EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2013. Scientific Opinion on Flavouring Group Evaluation 73, Revision 2 (FGE.73Rev2). Consideration of alicyclic primary alcohols, aldehydes, acids and related esters evaluated by JECFA (59th meeting) structurally related to primary saturated or unsaturated alicyclic alcohols, aldehydes, acids and esters evaluated by EFSA in FGE.12Rev3 (2012)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 73, Revision 2 (FGE.73Rev2): Consideration of alicyclic primary alcohols, aldehydes, acids and related esters evaluated by JECFA (59th meeting) structurally related to primary saturated or unsaturated alicyclic alcohols, aldehydes, acids and esters evaluated by EFSA in FGE.12Rev3 (2012)[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

This scientific opinion, published on 5 December 2013, replaces the earlier version published on 16 October 2013*.

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids 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 (the 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 17 alicyclic primary alcohols, aldehydes, acids and related esters and one phenethyl ester evaluated by the JECFA at the 59th meeting in 2002. This revision is made due to consideration of two additional substances, santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712], cleared for genotoxicity concern in FGE.207. The substances were evaluated through a stepwise approach that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. The Panel agrees with the application of the Procedure as performed by the JECFA for all 18 substances [FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.028, 09.034, 09.289, 09.488, 09.534, 09.536, 09.615 and 09.712], considered in this FGE and agrees with the JECFA conclusion, "No safety concern at estimated levels of intake as flavouring substances" based on the

[1] On request from the European Commission, Question Nos EFSA-Q-2013-00552 and EFSA-Q-2013-00553, adopted on 25 September 2013.

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* Minor changes of editorial nature were made. The changes do not affect the contents of this report. To avoid confusion, the original version of the opinion has been removed from the website, but is available on request, as is a version showing all the changes made.

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MSDI approach. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been considered and for all 18 substances, the information is adequate.

KEY WORDS

alicyclic, primary alcohols, aldehydes and esters, JECFA 59th meeting, FGE.12, FGE.73, FGE.207

SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was asked to deliver a scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the CEF Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

In the previous version of Flavouring Group Evaluation 73 (FGE.73), EFSA considered 16 alicyclic primary alcohols, aldehydes, acids and related esters evaluated by the JECFA at their 59th meeting.

This revision is made due to consideration of two additional substances, santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712], compared to the previous version of FGE.73 (FGE.73Rev1). These substances have been evaluated in FGE.207 due to structural concern for genotoxicity, and have been cleared from this concern and thus may be evaluated through the Procedure.

The present consideration therefore concerns 17 alicyclic primary alcohols, aldehydes, acids and related esters and one phenethyl alcohol evaluated by the JECFA (59th meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluation of 10 primary saturated or unsaturated alicyclic alcohols, aldehydes and esters evaluated in the Flavouring Group Evaluation 12, Revision 3 (FGE.12Rev3).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 18 substances considered in this FGE.

For all 18 substances evaluated through the Procedure use levels are needed to calculate the modified Theoretical Added Maximum Daily Intake (mTAMDI) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 18 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity tests are available for all 18 JECFA evaluated substances.

Thus, for all 18 substances [FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.028, 09.034, 09.289, 09.488, 09.534, 09.536, 09.615 and 09.712] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of flavourings is regulated under Regulation (EC) No 1334/2008 of the European Parliament and Council of 16 December 2008[4] 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[5]. The list contains flavouring substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000[6].

EFSA concluded that a genotoxic potential of the 11 α,β-unsaturated aldehydes and alcohol and related esters in the present FGE.201 could not be ruled out.

Information on one representative material 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] has now been submitted by the European Flavour Association. This information is intended to cover also the re-evaluation of the following four substances from FGR.19 subgroup 2.1 (FGE.207):

- 12-beta-Santalen-14-ol [FL-no: 02.216]
- 12-alpha-Santalen-14-ol [FL-no: 02.217]
- Santalyl acetate [FL-no: 09.034]
- Santalyl phenylacetate [FL-no: 09.712]

The Commission asks EFSA to evaluate this new information and depending on the outcome proceed to the full evaluation of the flavouring substances.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requests the European Food Safety Authority to carry out a safety assessment on the following five substances: 12-beta-santalen-14-ol [FL-no: 02.216], 12-alpha-santalen-14-ol [FL-no: 02.217], santalyl acetate [FL-no: 09.034], santalyl phenylacetate [FL-no: 09.712] and 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931], in accordance with Commission Regulation (EC) No 1565/2000.

INTERPRETATION OF THE TERMS OF REFERENCE

2,6-Dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931], first allocated to FGE.201, has subsequently been transferred to FGE.207 for evaluation with respect to genotoxicity. Based on the new genotoxicity data submitted, the Panel concluded that [FL-no: 09.931] does not give rise to concern with respect to genotoxicity. This conclusion can also be applied to the substances santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712] for which 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] is representative. Therefore, the European Commission request EFSA to carry out a safety assessment for 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931], in accordance with Commission Regulation (EC) No 1565/2000.

[4] 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.

[5] EC (European Commission), 2012. 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.

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

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000, hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996; JECFA, 1997; JECFA, 1999), hereafter named the "JECFA Procedure". The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the 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 evaluations 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.

Intake

In its evaluation, the Panel as a default uses the Maximised Survey-derived Daily Intake (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe.

In its evaluation, the 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 the 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 the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need 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 level 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 the 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).

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.

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

Threshold of 1.5 Microgram/Person/Day (Step B5) Used by the JECFA

The JECFA uses the threshold of concern of 1.5 microgram (µg)/person/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 per 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 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 per person per day.

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.

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.

Structural Relationship

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

1. History of the Evaluation of the Substances in the Present FGE

The JECFA has evaluated a group of 26 flavouring substances consisting of alicyclic primary alcohols, aldehydes, acids and related esters (JECFA, 2002a).

In FGE.73, which covered a group of 15 of the 26 JECFA-evaluated substances, the Panel considered that for nine substances [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534 and 09.615] additional data were needed (no European production volumes available, preventing them to be evaluated using the Procedure, and/or missing data on isomerism/composition). For the remaining six of the 15 JECFA evaluated substances [FL-no: 05.119, 05.123, 08.034, 08.060, 09.028 and 09.536] the Panel agreed with the JECFA conclusion "no safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

The first revision of FGE.73 (FGE.73Rev1), included the assessment of one additional candidate substance, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104]. No toxicity or metabolism data were provided for the substance. Furthermore, EU production volumes were provided for three substances [FL-no: 02.141, 09.488 and 09.534] (EFFA, 2010a). Additional information on stereoisomeric composition for six substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615] and further information on the composition for one substance [FL-no: 05.112] were received (EFFA, 2010b) after publication of FGE.73, information which was included in Revision 1.

FGE	Opinion adopted	Link	No. of substances
FGE.73	6 March 2008	http://www.efsa.europa.eu/en/efsajournal/pub/868.htm	15
FGE.73Rev1	22 March 2012	http://www.efsa.europa.eu/en/efsajournal/pub/2638.htm	16
FGE.73Rev2	25 September 2001		18

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

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

2. Presentation of the Substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA Status

The JECFA has at the 59th meeting evaluated a group of 26 flavouring substances consisting of alicyclic primary alcohols, aldehydes, acids and related esters (JECFA, 2002a; JECFA, 2003).

2.1.2. EFSA Considerations

One of the 26 JECFA evaluated substances is not in the Register [Mixture of 2-methyl-5-(2,3-dimethyltricyclo[2.2.1.0(2,6)]hept-3-yl)pent-2-en-1-ol and 2-methyl-5-(2-methyl-3-methylenebicyclo [2.2.1]hept-2-yl)pent-2-en-1-ol] (JECFA-no: 984).

Ten substances [FL-no: 02.060, 02.091, 05.104, 05.106, 05.117, 05.121, 09.034, 09.272, 09.278 and 09.302] are α,β-unsaturated aldehydes or may be metabolised to α,β-unsaturated aldehydes and have been considered together with other α,β-unsaturated aldehydes and ketones. One of these α,β-unsaturated substances, 2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104], has been considered with respect to genotoxicity in FGE.209 (EFSA CEF Panel, 2011) and was evaluated through the Procedure in FGE.73Rev1. One additional substance, santalyl acetate [FL-no: 09.034], has been considered with respect to genotoxicity in FGE.207 (EFSA CEF Panel, 2013), and the Panel concluded that the data available ruled out the concern for genotoxicity and thus concluded that the substance can be evaluated through the Procedure in this revision of FGE.73. The genotoxic properties of the remaining eight of these 10 α,β-unsaturated carbonyl substances were considered together with other α,β-unsaturated aldehydes and ketones in FGE.208 (EFSA, 2008) for which it was concluded that additional data were required for all eight substances.

The Panel also concluded that santalyl phenylacetate [FL-no: 09.712], evaluated by the JECFA at its 59th meeting together with other phenethyl substances, cleared for genotoxicity concern in FGE.207, should be included in this FGE.

The Panel concluded that all 18 substances in this FGE are structurally related to the group of primary saturated or unsaturated alicyclic alcohol, aldehyde and esters evaluated by EFSA in the Flavouring Group Evaluation 12, Revision 3 (FGE.12Rev3).

2.2. Isomers

2.2.1. Status

Ten substances in the group of the JECFA evaluated alicyclic primary alcohols, aldehydes, acids and related esters have one or more chiral centres [FL-no: 02.114, 02.141, 05.098, 05.119, 05.123, 08.067, 09.034, 09.289, 09.615 and 09.712].

2.2.2. EFSA Considerations

For the two stereoisomeric substances [FL-no: 05.119 and 05.123], the CAS register number (CASrn) is considered to specify the stereoisomeric composition (Table 1).

2.3. Specifications

2.3.1.1. Status

The JECFA specifications are available for all 18 substances (JECFA, 2002b) (See Table 1).

2.3.2. EFSA Considerations

The available specifications are considered adequate for all 18 substances (See Section 2.2).

3. Intake Estimation

3.1. Status

For all 18 substances evaluated through the JECFA Procedure, intake data are available for the EU, see Table 4.

SUMMARY OF SPECIFICATION DATA

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

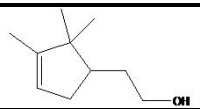
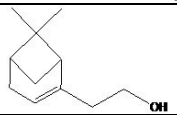
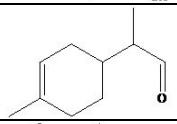
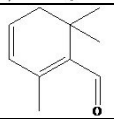
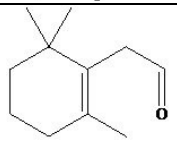
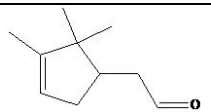
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [1] Solubility in ethanol [2]	Boiling point, °C [3] Melting point, °C ID test Assay minimum	Refrac. Index [4] Spec.gravity [5]	EFSA comments
02.114 970	2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol		3741 1901-38-8	Liquid $C_{10}H_{18}O$ 154.25	Slightly soluble Miscible	74 (0.8 hPa) NMR 96 %	1.470-1.478 0.882-0.894 (20°)	Racemate (EFFA, 2010a). Synonym (+/-)-campholene alcohol (EFFA, 2010a).
02.141 986	2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol		3938 128-50-7	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Miscible	230 IR NMR 95 %	1.490-1.500 0.965-0.973	Racemate (EFFA, 2010a).
05.098 971	p-Menth-1-en-9-al		3178 10347 29548-14-9	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	95 (13 hPa) NMR 99 %	1.458-1.466 0.904-0.916 (20°)	Racemate (EFFA, 2010a).
05.104 977	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		3389 10383 116-26-7	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	70 (1 hPa) NMR 96 %	1.525-1.533 0.968-0.980 (20°)	
05.112 978	2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde		3474 10338 472-66-2	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Miscible	58 (0.5 hPa) IR NMR 92 %	1.480-1.487 0.873-0.885 (20°)	Min. assay (92 %) secondary components ß-cyclocitral (2-3 %), ß-ionone (0.5-1 %), methyl ß-homocyclogeranate (2-4 %), ethyl ß-homocyclogeranate (0.6-1 %) (EFFA, 2010a).
05.119 967	2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde		3592 10325 4501-58-0	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	75 (137 hPa) NMR 99 %	1.462-1.469 0.918-0.924	CASrn in Register refers to (*R*)-isomer. Register name to be changed to (1*R*) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

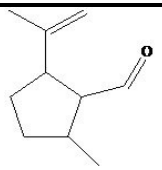
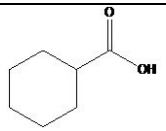
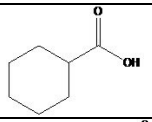
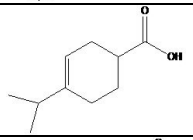
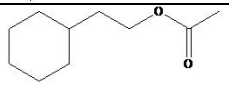
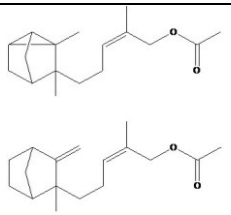
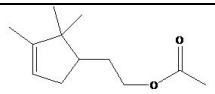
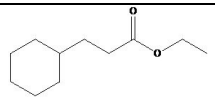
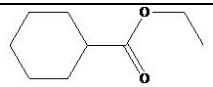
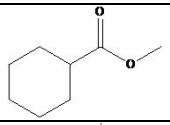
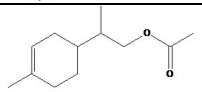
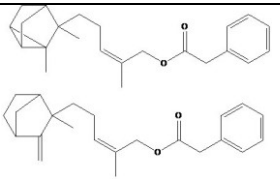
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [1] Solubility in ethanol [2]	Boiling point, °C [3] Melting point, °C ID test Assay minimum	Refrac. Index [4] Spec.gravity [5]	EFSA comments
05.123 968	5-Isopropenyl-2-methylcyclopentanecarboxaldehyde		3645 55253-28-6	Liquid $C_{10}H_{16}O$ 152.23	Insoluble Miscible	80 (14 hPa) IR 95 %	1.501-1.508 0.940-0.952 (20°)	CASrn in Register refers to (1*R*,2*R*,5*S*)-isomer. Register name to be changed to (1*R*,2*R*,5*S*) 5-Isopropenyl-2-methylcyclopentanecarboxaldehyde.
08.034 965	Cyclohexylacetic acid		2347 34 5292-21-7	Solid $C_8H_{14}O_2$ 142.20	Slightly soluble Miscible	242 28-33 NMR 98 %	1.459-1.467 1.001-1.009	
08.060 961	Cyclohexanecarboxylic acid		3531 11911 98-89-5	Solid $C_7H_{12}O_2$ 128.17	Slightly soluble Miscible	232-233 28-32 IR NMR 98 %	1.516-1.520 1.029-1.037	
08.067 976	1,2,5,6-Tetrahydrocuminic acid		3731 71298-42-5	Solid $C_{10}H_{16}O_2$ 168.24	Slightly soluble Soluble	n.a. 61 NMR 95 %	n.a. n.a.	Racemate (EFFA, 2010a). CASrn in Register does not specify stereoisomeric composition.
09.028 964	2-Cyclohexylethyl acetate		2348 218 21722-83-8	Liquid $C_{10}H_{18}O_2$ 170.25	Insoluble Miscible	211 (996 hPa) NMR 98 %	1.442-1.450 0.945-0.948	
09.034 985	Santalyl acetate		3007 224 1323-00-8	Liquid $C_{17}H_{26}O_2$ 262.40	Insoluble Miscible	20.8 (4 hPa) IR 95 %	1.485-1.493 0.980-0.986	CASrn in Register refers to incompletely defined substance. 60-65 % α-, 30-35 % β-form. 80-85 % *Z* versus 15-20 % *E* (for the alpha) and 75-80 % *Z* versus 20-25 % *E* (for the beta) (EFFA, 2013).
09.289 969	alpha-Campholene acetate		3657 36789-59-0	Liquid $C_{12}H_{20}O_2$ 196.29	Insoluble Miscible	96 (7 hPa) IR NMR 98 %	1.453-1.460 0.943-0.949	Commercial product (S)-enantiomer (EFFA, 2010a). Register name to be changed to (-)-

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [1] Solubility in ethanol [2]	Boiling point, °C [3] Melting point, °C ID test Assay minimum	Refrac. Index [4] Spec.gravity [5]	EFSA comments
								campholenyl acetate or (S)-campholenyl acetate (EFFA, 2010a).
09.488 966	Ethyl cyclohexanepropionate		2431 2095 10094-36-7	Liquid $C_{11}H_{20}O_2$ 184.28	Insoluble Miscible	91 (10 hPa) NMR 98 %	1.444-1.452 0.926-0.932	
09.534 963	Ethyl cyclohexanecarboxylate		3544 11916 3289-28-9	Liquid $C_9H_{16}O_2$ 156.22	Insoluble Miscible	82 (16 hPa) IR NMR 99 %	1.447-1.454 0.966-0.978 (20°)	
09.536 962	Methyl cyclohexanecarboxylate		3568 11920 4630-82-4	Liquid $C_8H_{14}O_2$ 142.19	Insoluble Miscible	183 IR NMR 98 %	1.439-1.447 0.990-0.999	
09.615 972	p-Menth-1-en-9-yl acetate		3566 10748 28839-13-6	Liquid $C_{12}H_{20}O_2$ 196.28	Insoluble Miscible	228-232 NMR 97 %	1.441-1.448 0.931-0.937	Racemate (EFFA, 2010a).
09.712 1022	Santalyl phenylacetate		3008 239 1323-75-7	Liquid $C_{23}H_{30}O_2$ 338.49	Insoluble Miscible	328 NMR 98 %	1.525-1.576 1.022-1.029	CASrn in Register refers to incompletely defined substance. 60-65 % α-, 30-35 % β-form. 80-85 % *Z* versus 15-20 % *E* (for the alpha) and 75-80 % *Z* versus 20-25 % *E* (for the beta) (EFFA, 2013).

1) Solubility in water, if not otherwise stated.
2) Solubility in 95 % ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.

4. Genotoxicity Data

4.1. Genotoxicity Studies – Text Taken[7] from the JECFA Report (JECFA, 2003)

No data on genotoxicity were available for the JECFA-evaluated substances. As these substances are rapidly metabolised *in vivo* to compounds of lower toxicological potential, the Committee concluded that the monocyclic and bicyclic terpenes with alkyl ring substituents and containing an alcohol, aldehyde or carboxylic acid group would have little genotoxic potential *in vivo*.

4.2. Genotoxicity Studies – Text Taken[8] from EFSA FGE.12Rev3 (EFSA CEF Panel, 2012a)

There are no studies available on genotoxicity neither for the 10 candidate substances nor for the 15 supporting substances. The genotoxic potential of this group of flavouring substances can therefore not be assessed properly. However, this does not preclude evaluation of the candidate substances in the present group using the Procedure.

4.3. Genotoxicity Studies – Text Taken[9] from EFSA FGE.209 (EFSA CEF Panel, 2011)

The Industry has submitted data concerning genotoxicity studies for 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal), which is the only substance considered in FGE.209.

In Vitro Data

In vitro genotoxicity assays have been performed on the α,β-unsaturated aldehyde safranal [FL-no: 05.104].

Bacterial Reverse Mutation Assay

Safranal has been tested for its ability to induce gene mutations in the bacterial reverse mutation assay according to OECD Guideline 471 (Beevers, 2010) (for details, see Table 2). The concentrations used in the different experiments were based on concentrations observed to give toxic effects in previous experiments. Positive and negative controls were included in all experiments according to current guidelines.

There were some increases in revertant numbers in TA102 in the absence and presence of S9 in the first experiment, but these were of insufficient magnitude to be considered as evidence of mutagenicity, they were not concentration-related, and were not reproducible in the other experiments. In all other strains there was no evidence of mutagenic activity either in the absence or presence of S9 in any of the experiments.

It is concluded that under the test conditions applied safranal did not induce gene mutations in bacteria.

Micronucleus Assays

Safranal was evaluated in an *in vitro* micronucleus assay in human peripheral blood lymphocytes for its ability to induce chromosomal damage or aneuploidy in the presence and absence of S9 (Whitwell, 2010). The maximum soluble concentration of 1250 µg/ml was selected as the maximum concentration for the cytotoxicity range finder test. The concentrations in the main tests were based on toxicity shown in this range finding study (for details, see Table 2).

[7] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.
[8] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.
[9] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

At the highest concentration used in the 3 + 21 hours treatment in the presence of S9, a small statistical increase in the frequency of micronucleated binucleate cells (MNBN) was observed, but this was set against a low mean concurrent vehicle control response. This concentration induced 62 % cytotoxicity, and there was no statistically significant increase in MNBN at the next lowest concentration, which induced 42 % cytotoxicity. Therefore, this isolated increase was not considered to be of biological importance. Outside of this isolated observation at a high level of toxicity, no evidence of chromosomal damage or aneuploidy was observed in terms of any increase in the frequency of MNBN in the presence or absence of S9.

It is concluded that under the conditions of this study, safranal did not induce micronuclei in cultured human lymphocytes.

In Vivo Data

Based on the *in vitro* data available, no *in vivo* data are needed.

Discussion of Mutagenicity/Genotoxicity Data

2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] was tested for all three genetic endpoints, gene mutations, structural and numerical chromosomal aberrations. The substance did not induce gene mutations in bacteria and was not clastogenic and/or aneugenic in mammalian cells *in vitro*.

Although this flavouring substance showed evidence of cytotoxicity at high concentrations, it did not induce biologically significant genotoxic responses.

For validation and study results, see Table 2.

Conclusion on Genotoxicity and Carcinogenicity

The *in vitro* genotoxicity data on 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] do not indicate genotoxic potential. 2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] will then be evaluated through the Procedure in FGE.73Rev1.

4.4. Genotoxicity Studies – Text Taken[10] from EFSA FGE.207 (EFSA CEF Panel, 2013a)

The Industry has submitted data concerning genotoxicity studies (EFFA, 2012) for one substance 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] of FGE.19 subgroup 1.1.2 (FGE.201). These data will cover four substances [FL-no: 02.216, 02.217, 09.034 and 09.712] from FGE.19 subgroup 2.1, evaluated in FGE.207.

The new data submitted for 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] covers *in vitro* assays in bacteria and mammalian cell systems.

In Vitro Data

Bacterial Reverse Mutation Assay

An Ames assay was conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 to assess the mutagenicity of 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931], both in the absence and in the presence of metabolic activation by S9-mix (from livers of rats induced with Aroclor 1254), in three experiments (King, 2000). An initial experiment was carried out in the absence and presence of S9-mix in the five strains, using final concentrations of 2,6-dimethyl-2,5,7-

[10] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

octatriene-1-ol acetate at 5 - 5000 μg/plate in the presence of S9-mix activation and 5 - 1500 μg/plate in the absence of S9-mix, plus negative (solvent) and positive controls. The standard plate incorporation assay was used. Evidence of toxicity, in terms of a decrease in revertant count, was apparent on all plates treated at 500 μg/plate and above in the absence of S9-mix. In the presence of S9-mix, the test article was toxic at concentrations of 1500 μg/plate and above for strains TA1537 and TA102, and at 5000 μg/plate for strains TA98, TA100 and TA1535. In all cases revertant counts were obtained from at least four different concentrations, and so these data were considered valid for mutation assessment. In the absence of S9-mix activation, no statistically significant increases in revertant numbers were observed in any of the test strains. In the presence of S9-mix activation no statistically significant increases in revertant numbers were observed for strains TA98, TA100, TA1535 or TA1537, but very small increases in revertant numbers were observed in strain TA102 at 15 and 50 μg/plate which, although statistically significant ($p \leq 0.05$), amounted to only 1.17-fold and 1.18-fold increases over background, respectively. Furthermore, no increases were observed at the higher test concentrations of 150 and 500 μg/plate.

In a second confirmatory experiment using the same conditions, no statistically significant increases in revertant numbers were observed at any concentration in any of the strains, either in the presence or absence of S9-mix activation. To further investigate the potential mutagenic effect in strain TA102 in the presence of S9-mix activation, a third experiment was conducted in that strain only. No statistically significant increases in revertant numbers were observed at any concentration tested.

On this basis, the very small increases seen in only a single experiment at the two lower test concentrations in the presence of S9-mix activation in strain TA102 were not reproducible or concentration-related, and were therefore considered to be chance occurrences and not related to treatment with 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] (King, 2000). It was concluded that 2,6-dimethyl-2,5,7-octatriene-1-ol acetate did not induce mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *S. typhimurium* when tested under the conditions of this study. These conditions included treatments at concentrations up to either the limit of toxicity or 5000 μg/plate (the maximum recommended concentration, according to current regulatory guidelines), in the absence and in the presence of a rat liver metabolic activation system (S9-mix).

Micronucleus Assays

2,6-Dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] was assayed for the induction of chromosome damage and potential aneugenicity in mammalian cells *in vitro* by examining the effect of compound treatment on the frequency of micronuclei in cultured human peripheral blood lymphocytes (whole blood cultures pooled from two healthy male volunteers in two separate experiments) treated in the absence and presence of a metabolising system (S9-mix) from livers of rats induced with Aroclor 1254 (Whitwell, 2012).

2,6-Dimethyl-2,5,7-octatriene-1-ol acetate was added at 48 hours following culture initiation (stimulation by phytohaemagglutinin) either for 3 hours treatment in the absence or presence of S9-mix plus 21 hours recovery, or for 24 hours treatment in the absence of S9-mix without recovery. Cytochalasin B (6 μg/ml) was added at the start of the 24-hour continuous treatment, or at the start of the 21-hour recovery periods following the 3-hour treatments, in order to block cytokinesis and generate binucleate cells for analysis. It remained in the cultures until they were harvested 24 hours after the start of treatment. A preliminary range-finding experiment had been conducted with and without S9-mix treatment in order to determine the effect of treatment upon Replication Index (RI), which was used as a basis for choosing a range of concentrations to be evaluated in Experiments 1 and 2.

In all of the different treatment conditions and separate experiments, frequencies of micronucleated binucleate cells (MNBN) were normal in negative controls and were significantly increased by treatment with the positive control chemical.

In Experiment 1, all three different treatment conditions described above were investigated. In the first treatment condition, 2,6-dimethyl-2,5,7-octatriene-1-ol acetate was added for 3 hours in the absence of S9-mix at concentrations of 70, 85, 100 or 120 µg/mL along with positive and negative controls, followed by 21 hours recovery. No significant increases in the frequency of MNBN were observed relative to concurrent vehicle controls at any of the concentrations analysed. Furthermore, the MNBN cell frequencies in all treated cultures under this treatment condition fell within the 95th percentile of the normal range.

In the second treatment condition, following 24 hours continuous treatment at 20, 40 or 60 µg/mL in the absence of S9-mix without recovery, no increases in the frequency of MNBN cells were obtained that were significantly higher ($p \leq 0.05$) than those observed in concurrent controls. Furthermore, the MNBN cell frequencies in all treated cultures under this treatment condition fell within the 95th percentile of the normal range.

In the third treatment condition, following 3 hours treatment with 2,6-dimethyl-2,5,7-octatriene-1-ol acetate at concentrations of 120, 140, 180 or 225 µg/mL in the presence of S9-mix, followed by 21 hours recovery, the frequency of MNBN cells were significantly higher ($p \leq 0.05$) than concurrent controls at the top concentration analysed. This concentration induced a 57 % mean level of cytotoxicity, which is close to the recommended upper limit for this test procedure. Furthermore, increases in the frequency of MNBN cells were only seen in one replicate (A) where only 394 binucleate cells could be analysed for this test concentration, where cytotoxicity actually exceeded 60 %, and where examination of the slides indicated a concentration-related effect on cells without intact cytoplasm. This may have resulted in an underestimation of the cytotoxicity, but it was not observed in the other replicate culture (B).

In Experiment 2, the weak induction of micronuclei that was observed in Experiment 1 in the presence of S9-mix was further investigated. Following treatment for 3 hours followed by 21 hours recovery in the presence of S9-mix with 2,6-dimethyl-2,5,7-octatriene-1-ol acetate at concentrations of 119.2, 180, 250 or 290 µg/mL, which induced 5 %, 19 %, 39 % and 54 % cytotoxicity, respectively, small but statistically significant ($p \leq 0.05$) increases in MNBN cell frequencies were observed at the lowest and highest concentrations analysed. At the highest concentration analysed only a single replicate culture gave MNBN cell frequencies that exceeded normal historical control values, and it is also noteworthy that the vehicle control frequency was quite low for this particular experiment which might have contributed to the test outcome. Furthermore, additional analysis of spare slides from the replicate cultures at the lowest and highest concentrations analysed resulted in the overall micronucleus frequencies falling within normal ranges. On this basis, the weak statistical significance observed in the first experiment was not reproduced at higher concentrations and similar levels of toxicity, and was therefore not considered to be of biological relevance.

In conclusion, 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] was not considered to demonstrate induction of micronuclei in a robust study that achieved required levels of toxicity (Whitwell, 2012).

Conclusion

2,6-Dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] did not induce any biologically significant increases in bacterial mutation when evaluated in an Ames test in the presence and absence of S9 metabolic activation. It did induce weak genotoxic effects in the *in vitro* micronucleus assay in an initial experiment in the presence of S9-mix at the highest concentration only. In a second experiment, although statistically significant increases were observed at the lowest and highest concentrations tested, these increases fell within the historical control range for the testing laboratory, and were not considered to be biologically important. The Panel therefore concluded that 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931], from subgroup 1.1.2 of FGE.19 (FGE.201), does not give rise to concern with respect to genotoxicity and can accordingly be evaluated through the Procedure. Furthermore, as 2,6-dimethyl-2,5,7-octatriene-1-ol acetate is considered representative for the four

precursors for α,β-unsaturated alicyclic aldehydes [FL-no: 02.216, 02.217, 09.034 and 09.712] from subgroup 2.1 of FGE.19 (FGE.207), the genotoxicity concern can also be lifted for these four substances and accordingly they can also be evaluated through the Procedure as well (in FGE.12Rev4 and FGE.73Rev2).

For a summary of *in vitro* genotoxicity data considered by the EFSA in FGE.207, see Table 3.

4.5. EFSA Considerations

The present revision of FGE.73, Revision 2, contains 18 substances, which includes the assessment of two additional flavouring substances, santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712]. These substances have a structural alert for genotoxicity, but this concern has been alleviated as described in FGE.207 (EFSA CEF Panel, 2013a), where the Panel based on submitted data on the representative substance 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] concluded that it does not give rise to concern with respect to genotoxicity. This conclusion can also be applied to the substances santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712] for which 2,6-dimethyl-2,5,7-octatriene-1-ol acetate [FL-no: 09.931] is representative. Therefore, these substances can also be evaluated through the Procedure in this FGE.73Rev2 ([FL-no: 09.931] is evaluated through the Procedure in FGE.72Rev1(EFSA CEF Panel, 2013b)). No genotoxicity data are available for any of the remaining 16 JECFA evaluated substances. However, this will not preclude the evaluation of these substances using the Procedure, and the Panel agreed with the JECFA that these 16 substances can be evaluated using the Procedure.

5. Application of the Procedure

5.1. Application of the Procedure to 17 Alicyclic Primary Alcohols, Aldehydes, Acids and Related Esters and One Ester of a Phenethyl Derivative by the JECFA (JECFA, 2002a)

According to the JECFA all 18 substances belong to structural class I using the decision tree approach presented by Cramer et al. (Cramer et al., 1978).

The JECFA concluded for 16 of the alicyclic primary alcohols, aldehydes, acids and related esters and for santalyl phenylacetate [FL-no: 09.712], an ester of the phenethyl derivatives, at step A3 in the JECFA Procedure – i.e. the substances are expected to be metabolised to innocuous products (step 2) and the intakes for all substances are below the thresholds for their structural class I (step A3).

The JECFA concluded for 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal) at step B4 in the JECFA Procedure – i.e. the substance cannot be expected to be metabolised to innocuous products (step 2) and an adequate NOAEL exists to provide a margin of safety (step B4). This evaluation was reached by the following procedure: Step B3. The daily per capita intake of the monocyclic substance with two endocyclic double-bonds evaluated at this step, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104], was below the threshold for daily human intake of compounds of structural class I, and its evaluation therefore proceeded to step B4.

Step B4. As the agent evaluated at this step, 2,6,6-trimethy1cyclohexa-l,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal), is structurally related to perillyl alcohol [FL-no: 02.060], data on the toxicity of perillyl alcohol were used to evaluate its safety. Perillyl alcohol given by intragastric gavage changed the weights of several organs in female rats when given at 400 mg/kg bw per day, but not at 120 mg/kg bw per day, in a 90-day study; changes in organ weights were not reported in male rats. Doses of 40, 120 and 400 mg/kg bw per day produced hyperexcitability and salivation, which the authors considered may have been due to its irritating properties (National Cancer Institute, 1996). A daily dose of 120 mg/kg bw was well tolerated by dogs in a 90-day study (National Cancer Institute, 1996). The daily intake of 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal) is 0.058 µg/kg bw in Europe and 0.001 µg/kg bw in the USA. The margin of safety between these intakes and 120 mg/kg bw per day is > 2000000. The compound also shares structural similarities with alpha-ionone and beta-ionone [FL-no: 07.007] and [FL-no: 07.008], which were evaluated by the

Committee at its fifty-first meeting (JECFA, 2000). The NOELs for these compounds were 10 mg/kg bw per day in a 90-day study in rats, providing a margin of safety of about 200000. Therefore, 2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde [FL-no: 05.104] (safranal) would not be a safety concern.

In conclusion, the JECFA evaluated all 18 substances as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 18 substances are summarised in Table 4: Summary of Safety Evaluation by the JECFA (JECFA, 2003).

5.2. Application of the Procedure to Ten Primary Saturated or Unsaturated Alicyclic Alcohol, Aldehyde and Esters by EFSA in FGE.12Rev3 (EFSA CEF Panel, 2012a)

Ten candidate substances were evaluated in FGE.12Rev3. All 10 substances were classified into structural class I, using the decision tree approach presented by Cramer et al. (Cramer et al., 1978).

It was anticipated that all 10 substances will be metabolised to innocuous products at the estimated levels of intake and accordingly proceed via the A-side of the Procedure. The estimated daily *per capita* intakes of the 10 substances range from 0.011 to 43 µg, which is below the threshold of concern of 1800 µg/person/day for structural class I.

The Panel concluded all substances in FGE.12Rev3 at step A3 as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The stepwise evaluations of the 10 substances are summarised in Table 5: Summary of Safety Evaluation Applying the Procedure (EFSA CEF Panel, 2012a).

5.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 18 substances in the group of alicyclic primary alcohols, aldehydes, acids and related esters.

The Panel noted that one substance [FL-no: 05.123] has a terminal double bond. Although theoretically, the double bond may be oxidised to give reactive epoxides, it is expected that for this substance, the metabolism via this pathway is negligible, since the terminal double bond is present in a molecule that has an aldehyde function at the end distal from the double bond. The aldehyde function is expected to be readily attacked by oxidation processes, ultimately yielding unsaturated carboxylic acids. Biochemical attack of these carboxylic acids via e.g. beta-oxidation or conjugation with glucuronic acid is expected to be much more efficient and rapid than microsomal oxidation.

CONCLUSION

In Flavouring Group Evaluation 73, Revision 1 (FGE.73Rev1), the EFSA considered 16 flavouring substances (EFSA CEF Panel, 2012a) from a group of 26 alicyclic primary alcohols, aldehydes, acids and related esters evaluated by the JECFA of at the 59th meeting in 2002 (JECFA, 2002a). The present revision of FGE.73, FGE.Rev2, includes the consideration of two additional substances, santalyl acetate [FL-no: 09.034] and santalyl phenylacetate [FL-no: 09.712]. These substances were considered with respect to genotoxicity in FGE.207 (EFSA CEF Panel, 2013a), and the Panel concluded that the data available ruled out the concern for genotoxicity and thus concluded that the substances can be evaluated through the Procedure.

Therefore, the present revision of FGE.73Rev2 considers 18 flavouring substances evaluated by the JECFA.

The Panel concluded that the 18 substances are structurally related to the group of 10 primary saturated or unsaturated alicyclic alcohol, aldehyde and esters evaluated by EFSA in the Flavouring Group Evaluation 12, Revision 3 (FGE.12Rev3).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 18 substances considered in this FGE.

For all 18 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 the evaluation.

In order to determine whether the conclusion for the 18 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity tests are available for all 18 JECFA evaluated substances.

Thus, for all 18 substances [FL-no: 02.114, 02.141, 05.098, 05.104, 05.112, 05.119, 05.123, 08.034, 08.060, 08.067, 09.028, 09.034, 09.289, 09.488, 09.534, 09.536, 09.615 and 09.712] the Panel agrees with the JECFA conclusion "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

SUMMARY OF GENOTOXICITY DATA

Table 2: Genotoxicity Data (*in vitro*) EFSA / FGE.209 (EFSA CEF Panel, 2011)

FL-no	Chemical Name	Test System *in vitro*	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
[05.104]	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde	Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA102	1.6, 8, 40, 200, 1000, 5000 µg/plate	Negative [4]	(Beevers, 2010)	Valid study. First experiment: Standard plate ± S9. Toxicity was observed in all strains with and without S9 at 5000 µg/plate and in TA1537 and TA102 with S9 at 1000 µg/plate.
			S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	125, 250, 500, 1000, 2000, 5000 µg/plate	Negative [4]	(Beevers, 2010)	Valid study. Second experiment: Standard plate without S9. Toxicity was observed at 2000 µg/plate and above.
			S. typhimurium TA98, TA100 and TA1535	62.5, 125, 250, 500, 1000, 2000, 5000 µg/plate	Negative [4]	(Beevers, 2010)	Valid study. Second experiment with S9 and preincubation: Toxicity was observed at 500 µg/plate and above.
			S. typhimurium TA1537 and TA102	62.5, 125, 250, 500, 1000, 2000 µg/plate	Negative [4]	(Beevers, 2010)	Valid study. Second experiment with S9 and preincubation: Toxicity was observed at 500 µg/plate and above.
			S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	15.625, 31.25, 62.5, 125, 250, 500 µg/plate	Negative [4]	(Beevers, 2010)	Valid study. Third experiment with S9 and preincubation: Toxicity was observed at 250 µg/plate and above.
		Micronucleus induction	Human peripheral blood lymphocytes	0, 40, 60, 90 µg/ml[1] 0, 80, 100, 120, 140 µg/ml[2] 0, 4, 8, 12 µg/ml[3]	Negative [5]	(Whitwell, 2010)	Valid study.

1) 3 hours treatment 21 hours recovery without S9.
2) 3 hours treatment 21 hours recovery with S9.
3) 24 hours treatment no recovery without S9.
4) The assays were performed according to OECD Guideline 471 and in compliance with GLP.
5) This assay is performed in accordance with OECD 487.

Table 3: Summary of Additionally Genotoxicity Data for [FL-no: 09.931] of Subgroup 1.1.2

Chemical Name [FL-no:]	Test System *in vitro*	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
2,6-Dimethyl-2,5,7-octatriene-1-ol acetate [09.931]	Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA102	5 - 1500 µg/plate [1,3]; 5 - 5000 µg/plate [2,3]	Negative [1,3]; Equivocal [2,3]	(King, 2000)	Reliable without restriction. GLP study in compliance with OECD Guideline 471. A small increase in TA102 revertant numbers was seen at 15 and 50 µg/plate in the presence of S9-mix, but not at higher concentrations.
		S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	5 - 1500 µg/plate [1,3]; 5 - 5000 µg/plate [2,3]	Negative [1,3]; Negative [2,3]		The small increase in TA102 revertant numbers seen in the first experiment at 15 and 50 µg/plate in the presence of S9-mix was not reproduced in the second experiment.
		S. typhimurium TA102	5 - 1500 µg/plate [2,3]	Negative		The small increase in TA102 revertant numbers seen in the first experiment at 15 and 50 µg/plate in the presence of S9-mix was not reproduced in the third experiment.
	Micronucleus Assay	Human peripheral blood lymphocytes (Male Donors)	70 - 120 µg/ml [1,4]; 120-225 µg/mL [2,4]; 20 - 60 µg/mL [1,5]; 119.2 - 290 µg/mL [2,4]	Weak positive +S9; Re-test within normal values	(Whitwell, 2012)	Reliable without restriction. GLP study in compliance with OECD Guideline 487. Weak evidence of inducing micronuclei in the presence of S9-mix in a first experiment (increases only in one culture). A re-test under the same conditions and using a higher top concentration resulted in MNBN frequencies within the historical negative control range at 95th percentile, but were statistically significant due to low vehicle control values.

[1] Without S9-mix metabolic activation.
[2] With S9-mix metabolic activation.
[3] Plate incorporation method.
[4] 3 hour incubation with 21-hour recovery period.
[5] 24 hour incubation with no recovery period.

SUMMARY OF SAFETY EVALUATIONS

Table 4: Summary of Safety Evaluation by the JECFA (JECFA, 2003)

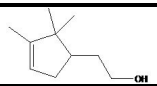
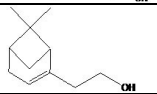
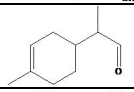
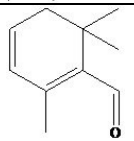
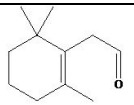
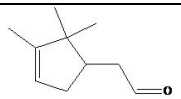
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI [1] US MSDI (µg/*capita*/day)	Class [2] Evaluation procedure path [3]	Outcome on the named compound [4] or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.114 970	2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol		0.012 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
02.141 986	2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol		33 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
05.098 971	p-Menth-1-en-9-al		0.12 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
05.104 977	2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde		3.5 0.07	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Evaluated in FGE.209. Genotoxicity concern could be ruled out (EFSA, 2011). No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
05.112 978	2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde		0.24 2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is "92 %". Secondary components ß-cyclocitral (2-3 %), ß-ionone (0.5-1 %), methyl ß-homocyclogeranate (2-4 %), ethyl ß-homocyclogeranate (0.6-1 %) (EFFA, 2010a). No safety concern at the estimated level of intake based on the MSDI approach.
05.119 967	2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde		5.0 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	CASrn in Register refers to (R)-isomer. Register name to be changed to (1R) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde. No safety concern at the estimated level of intake based on

Table 4: Summary of Safety Evaluation by the JECFA (JECFA, 2003)

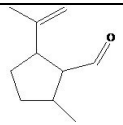
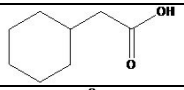
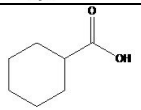
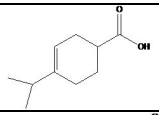
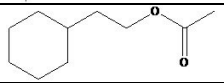
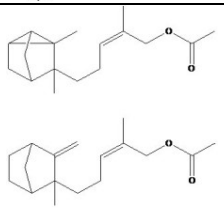
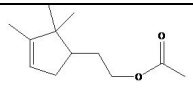
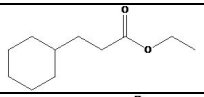
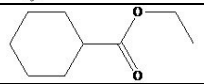
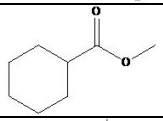
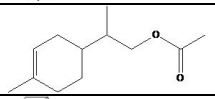
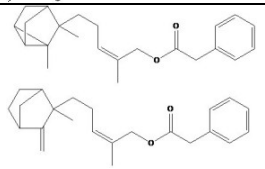
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI [1] US MSDI (μg/*capita*/day)	Class [2] Evaluation procedure path [3]	Outcome on the named compound [4] or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
							the MSDI approach.
05.123 968	5-Isopropenyl-2-methylcyclopentanecarboxaldehyde		0.012 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	CASrn in Register refers to (1R,2R,5S)-isomer. Register name to be changed to (1R,2R,5S) 5-Isopropenyl-2-methylcyclopentanecarboxaldehyde. No safety concern at the estimated level of intake based on the MSDI approach.
08.034 965	Cyclohexylacetic acid		0.12 0.4	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
08.060 961	Cyclohexanecarboxylic acid		0.061 4	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
08.067 976	1,2,5,6-Tetrahydrocuminic acid		0.012 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.028 964	2-Cyclohexylethyl acetate		0.97 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.034 985	Santalyl acetate		0.1 0.01	Class I A3: Intake below threshold	4)	Evaluated in FGE.207. No safety concern at the estimated level of intake based on the MSDI approach.	CASrn in Register refers to incompletely defined substance According to JECFA: Min. assay value is ”95 %” and secondary components ”60-65 % α-, 30-35% β-form”. No safety concern at the estimated level of intake based on the MSDI approach.
09.289 969	alpha-Campholene acetate		0.061 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to (-)-campholenyl acetate or (S)-campholenyl acetate. No safety concern at the

Table 4: Summary of Safety Evaluation by the JECFA (JECFA, 2003)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI [1] US MSDI (µg/*capita*/day)	Class [2] Evaluation procedure path [3]	Outcome on the named compound [4] or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
							estimated level of intake based on the MSDI approach.
09.488 966	Ethyl cyclohexanepropionate		0.12 0.1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.534 963	Ethyl cyclohexanecarboxylate		0.24 0.1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.536 962	Methyl cyclohexanecarboxylate		0.073 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.615 972	p-Menth-1-en-9-yl acetate		0.85 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
09.712 1022	Santalyl phenylacetate		0.029 1	Class I A3: Intake below threshold	4)	Evaluated in FGE.207. No safety concern at the estimated level of intake based on the MSDI approach.	CASrn in Register refers to incompletely defined substance According to JECFA 60-65 % is on α-form and 30-35 % on β-form. No safety concern at the estimated level of intake based on the MSDI approach.

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
ND) Not determined.

Table 5: Summary of Safety Evaluation by the EFSA (FGE.12Rev3) (EFSA CEF Panel, 2012a)

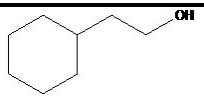
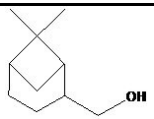
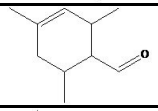
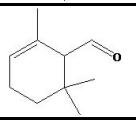
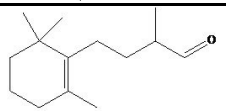
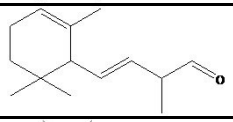
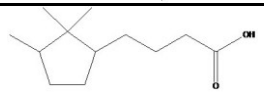
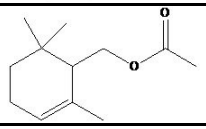
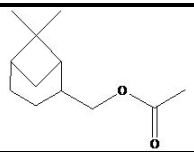
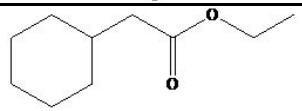
FL-no	EU Register name	Structural formula	MSDI [1] (µg/capita/ day)	Class [2] Evaluation procedure path [3]	Outcome on the named compound [4] or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.134	2-Cyclohexylethan-1-ol		0.011	Class I A3: Intake below threshold	4)	6)	
02.186	Myrtanol		0.37	Class I A3: Intake below threshold	4)	6)	
05.157	Isocyclocitral		0.011	Class I A3: Intake below threshold	4)	6)	
05.182	2,6,6-Trimethylcyclohex-2-ene-1-carboxaldehyde		0.061	Class I A3: Intake below threshold	4)	6)	
05.183	4-(2,6,6-Trimethylcyclohexenyl) -2-methylbutanal		0.012	Class I A3: Intake below threshold	4)	6)	
05.198	alpha-Methyl ional		0.011	Class I A3: Intake below threshold	4)	6)	
08.135	4-(2,2,3-Trimethylcyclopentyl)butanoic acid		43	Class I A3: Intake below threshold	4)	6)	
09.342	Cyclogeranyl acetate		0.24	Class I A3: Intake below threshold	4)	6)	

Table 5: Summary of Safety Evaluation by the EFSA (FGE.12Rev3) (EFSA CEF Panel, 2012a)

FL-no	EU Register name	Structural formula	MSDI [1] (µg/capita/day)	Class [2] Evaluation procedure path [3]	Outcome on the named compound [4] or 5]	Outcome on the material of commerce [6], 7), or 8)]	Evaluation remarks
09.670	Myrtanyl acetate		0.58	Class I A3: Intake below threshold	4)	6)	
09.829	Ethyl cyclohexyl acetate		0.61	Class I A3: Intake below threshold	4)	6)	

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/*capita*/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
6) No safety concern at the estimated level of intake of the material of commerce meeting the specification requirement (based on intake calculated by the MSDI approach).
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

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ABBREVIATIONS

bw	Body Weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EC	European Commission
EFFA	European Flavour and Fragrance Association
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practice
ID	Identity
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MNBN	Micronucleated Binucleate cells
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
No	Number
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
RI	Replication Index
SCF	Scientific Committee on Food
WHO	World Health Organization