Flavouring Group Evaluation 73, (FGE.73)¹

Consideration of alicyclic primary alcohols, aldehydes, acids and related esters evaluated by JECFA (59th meeting) structurally related to primary saturated or unsaturated alicyclic alcohol, aldehyde and esters evaluated by EFSA in FGE.12 (2005)

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

(EFSA-Q-2008-057)

Adopted on 6 March 2008

PANEL MEMBERS


SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) is asked to advise 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 Scientific Panel is 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.

The present consideration concerns 15 alicyclic primary alcohols, aldehydes, acids and related esters evaluated by the JECFA (59th meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluation of four primary saturated or unsaturated alicyclic alcohol, aldehyde, and esters evaluated in the Flavouring Group Evaluation 12 (FGE.12).

The Panel concluded that the 15 substances in the JECFA flavouring group are structurally related to the group of four primary saturated or unsaturated alicyclic alcohol, aldehyde, and esters evaluated by EFSA in FGE.12.

A further 11 substances were evaluated by the JECFA in this group, one substance [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) is not in the Register, and ten substances are alpha,beta-unsaturated aldehydes or precursors for such [FL-no: 02.060, 02.091, 05.104, 05.106, 05.117, 05.121, 09.034, 09.272, 09.278 and 09.302]. These substances will be evaluated together with other alpha,beta-unsaturated aldehydes and ketones.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 substances considered in this FGE.

For three substances [FL-no: 02.141, 09.488 and 09.534] the JECFA evaluation is only based on Maximised Survey-derived Daily Intakes (MSDI) values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances.

For all 15 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 15 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 eight of the 15 JECFA evaluated substances. For six substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615] information on the stereoisomeric composition is lacking and for one substance [FL-no: 05.112] further information on the composition is requested.

Thus, for nine substances [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534 and 09.615] the Panel has reservations (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 alicyclic primary alcohols, aldehydes, acids and related esters [FL-no: 05.119, 05.123, 08.034, 08.060, 09.028 and 09.536] the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

**KEYWORDS**

Alicyclic, primary, alcohols, aldehyde, esters, JECFA, 59th meeting, FGE.12.
BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2006/252/EC (EC, 2006). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000), which is broadly based on the opinion of the Scientific Committee on Food (SCF, 1999).

Commission Regulation (EC) 1565/2000 lays down that substances that are contained in the Register and will be classified in the future by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) so as to present no safety concern at current levels of intake will be considered by the European Food Safety Authority (EFSA), who may then decide that no further evaluation is necessary.

In the period 2000 – 2006, during its 55th, 57th, 59th, 61st, 63rd and 65th meetings, the JECFA evaluated about 900 substances, which are in the EU Register.

TERMS OF REFERENCE

EFSA is requested to consider 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 (EC, 2000). These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC (EC, 1999a) and its consecutive amendments.

ACKNOWLEDGEMENTS

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food wishes to thank Vibe Beltoft, Frederikke Bentzen, Jørn Gry, Pia Lund and Karin Nørby for their contribution to the draft Opinion.
ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 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, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the “JECFA Procedure”. The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (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 Flavouring 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, 2006c).

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
JECFA uses the threshold of concern of 1.5 microgram/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 microgram 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 microgram per day?”)” (JECFA, 1999b).

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 microgram 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 the 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. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has evaluated a group of 26 flavouring substances consisting of alicyclic primary alcohols, aldehydes, acids and related esters. One of the 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), and 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 alpha,beta-unsaturated aldehydes or may be metabolised to alpha,beta-unsaturated aldehydes and will be considered together with other alpha,beta-unsaturated aldehydes and ketones. This consideration will therefore only deal with 15 JECFA evaluated substances.
1.1.2. **EFSA Considerations**

The Panel concluded that the 15 substances in the JECFA flavouring group of alicyclic primary alcohols, aldehydes, acids and related esters are structurally related to the group of four primary saturated or unsaturated alicyclic alcohol, aldehyde and esters evaluated by EFSA in the Flavouring Group Evaluation 12 (FGE.12).

1.2. **Isomers**

1.2.1. **JECFA Status**

Eight 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, 09.289 and 09.615].

1.2.2. **EFSA Considerations**

Information is lacking about the stereoisomerism for six of these eight substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615].

1.3. **Specifications**

1.3.1. **JECFA Status**

The JECFA specifications are available for all 15 substances (JECFA, 2002d). See Table 1.

1.3.2. **EFSA Considerations**

The available specifications are considered adequate for eight substances. Information on stereoisomerism is lacking for six substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615] (See Section 1.2) and further information on the composition of [FL no: 05.112] is requested.

2. **Intake Estimations**

2.1. **JECFA Status**

For 12 substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining three substances [FL-no: 02.141, 09.488 and 09.534] production figures are only available for the USA.

2.2. **EFSA Considerations**

As production figures are only available for the USA for three substances, MSDI values for the EU cannot be calculated for these [FL-no: 02.141, 09.488 and 09.534].

3. **Genotoxicity Data**

3.1. **Genotoxicity Studies – Text Taken from JECFA (JECFA, 2003a)**

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.
3.2. Genotoxicity Studies – Text Taken from EFSA (EFSA, 2005g)

*In vitro/in vivo.*

There are no studies available on genotoxicity for the four candidates or for the 15 supporting substances. The genotoxic potential of this group of flavouring substances can therefore not be assessed.

**Conclusion on genotoxicity**

The genotoxic potential of this group of candidate substances cannot be assessed since information on the candidate and supporting substances is not available. Nevertheless, this does not preclude applying the Procedure for the flavouring substances (SCF, 1999).

3.3. EFSA Considerations

Although no genotoxicity data are available for the JECFA evaluated substances or for structurally related substances in this consideration, the Panel agreed with the JECFA that all the substances can be evaluated using the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 15 Alicyclic Primary Alcohols, Aldehydes, Acids and Related Esters by JECFA (JECFA, 2003a):

According to JECFA all 15 substances belong to structural class I using the decision tree approach presented by Cramer et al. (1978).

The JECFA concluded the 15 alicyclic primary alcohols, aldehydes, acids and related esters 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).

In conclusion, the JECFA evaluated all 15 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 15 substances are summarised in Table 3.1: Summary of Safety Evaluation of 15 alicyclic primary alcohols, aldehydes, acids and related esters (JECFA, 2003a).

4.2. Application of the Procedure to Four Primary Saturated or Unsaturated Alicyclic Alcohol, Aldehyde and Esters by EFSA in FGE.12 (EFSA, 2005g):

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

It was anticipated that all four 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 four substances range from 0.012 to 0.58 microgram, which is below the threshold of concern of 1800 microgram/person/day for structural class I.

The Panel concluded all four substances in FGE.12 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 four substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA, 2005g).
4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 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. The terminal double bond is present in a molecule that has 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.

However, for three substances [FL-no: 02.141, 09.488 and 09.534] no European production figures were available and consequently no European exposure estimates could be calculated. Accordingly, the safety in use could not be assessed using the Procedure for these three substances.

CONCLUSION

The Panel concluded that the 15 substances in the JECFA flavouring group of alicyclic primary alcohols, aldehydes, acids and related esters are structurally related to the group of four primary saturated or unsaturated alicyclic alcohol, aldehyde, and esters evaluated by EFSA in the Flavouring Group Evaluation 12 (FGE.12).

A further 11 substances were evaluated by the JECFA in this group, one substance [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) is not in the Register, and ten substances are alpha,beta-unsaturated aldehydes or precursors for such [FL-no: 02.060, 02.091, 05.104, 05.106, 05.117, 05.121, 09.034, 09.272, 09.278 and 09.302]. These substances will be evaluated together with other alpha,beta-unsaturated aldehydes and ketones.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 substances considered in this FGE.

For three substances [FL-no: 02.141, 09.488 and 09.534] the JECFA evaluation is only based on MSDI values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these three substances.

For all 15 substances evaluated through the Procedure use levels are needed to calculate the mTAMDI$s 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 15 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 eight of the 15 JECFA evaluated substances. For six substances [FL-no: 02.114, 02.141, 05.098, 08.067, 09.289 and 09.615] information on the stereoisomeric composition is lacking and for one substance [FL-no: 05.112] further information on the composition is requested.

Thus, for nine substances [FL-no: 02.114, 02.141, 05.098, 05.112, 08.067, 09.289, 09.488, 09.534 and 09.615] the Panel has reservations (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 alicyclic primary alcohols, aldehydes, acids and related esters [FL-no: 05.119, 05.123, 08.034, 08.060, 09.028 and 09.536] the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.
### Table 1: Specification Summary for JECFA Evaluated Substances in the Present Group

<table>
<thead>
<tr>
<th>FL-no</th>
<th>JECFA-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>FEMA no</th>
<th>CoE no</th>
<th>CAS no</th>
<th>Phys. form</th>
<th>Mol. formula</th>
<th>Mol. weight</th>
<th>Solubility 1)</th>
<th>Solubility in ethanol 2)</th>
<th>Boiling point, °C 3)</th>
<th>Melting point, °C</th>
<th>ID test</th>
<th>Assay minimum</th>
<th>Refrac. Index 4)</th>
<th>Spec. gravity 5)</th>
<th>EFSA comments</th>
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<tbody>
<tr>
<td>02.114</td>
<td>970</td>
<td>2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol</td>
<td><img src="image1" alt="Structure" /></td>
<td>3741</td>
<td>1901-38-8</td>
<td>10347</td>
<td>Liquid</td>
<td>C₁₀H₁₈O₂</td>
<td>154.25</td>
<td>Slightly soluble</td>
<td>Miscible</td>
<td>74 (0.8 hPa)</td>
<td>IR NMR 96%</td>
<td>NMR</td>
<td>96%</td>
<td>1.470-1.478</td>
<td>0.882-0.894 (20°)</td>
<td>CASrn in Register does not specify stereoisomers.</td>
</tr>
<tr>
<td>02.141</td>
<td>986</td>
<td>2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol</td>
<td><img src="image2" alt="Structure" /></td>
<td>3938</td>
<td>128-50-7</td>
<td>10338</td>
<td>Liquid</td>
<td>C₁₁H₁₈O₂</td>
<td>166.26</td>
<td>Insoluble</td>
<td>Miscible</td>
<td>230</td>
<td>IR NMR 95%</td>
<td>NMR</td>
<td>95%</td>
<td>1.490-1.500</td>
<td>0.965-0.973</td>
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<td>05.098</td>
<td>971</td>
<td>p-Menth-1-en-9-al</td>
<td><img src="image3" alt="Structure" /></td>
<td>3178</td>
<td>10347</td>
<td>29548-14-9</td>
<td>Liquid</td>
<td>C₁₀H₁₆O₁</td>
<td>152.23</td>
<td>Insoluble</td>
<td>Miscible</td>
<td>95 (13 hPa)</td>
<td>IR NMR 99%</td>
<td>NMR</td>
<td>99%</td>
<td>1.458-1.466</td>
<td>0.904-0.916 (20°)</td>
<td>CASrn in Register does not specify stereoisomers.</td>
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<tr>
<td>05.112</td>
<td>978</td>
<td>2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde</td>
<td><img src="image4" alt="Structure" /></td>
<td>3474</td>
<td>10338</td>
<td>472-66-2</td>
<td>Liquid</td>
<td>C₁₁H₁₈O₂</td>
<td>166.26</td>
<td>Insoluble</td>
<td>Miscible</td>
<td>58 (0.5 hPa)</td>
<td>IR NMR 92%</td>
<td>NMR</td>
<td>92%</td>
<td>1.480-1.487</td>
<td>0.873-0.885 (20°)</td>
<td>According to JECFA: Min. assay value is &quot;92%&quot; and secondary components &quot;Methyl beta-homocyclogeranate; beta-Cyclocitral; beta-Ionone; Ethyl beta-homocyclogeranate&quot;.</td>
</tr>
<tr>
<td>05.119</td>
<td>967</td>
<td>2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde</td>
<td><img src="image5" alt="Structure" /></td>
<td>3592</td>
<td>10325</td>
<td>4501-58-0</td>
<td>Liquid</td>
<td>C₁₀H₁₈O₂</td>
<td>152.23</td>
<td>Insoluble</td>
<td>Miscible</td>
<td>75 (137 hPa)</td>
<td>IR NMR 99%</td>
<td>NMR</td>
<td>99%</td>
<td>1.462-1.469</td>
<td>0.918-0.924</td>
<td>CASrn in Register refers to (R)-isomer. Register name to be changed to (1R) 2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde.</td>
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### Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Alicyclic Primary Alcohols, Aldehydes, Acids and Related Esters

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>FEMA no</th>
<th>CoE no</th>
<th>CAS no</th>
<th>Phys. form</th>
<th>Mol. formula</th>
<th>Mol. weight</th>
<th>Solubility 1)</th>
<th>Solubility in ethanol 2)</th>
<th>Boiling point, °C 3)</th>
<th>Melting point, °C</th>
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<th>Assay minimum</th>
<th>Refrac. Index 4)</th>
<th>Spec. gravity 5)</th>
<th>EFSA comments</th>
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<tr>
<td>05.123 968</td>
<td>5-Isopropenyl-2-methylcyclopentanecarboxaldehyde</td>
<td><img src="#" alt="Formula" /></td>
<td>3645</td>
<td>55253-28-6</td>
<td>Liquid C_{10}H_{16}O 152.23</td>
<td>Insoluble Miscible</td>
<td>80 (14 hPa) IR 95 %</td>
<td>1.501-1.508 0.940-0.952 (20°)</td>
<td>CASm in Register refers to (1R,2R,5S)-isomer. Register name to be changed to (1R,2R,5S) 5-Isopropenyl-2-methylcyclopentanecarboxaldehyde.</td>
<td></td>
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<tr>
<td>08.034 965</td>
<td>Cyclohexylacetic acid</td>
<td><img src="#" alt="Formula" /></td>
<td>2347</td>
<td>34</td>
<td>Solid C_{8}H_{14}O_{2} 142.20</td>
<td>Slightly soluble Miscible</td>
<td>242 28-33 NMR 98 %</td>
<td>1.459-1.467 1.001-1.009</td>
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<tr>
<td>08.060 961</td>
<td>Cyclohexanecarboxylic acid</td>
<td><img src="#" alt="Formula" /></td>
<td>3531 11911 98-89-5</td>
<td>Solid C_{7}H_{12}O_{2} 128.17</td>
<td>Slightly soluble Miscible</td>
<td>232-233 28-32 IR NMR 98 %</td>
<td>1.516-1.520 1.029-1.037</td>
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<td>08.067 976</td>
<td>1,2,5,6-tetrahydrocuminic acid 6)</td>
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<td>3731 71298-42-5</td>
<td>Solid C_{10}H_{16}O_{2} 168.24</td>
<td>Slightly soluble Soluble</td>
<td>n.a. 61 NMR 95 %</td>
<td>n.a. n.a. CASm in Register does not specify stereoisomers.</td>
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<td></td>
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</tr>
<tr>
<td>09.028 964</td>
<td>2-Cyclohexylethyl acetate</td>
<td><img src="#" alt="Formula" /></td>
<td>2348 218 21722-83-8</td>
<td>Liquid C_{10}H_{18}O_{2} 170.25</td>
<td>Insoluble Miscible</td>
<td>211 (996 hPa) NMR 98 %</td>
<td>1.442-1.450 0.945-0.948</td>
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</tr>
<tr>
<td>09.289 969</td>
<td>alpha-Campholene acetate 6)</td>
<td><img src="#" alt="Formula" /></td>
<td>3657 36789-59-0</td>
<td>Liquid C_{12}H_{20}O_{2} 196.29</td>
<td>Insoluble Miscible</td>
<td>96 (7 hPa) IR NMR 98 %</td>
<td>1.453-1.460 0.943-0.949 CASm in Register does not specify stereoisomers.</td>
<td></td>
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</tr>
<tr>
<td>09.488 966</td>
<td>Ethyl cyclohexanopropionate</td>
<td><img src="#" alt="Formula" /></td>
<td>2431 2095 10094-36-7</td>
<td>Liquid C_{11}H_{20}O_{2} 184.28</td>
<td>Insoluble Miscible</td>
<td>91 (10 hPa) NMR 98 %</td>
<td>1.444-1.452 0.926-0.932</td>
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</tr>
</tbody>
</table>
### Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Alicyclic Primary Alcohols, Aldehydes, Acids and Related Esters

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>FEMA no</th>
<th>CoE no</th>
<th>CAS no</th>
<th>Phys. form</th>
<th>Mol. formula</th>
<th>Mol. weight</th>
<th>Solubility 1) Solubility in ethanol 2)</th>
<th>Boiling point, °C 3)</th>
<th>Melting point, °C 4)</th>
<th>ID test Assay minimum</th>
<th>Refrac. Index 4) Spec. gravity 5)</th>
<th>EFSA comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.534 963</td>
<td>Ethyl cyclohexanecarboxylate</td>
<td><img src="image1" alt="Ethyl cyclohexanecarboxylate" /></td>
<td>3544</td>
<td>11916</td>
<td>3289-28-9</td>
<td>Liquid</td>
<td>C₉H₁₆O₂</td>
<td>156.22</td>
<td>Insoluble Miscible</td>
<td>82 (16 hPa)</td>
<td>IR NMR 99 %</td>
<td>1.474-1.454</td>
<td>0.966-0.978 (20°C)</td>
<td>CASrn in Register does not specify stereoisomers.</td>
</tr>
<tr>
<td>09.536 962</td>
<td>Methyl cyclohexanecarboxylate</td>
<td><img src="image2" alt="Methyl cyclohexanecarboxylate" /></td>
<td>3568</td>
<td>11920</td>
<td>4630-82-4</td>
<td>Liquid</td>
<td>C₈H₁₄O₂</td>
<td>142.19</td>
<td>Insoluble Miscible</td>
<td>183</td>
<td>IR NMR 98 %</td>
<td>1.439-1.447</td>
<td>0.990-0.999</td>
<td></td>
</tr>
<tr>
<td>09.615 972</td>
<td>p-Menth-1-en-9-yl acetate 6)</td>
<td><img src="image3" alt="p-Menth-1-en-9-yl acetate" /></td>
<td>3566</td>
<td>10748</td>
<td>28839-13-6</td>
<td>Liquid</td>
<td>C₁₂H₂₀O₂</td>
<td>196.28</td>
<td>Insoluble Miscible</td>
<td>228-232</td>
<td>NMR 97 %</td>
<td>1.441-1.448</td>
<td>0.931-0.937</td>
<td></td>
</tr>
</tbody>
</table>

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.
6) Stereoisomeric composition not specified.

n.a. not applicable.
**TABLE 2: GENOTOXICITY DATA**

**Table 2.1: Genotoxicity Data (in vitro/in vivo) JECFA**

No data available for the substances.

**Table 2.2: Genotoxicity (in vitro) EFSA/FGE.12**

No *in vitro* genotoxicity data available for the substances in the FGE.12.

**Table 2.3: Genotoxicity (in vivo) EFSA/FGE.12**

No *in vivo* genotoxicity data available for the substances in the FGE.12.
### Table 3: Summary of Safety Evaluation Tables

#### Table 3.1: Summary of Safety Evaluation of Alicyclic Primary Alcohols, Aldehydes, Acids and Related Esters (JECFA, 2003a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>JECFA-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>EU MSDI 1) (μg/capita/day)</th>
<th>US MSDI (μg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3)</th>
<th>Outcome on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)</th>
<th>EFSA conclusion on the material of commerce</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.114</td>
<td>970</td>
<td>2-(2,2,3-Trimethylcyclopent-3-enyl)ethan-1-ol</td>
<td><img src="image1" alt="Structural formula" /></td>
<td>0.012 ND</td>
<td>ND</td>
<td>Class I A3: Intake below threshold</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>Stereoisomeric composition to be specified.</td>
</tr>
<tr>
<td>02.141</td>
<td>986</td>
<td>2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethan-1-ol</td>
<td><img src="image2" alt="Structural formula" /></td>
<td>ND 0.01</td>
<td>Class I A3: Intake below threshold</td>
<td>4) MSDI based on USA anticipated production figure.</td>
<td>Stereoisomeric composition to be specified. MSDI based on USA anticipated production figure.</td>
<td></td>
</tr>
<tr>
<td>05.098</td>
<td>971</td>
<td>p-Menth-1-en-9-al</td>
<td><img src="image3" alt="Structural formula" /></td>
<td>0.12 ND</td>
<td>ND</td>
<td>Class I A3: Intake below threshold</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>Stereoisomeric composition to be specified.</td>
</tr>
<tr>
<td>05.112</td>
<td>978</td>
<td>2,6,6-Trimethylcyclohex-1-en-1-acetaldehyde</td>
<td><img src="image4" alt="Structural formula" /></td>
<td>0.24 2</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>According to JECFA: Min. assay value is &quot;92%&quot; and secondary components &quot;Methyl beta-homocyclogeranate; beta-Cyclocitral; beta-Ionone; Ethyl beta-homocyclogeranate&quot; Composition of mixture to be specified.</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.1: Summary of Safety Evaluation of 15 JECFA evaluated Substances (JECFA, 2003a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>EU MSDI 1) US MSDI (μg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3)</th>
<th>Outcome on the named compound [4) or 5)]</th>
<th>EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)</th>
<th>EFSA conclusion on the material of commerce</th>
</tr>
</thead>
<tbody>
<tr>
<td>05.119</td>
<td>2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde</td>
<td><img src="image1" alt="Structural formula" /></td>
<td>5.0 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>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 as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>05.123</td>
<td>5-Isopropenyl-2-methylcyclopentanecarboxaldehyde</td>
<td><img src="image2" alt="Structural formula" /></td>
<td>0.012 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>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 as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>08.034</td>
<td>Cyclohexylacetic acid</td>
<td><img src="image3" alt="Structural formula" /></td>
<td>0.12 0.4</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>08.060</td>
<td>Cyclohexanecarboxylic acid</td>
<td><img src="image4" alt="Structural formula" /></td>
<td>0.061 4</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>08.067</td>
<td>1,2,5,6-Tetrahydrocuminic acid</td>
<td><img src="image5" alt="Structural formula" /></td>
<td>0.012 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>Stereoisomeric composition to be specified.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3.1: Summary of Safety Evaluation of 15 JECFA evaluated Substances (JECFA, 2003a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>EU MSDI 1) US MSDI (µg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3)</th>
<th>Outcome on the named compound [4) or 5)]</th>
<th>EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)</th>
<th>EFSA conclusion on the material of commerce</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.028</td>
<td>2-Cyclohexylethyl acetate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.97 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>09.289</td>
<td>alpha-Campholene acetate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.061 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>Stereoisomeric composition to be specified.</td>
</tr>
<tr>
<td>09.488</td>
<td>Ethyl cyclohexanepropionate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ND 0.1</td>
<td>Class I A3: Intake below threshold</td>
<td>4) MSDI based on USA production figure.</td>
<td>MSDI based on USA production figure.</td>
<td></td>
</tr>
<tr>
<td>09.534</td>
<td>Ethyl cyclohexanecarboxylate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ND 0.1</td>
<td>Class I A3: Intake below threshold</td>
<td>4) MSDI based on USA anticipated production figure.</td>
<td>MSDI based on USA anticipated production figure.</td>
<td></td>
</tr>
<tr>
<td>09.536</td>
<td>Methyl cyclohexanecarboxylate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.073 0.01</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>09.615</td>
<td>p-Menth-1-en-9-yl acetate</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.85 ND</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>Stereoisomeric composition to be specified.</td>
</tr>
</tbody>
</table>

---

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, Class II = 540, 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 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.12)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>MSDI 1) (µg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3)</th>
<th>Outcome on the named compound [4) or 5])</th>
<th>Outcome on the material of commerce [6), 7), or 8])</th>
<th>Evaluation remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.186</td>
<td>Myrtanol</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.37</td>
<td>Class I A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>05.183</td>
<td>4-(2,6,6-Trimethylcyclohexenyl)-2-methylbutanal</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.012</td>
<td>Class I A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>09.342</td>
<td>Cyclogeranyl acetate</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.24</td>
<td>Class I A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>09.670</td>
<td>Myrtanyl acetate</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.58</td>
<td>Class I A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
</tbody>
</table>

---

1) 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, Class II = 540, 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 estimated level of intake of the material of commerce meeting the specification of Table 1 (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.

8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.
REFERENCES


