

The present revision of FGE.82 (FGE.82Rev2) is based on new toxicological data, information on stereoisomeric composition and updated information on uses and use levels for beta-ionone epoxide [FL-no: 07.170]. In addition, new information on uses and use levels for four flavouring substances [FL-no: 16.015, 16.018, 16.040 and 16.043] has been provided and considered for the estimation of their intake with the MSDI and mTAMDI approach.

The new information provided on the stereochemical composition of [FL-no: 07.170] is considered sufficient by the Panel.

Taking into account the ADME considerations (Section 3.3.1), the Panel did not agree with the application of the Procedure for the epoxides as performed by JECFA. Since the Panel cannot confirm that the flavouring substances in this group can be predicted to be completely metabolised to innocuous products, beta-ionone epoxide [FL-no: 07.170] was assessed via the B-side of the Procedure, in line with the assessment performed by the CEF Panel for the other four epoxides in the previous revisions (EFSA, 2009b; EFSA CEF Panel, 2014a).

The Panel identified the dose of 39 mg/kg bw per day as the NOAEL in the 90-day study on [FL-no: 07.170] based on the findings observed in adrenal glands in males of the high dose group suggesting steroid synthesis impairment with lipid accumulation. Based on the NOAEL and on the estimated MSDI, an adequate margin of exposure (of almost 6 million) was calculated. Therefore, the Panel considered that [FL-no: 07.170] does not pose a safety concern when used as flavouring substance at estimated levels of intake, when based on the MSDI approach.

For all five substances [FL-no: 07.170, 16.015, 16.018, 16.040, 16.043] in FGE.82Rev2, mTAMDI estimates exceeded the TTC of 90 μg/person per day for structural class III substances. For these substances, more reliable data on uses and use levels should be provided to refine the exposure assessment to finalise their safety evaluation.

The Panel considered that the available specifications for the five substances in FGE.82Rev2 are adequate and that the conclusions in FGE.82Rev2 can be applied to the materials of commerce.

5 | CONCLUSIONS

The Panel evaluated beta-ionone epoxide [FL-no: 07.170] through the Procedure and concluded in agreement with JECFA that there is 'no safety concern at estimated levels of intake as flavouring substance', when based on the MSDI approach.

For the other four substances included in FGE.82Rev2, [FL-no: 16.015, 16.018, 16.040, 16.043] the same conclusion, i.e. 'no safety concern at estimated levels of intake as flavouring substances', when based on the MSDI approach, was already drawn in the previous opinions (FGE.82 and FGE.82Rev1).

However, for all the five substances [FL-no: 07.170, 16.015, 16.018, 16.040, 16.043] in FGE.82Rev2, mTAMDI estimates exceed the TTC of 90 μg/person per day for structural class III substances. Therefore, for these substances, more reliable data on uses and use levels would be needed to refine the exposure assessments and to finalise their safety evaluation.

6 | RECOMMENDATION

The stereochemical information available for [FL-no: 07.170, 16.015, 16.018, 16.040, 16.043] and presented in Table B.1 (Appendix B) should be included into the Union List.

[10]Margin of exposure (MOE is the ratio between a reference point and the estimated exposure): MOE = NOAEL ((39 mg/kg bw per day) × (60 kg as value for human bw)) × 1000/MSDI (0.4 μg/capita per day).

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ABBREVIATIONS

ADME	absorption, distribution, metabolism, excretion
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
bw	body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFFA	European Flavour Association
F	female
FAF	Panel on Food Additives and Flavourings
FAO	Food and Agriculture Organisation
FEMA	Flavour and Extract Manufacturer Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good Laboratory Practice
ID	identity
IR	infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
M	male
MS	mass spectrometry
MSDI	maximised survey-derived daily intake
mTAMDI	modified theoretical added maximum daily intake
NMR	nuclear magnetic resonance
No	number
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
(Q)SAR	(quantitative) structure–activity relationship
SC	Scientific Committee
SCF	Scientific Committee on Food
TTC	toxicological threshold of concern
USA	United States of America
WHO	World Health Organization

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PANEL MEMBERS

Laurence Castle, Monica Andreassen, Gabriele Aquilina, Maria Bastos, Polly Boon, Biagio Fallico, Rex FitzGerald, María José Frutos Fernández, Bettina Grasl-Kraupp, Ursula Gundert-Remy, Rainer Gürtler, Eric Houdeau, Marcin Kurek, Henriqueta Louro, Patricia Morales, Sabina Passamonti

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APPENDIX A

Procedure for the safety evaluation

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000,[3] 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'.[11]

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 1800, 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[12] products (step 2)?
- Do their exposures exceed the TTC for the structural class (steps A3 and B3)?
- Are the flavourings or their metabolites endogenous[12] (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).

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

[12]*Innocuous products*: products that are known or readily predicted to be harmless to humans at the estimated intake of the flavouring agent (JECFA, 1997). *Endogenous substances*: intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997).

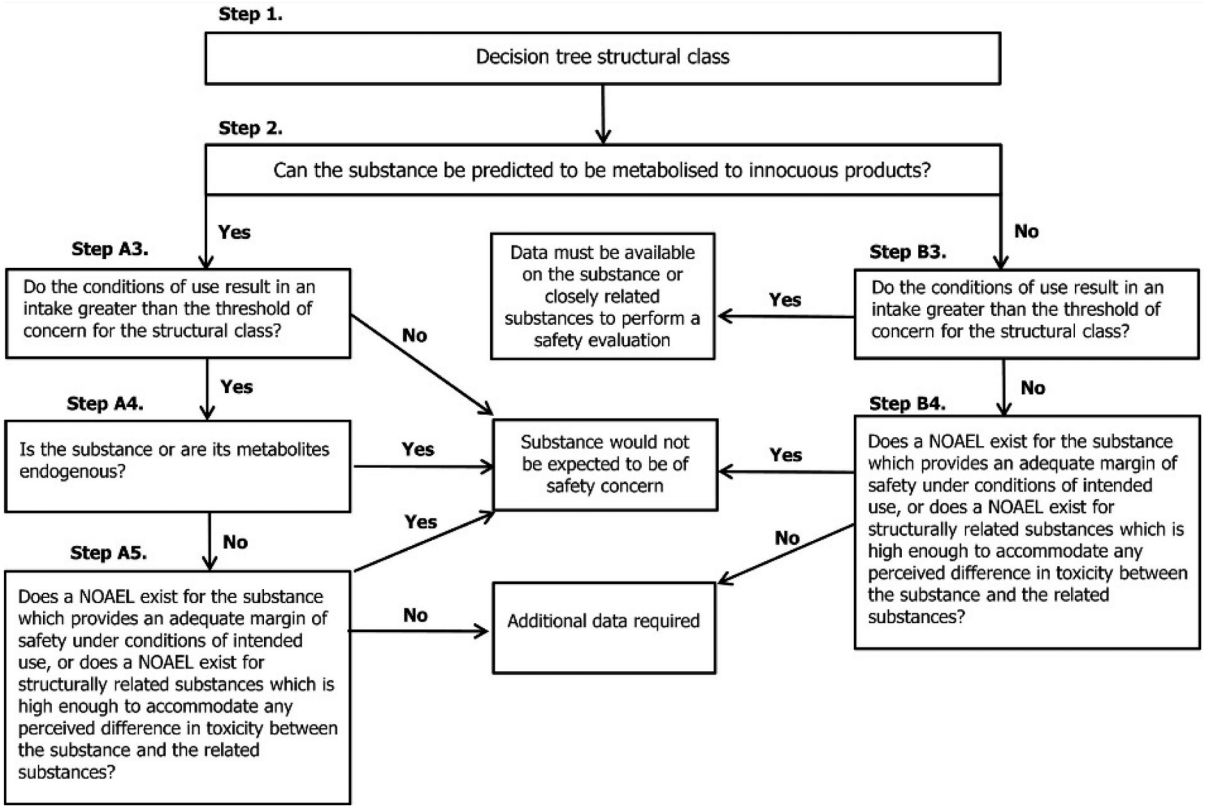


FIGURE A.1 Procedure for the safety evaluation of chemically defined flavouring substances.

For the flavouring substances considered in this FGE, the FAF Panel 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)[13] 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[14] for which this is the case, the Panel needs 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, 2006a, 2006b).

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).

[13]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.

[14]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.

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

b. Threshold of 1.5 μg/person per day (step B5) used by JECFA

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

The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 μg/person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the 46th meeting be amended to include the last step on the right-hand side of the original procedure ('Do the condition 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 (SCF, 1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential in vitro will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential in vivo has been concluded will not be evaluated through the Procedure.

d. Specifications

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

e. Structural Relationship

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

APPENDIX B

Specifications

TABLE B.1 Summary table on specifications data for flavouring substances in FGE.82Rev2 (for chemical structures see Appendix E) that are included in the Union List.

Information included in the EU Union list regulation (EC) No 1334/2008 as amended			Most recent available specifications data[a]			
FL-no **JECFA 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/ secondary components)**	**Refrac. Index[f]** **spec. Gravity[g]**
07.170 1571 11202 23267-57-4	beta-Ionone epoxide	[b]	Solid $C_{13}H_{20}O_2$ 208.30	Insoluble Soluble	n.a. 48 NMR MS 95% Racemic mixture of 50%–70% (*E*)- and 30%–50% (*Z*)-isomers	n.a. n.a.
16.015 1577 6002 77-83-8	Ethyl methylphenylglycidate	[b]	Liquid $C_{12}H_{14}O_3$ 206.24	Insoluble Soluble	272–275 n.a. IR 98% Mixture of diastereoisomers (two cis (15%–25% each) - and two trans-forms (25%–35% each) around oxirane ring)	1.504–1.513 1.086–1.096
16.018 1576 11844 121-39-1	Ethyl 3-phenyl-2,3-epoxypropionate	[b]	Liquid $C_{11}H_{12}O_3$ 192.21	Insoluble Soluble	96 (0.7 hPa) n.a. IR 98% Mixture of diastereoisomers (two cis (15%–25% each) - and two trans-forms (25%–35% each) around oxirane ring)	1.516–1.521 1.120–1.125
16.040 1578 11707 74367-97-8	Ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate	[b]	Liquid $C_{13}H_{16}O$ 220.27	Insoluble Soluble	123–125 n.a. NMR 96% Mixture of diastereoisomers (two cis (15%–25% each) - and two trans-forms (25%–35% each) around oxirane ring)	1.523–1.529 1.081–1.087 (20°)

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** **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/ secondary components)**	**Refrac. Index[f]** **spec. Gravity[g]**
16.043 1575 10500 1139-30-6	Beta-Caryophyllene epoxide	[b]	Solid $C_{15}H_{24}O$ 220.35	Insoluble Soluble	n.a. 55–63 NMR MS 95% Mixture of diastereoisomers: 84%–89% (1*R*,4*R*,6*R*,10*S*), 7–9% (1*R*,4*R*,6*S*,10*S*), 0.3–2% (1*R*,4*S*,6*S*,10*S*). Secondary component: 1–2% humulene-1,2-epoxide.	n.a. n.a.

Abbreviations: CAS, Chemical Abstract Service; CoE, Council of Europe; FL-no, FLAVIS number; ID, identity; IR, infrared spectroscopy; JECFA, The Joint FAO/WHO Expert Committee on Food Additives; MS, mass spectrometry; n.a., not applicable; NMR, nuclear magnetic resonance.

[a]JECFA (2005, 2020); EFSA CEF Panel (2014a) and documentation provided to EFSA No. 1.

[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: 07.170] and for the substances [FL-no: 16.015, 16.018, 16.040 and 16.043] data on uses and use levels were provided by industry for the different food categories reported in Annex III of Regulation (EC) 1565/2000[3] (Documentation provided to EFSA No. 1 and 3, respectively). These data were included in the present revision, FGE.82Rev2 and used for the calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) estimates (Tables C.1 and C.4).

TABLE C.1 Normal and maximum use levels (mg/kg) for the five flavouring substances considered in FGE.82Rev2 (Documentation provided to EFSA No. 1 and No. 3).

	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
07.170	3.2	0.03	2.9	–	–	3.7	3.7	–	–	–	–	–	–	0.02	–	1.0	–	–	–
	6.4	0.06	2.9	–	–	95.0	95.0	–	–	–	–	–	–	0.1	–	6.6	–	–	–
16.015	0.9	0.1	0.3	0.1	–	1.9	–	1.4	1.7	0.04	–	–	–	0.3	–	1.2	2.1	–	0.3
	5.4	0.3	11.0	1.9	–	330.0	–	9.6	20.0	0.2	–	–	–	0.5	–	6.8	14.0	–	0.5
16.018	3.6	–	0.4[c]	–	–	0.8	–	–	3.6	–	–	–	–	–	–	0.4	–	–	–
	39.0	–	0.00002	–	–	41.0	–	–	39.0	–	–	–	–	–	–	46.0	–	–	–
16.040	–	–	3.0	–	–	4.0	–	–	2.0	–	–	–	–	1.5	–	1.0	1.0	–	–
	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
16.043	0.9[c]	0.3	0.2	–	–	1.3[c]	–	0.2	1.7	0.01	–	–	–	1.1	–	1.3	0.5[c]	–	0.2
	0.6[c]	0.5	0.2	–	–	0.3[c]	–	0.3	2.0	0.03	–	–	–	1.2	–	87.0	0.4[c]	26.0[d]	0.3

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 uses and 'maximum use' is defined as the 95th percentile of reported use levels (EFFA, 2002)

[b]Additional food category 05.3 (chewing gum as per Annex II part D of Regulation (EC) 1333/2008[15]) for which industry submitted use levels (Documentation provided to EFSA No. 1). Food category 5.3 is not present in the food categorisation system reported in Annex III of Regulation (EC) 1565/2000.[3] However, these data were considered in the calculation of mTAMDI.

[c]The Panel noted that the normal and maximum use levels for this food category for [FL-no: 16.018 and 16.043] are not plausible. However, the lower value was provisionally used for the calculation of mTAMDI.

[d]For this food category only the maximum use level was provided. In absence of a normal use level the maximum use level has been used in the calculation of mTAMDI for [FL-no: 16.043].

[15]Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

C.2 | mTAMDI calculations

The method to calculate mTAMDI estimates is based on the approach used by the SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amounts of flavourable foods and beverages as listed in Table C.2. These consumption amounts are then multiplied by the reported use levels in the different food categories and summed up.

TABLE C.2 Estimated consumption amounts per person per day of flavourable foods and beverages, and five exceptions (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

The resulting mTAMDI estimates are listed in Table C.4 as well as the MSDI estimates.

TABLE C.3 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000[16] 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		

[16]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, pp. 8–16.

TABLE C.4 Estimated intakes based on the MSDI approach and the mTAMDI approach (Documentation provided to EFSA No. 1 and 3).

FL-no	EU Union list chemical name	MSDI – EU[a] (μg/capita per day)	mTAMDI (μg/person per day)	Structural class	TTC (μg/person per day)
07.170	beta-Ionone epoxide	0.4	840	Class III	90
16.015	Ethyl methylphenylglycidate	1340	710	Class III	90
16.018	Ethyl 3-phenyl-2,3-epoxypropionate	170	630	Class III	90
16.040	Ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate	0.01	880	Class III	90
16.043	beta-Caryophyllene epoxide	12	1200	Class III	90

Abbreviations: FL-no, FLAVIS number; MSDI, maximised survey-derived daily intake; mTAMDI, modified theoretical added maximum daily intake; TTC, threshold of toxicological concern.

[a]MSDI value is updated based on data provided in 2014 (Documentation provided to EFSA No. 3). For beta-ionone epoxide [FL-no: 07.170], the updated MSDI value is considered in the current opinion (see Section 3.4). The updated MSDI values for the other substances [FL-no: 16.015, 16.018, 16.040 and 16.043] would not have an impact on the conclusions reached in FGE.82Rev1.

C.3 | Natural occurrence

JECFA status (JECFA, 2006a, 2006b)

'Five of the nine flavouring agents (Nos 1570-1572, 1574 and 1575)[17] have been reported to occur naturally in fruits (e.g. citrus fruit, currants, mango and guava), beverages (beer) and a wide variety of spices and essential oils (e.g. scotch spearmint oil, celery seed, cinnamon bark and leaf oil, clove stem oil, ginger, peppermint oil, cornmint oil, pepper, thyme, hop oil, calamus, basil, rosemary, lemon balm, sage, pimento leaf, winter savoury, angelica seed oil, German camomile oil and mastic gum oil)'.

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

Beta-ionone epoxide [FL-no: 07.170] has been reported to occur in: acerola, buckwheat, cape gooseberry, dill, endive, guava, feyoa, lemon balm, mate, melon, mushroom, rooibos tea, tea, tomato.

[17]From this list of substances evaluated by JECFA, the flavouring substances considered in FGE.82Rev2 are [FL-no: 07.170] (JECFA no. 1571) and [FL-no: 16.043] (JECFA no. 1575).

APPENDIX D

Summary of Toxicity data for [FL-no: 07.170]

TABLE D.1 Summary of toxicity studies for beta-ionone epoxide [FL-no: 07.170] (Documentation provided to EFSA no. 1, 7, 8).

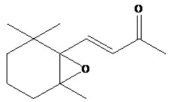
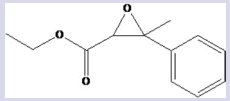
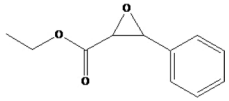
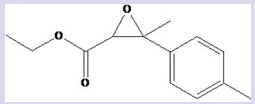
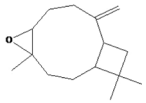
Species; sex No./group	Route of administration	Dose levels (mg/kg bw per day)	Duration (days)	Results	Reference	Comments
Repeated dose toxicity studies						
CRL Sprague–Dawley® CD® IGS Rats; M, F 5/sex/group	Oral (diet)	0, 100, 200, 400 Actual doses: 0, 106, 214, 419 (M) 0, 103, 211, 421 (F)	14	No toxicity observed	[redacted], 2015	Dose range-finding study. Treatment with beta-ionone epoxide was well tolerated at doses up to 400 mg/kg bw per day (the highest dose tested).
CRL Sprague–Dawley® CD® IGS Rats; M, F 10/sex/group	Oral (diet)	0, 20, 40, 80 Actual doses: 0, 19, 39, 77 (M) 0, 20, 39, 78 (F)	90	In males, the adrenal glands exhibited vacuolation of the zona fasciculata, which could be the result of chemically-induced impairment of steroid synthesis leading to lipid accumulation. These adrenal findings at high dose, despite the lack of degenerative changes, were considered as adverse based on the severity (moderate) that is above the threshold of concern (i.e. minimal to mild).	[redacted], 2016	Study performed according to OECD TG 408 and in compliance with GLP. The Panel identified the dose of 39 mg/kg bw per day as the NOAEL in this study.

Abbreviations: F, female; GLP, Good Laboratory Practice; M, male; OECD, Organization for Economic Co-operation and Development.

APPENDIX E

Summary of safety evaluations

TABLE E.1 Summary of Safety Evaluation performed by JECFA (2006a, 2006b) and EFSA conclusions on flavouring substances in FGE.82Rev2.

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 conclusions Procedural path if different from JECFA, conclusion based on the MSDI[c] approach on the named compound and on the material of commerce
07.170 1571	beta-Ionone epoxide		Class III A3: Intake below threshold No safety concern	B3: Intake below threshold B4: Adequate NOAEL (39 mg/kg bw per day) exists Concluded in FGE.82Rev2
16.015 1577	Ethyl methylphenylglycidate		Class III A3: Intake above threshold A4: Not endogenous A5: Adequate NOAEL (35 mg/kg bw per day) exists An ADI of 0–0.5 mg/kg bw was established at the 28th meeting and maintained at the 65th meeting. No safety concern	B3: Intake above threshold B4: Adequate NOAEL (35 mg/kg bw per day) exists Concluded in FGE.82
16.018 1576	Ethyl 3-phenyl-2,3-epoxypropionate		Class III A3: Intake above threshold A4: Not endogenous A5: Adequate NOAEL (35 mg/kg bw per day) exists No safety concern	B3: Intake above threshold B4: Adequate NOAEL (35 mg/kg bw per day) exists Concluded in FGE.82
16.040 1578	Ethyl 2,3-epoxy-3-methyl-3-p-tolylpropionate		Class III A3: Intake below threshold No safety concern	B3: Intake below threshold B4: Adequate NOAEL (35 mg/kg bw per day) exists Concluded in FGE.82
16.043 1575	beta-Caryophyllene epoxide		Class III A3: Intake below threshold No safety concern	B3: Intake below threshold B4: Adequate NOAEL (109 mg/kg bw per day) exists Concluded in FGE.82Rev1

Abbreviations: bw, body weight; FGE, Flavouring Group Evaluation; FL-no, FLAVIS number; JECFA, Joint FAO/WHO Expert Committee on Food Additives; NOAEL, no observed adverse effect level.

[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]JECFA (2006a, 2006b).

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