Flavouring Group Evaluation 75 (FGE.75)

Consideration of tetrahydrofuran derivatives and a furanone derivative evaluated by JECFA (63rd meeting) structurally related to tetrahydrofuran derivatives evaluated by EFSA in FGE.33 (2008)

Scientific Opinion of the Panel on Food Additives,

Flavourings, Processing Aids and Materials in Contact with Food

(Question No EFSA-Q-2008-059)

Adopted on 1 April 2008


JECFA evaluation:
http://whqlibdoc.who.int/publications/2006/9241660546_eng.pdf

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 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 11 of 18 flavouring substances consisting of tetrahydrofuran derivatives and a furanone derivative evaluated by the JECFA (63rd meeting). The Panel concluded that the 11 substances evaluated by the JECFA were structurally related to six tetrahydrofuran derivatives evaluated by the European Food Safety Authority (EFSA) in Flavouring Group Evaluation 33 (FGE.33).

Seven other substances were also evaluated by the JECFA in this group, but two are not in the Register [2-hexyl-4-acetoxytetrahydrofuran (JECFA-no: 1440) and (+/-)-2-(5-methyl-5-vinyltetrahydrofuran-2-yl)propionaldehyde (JECFA-no: 1457)] and five are alpha,beta-unsaturated
ketones. These five substances will be evaluated together with other alpha,beta-unsaturated ketones and aldehydes.

The JECFA concluded all the 11 tetrahydrofuran derivatives at step A3. The Panel agrees with the application of the Procedure as performed by the JECFA for 10 of the 11 substances. For the remaining substance [FL-no: 13.097] the Panel did not find that it could be metabolised to innocuous products and should accordingly be evaluated via the B-side of the Procedure scheme. A No Observed Adverse Effect Level (NOAEL) could not be identified for the substance or for structurally related substances and accordingly, additional data are required for this substance.

For one substance [FL-no: 13.060] the JECFA evaluation is based on a MSDI derived from an production figure from the USA. An EU production figure is needed in order to finalise the evaluation of this substance.

For all 11 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 11 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

The available specifications for all 11 substances are not fully complete as information on stereoisomerism is lacking for all the substances [FL-no: 13.007, 13.020, 13.042, 13.048, 13.049, 13.060, 13.090, 13.097, 13.140 and 13.166] (see Section 1.2). In addition, solubility data are lacking for three substances [FL-no: 13.042, 13.097 and 13.140].

Thus, for all 11 substances [FL-no: 13.007, 13.020, 13.042, 13.048, 13.049, 13.060, 13.090, 13.095, 13.097, 13.140, 13.166] the Panel has reservations (no European production volumes available, preventing them from being evaluated using the Procedure, and/or missing information on stereoisomerism and solubility, and/or additional toxicity data required).

**KEYWORDS**

Tetrahydrofuran, furanone derivatives, food safety, JECFA, 63rd meeting, FGE.33.
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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 flavouring 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, 2000a), 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, 2000a). These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217 EC (EC, 1999a) and its consecutive amendments.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), 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.

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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, the MSDI figures only 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, 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

The 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 \textit{in vitro}, will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential \textit{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 18 flavouring substances consisting of tetrahydrofuran and furanone derivatives. Two of the JECFA evaluated substances are not in the Register [2-hexyl-4-acetoxytetrahydrofuran (JECFA-no: 1440) and (±/-)-2-(5-methyl-5-vinyltetrahydrofuran-2-yl)propionaldehyde (JECFA-no: 1457)] and 5 substances [FL-no: 13.010, 13.084, 13.085, 13.089 and 13.099] are alpha, beta-unsaturated ketones and will be considered together with other alpha, beta-unsaturated aldehydes and ketones. This consideration will therefore only deal with 11 JECFA evaluated substances.

1.1.2. EFSA Considerations
The Panel concluded that the 11 substances in the JECFA evaluated group of tetrahydrofuran and furanone derivatives are structurally related to six tetrahydrofuran derivatives evaluated by EFSA in the Flavouring Group Evaluation 33 (FGE.33).

1.2. Isomers

1.2.1. JECFA Status
All 11 substances in the JECFA evaluated group of tetrahydrofuran derivatives and a furanone derivative have one or more chiral centres.

1.2.2. EFSA Considerations
1.3. Specifications

1.3.1. JECFA Status

JECFA specifications are available for all 11 substances (JECFA, 2006a) (see Table 1).

1.3.2. EFSA Considerations

The available specifications for all 11 substances are not fully complete as information on stereoisomerism is lacking [FL-no: 13.007, 13.020, 13.042, 13.048, 13.049, 13.060, 13.060, 13.095, 13.097, 13.140 and 13.166] (see Section 1.2). In addition, solubility data are lacking for three substances [FL-no: 13.042, 13.097 and 13.140].

2. Intake Estimations

2.1. JECFA Status

For 10 substances evaluated through the JECFA Procedure intake data are available for the EU (see Table 3.1). For one substance, tetrahydrofurfuryl cinnamate [FL-no: 13.060], production figures are only available for the USA (see Table 3.1).

2.2. EFSA Considerations

As a production figure is only available for the USA for tetrahydrofurfuryl cinnamate [FL-no: 13.060] an MSDI value for the EU cannot be calculated for this substance.

3. Genotoxicity Data

3.1. Genotoxicity Studies - Text Taken from the JECFA (JECFA, 2006a)

In vitro

No evidence was found for reverse mutation in tests in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA100, TA98 and TA102 with tetrahydrofurfurylalcohol (1–102100 µg/plate) [FL-no: 13.020], tetrahydrofurfuryl propionate (≤3600 µg/plate) [FL-no: 13.049] or 2-(3-phenylpropyl)tetrahydrofuran (≤3600 µg/plate) [FL-no: 13.007] (Wild et al., 1983; Aeschbacher et al., 1989).

Conclusion on genotoxicity

After consideration of the available data, the JECFA concluded that it is highly unlikely that tetrahydrofurans would pose any significant genotoxic risk to humans under the conditions of use as flavouring agents.

For a summary of in vitro/in vivo genotoxicity data considered by the JECFA, see Table 2.1.

3.2. Genotoxicity Studies - Text Taken from EFSA (FGE.33)

In vitro

Data from in vitro genotoxicity tests were available for one candidate substance and three supporting substances.
A good quality reverse mutation assay using the candidate substance 3,6-dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran [FL-no: 13.198] in *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA100 and TA98 gave negative results at concentrations of up to 316 microgram/plate (Stien, 2005a).

Three valid, but limited reverse mutation assays were available for three supporting substances [FL-no: 13.007, 13.020 and 13.049]. At concentrations of up to 3600 microgram/plate, two substances [FL-no: 13.007 and 13.049] gave negative results using *S. typhimurium* strains TA1535, TA1537, TA1538, TA100 and TA98 (Wild et al., 1983). At concentrations of up to 100 mg/plate, one supporting substance [FL-no: 13.020] produced negative results using *S. typhimurium* strains TA100, TA102 and TA98 (Aeschbacher et al., 1989).

A positive result was seen in a sister chromatid exchange (SCE) study on the supporting substance 1,8-cineole [FL-no: 03.001] (Galloway et al., 1987). This study was only positive without S9 activation and at levels of 1,8-cineole of 200 and 500 microgram/ml, which induced cell cycle delay and therefore were cytotoxic. There are several other genotoxicity tests on this substance, including another SCE study (although the concentrations of test substance were much lower in this study), that have given negative results. In the light of these results in several genotoxicity studies at gene and chromosomal level the positive result in the SCE assay by Galloway (Galloway et al., 1987) is considered not to be of relevance for the overall evaluation. It is therefore concluded that 1,8-cineole is not genotoxic.

Negative results on the structurally related 2-methyltetrahydrofuran [FL-no: 13.158] were seen in Ames test with *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1535 and TA1537 (CCRIS, 2002; NTP, 2003g).

**In vivo**

One *in vivo* genotoxicity study was available on the supporting substance tetrahydrofurfuryl propionate [FL-no: 13.049] with negative results. This micronucleus assay using doses of 316-949 mg/kg bw was not considered valid as only one time point was assessed, no PCE/NCE ratio was given and no positive control was used (Wild et al., 1983).

**Conclusion on genotoxicity**

Genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of the candidate substances using the Procedure.

For a summary of *in vitro/in vivo* genotoxicity data considered by EFSA, see Table 2.2 and 2.3.

### 3.3. EFSA Considerations

After consideration of the limited data available, the Panel concluded these data do not preclude evaluation of the 11 flavouring substances in the present group of JECFA evaluated tetrahydrofuran derivatives using the Procedure.
4. Application of the Procedure

4.1. Application of the Procedure to 11 Tetrahydrofuran Derivatives by the JECFA (JECFA, 2006a):

According to the JECFA five of the substances belong to structural class II and six to structural class III using the decision tree approach presented by Cramer et al. (1978).

The JECFA concluded all the 11 tetrahydrofuran 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 classes II and III (step A3).

In conclusion, the JECFA evaluated all 11 substances to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 11 tetrahydrofuran derivatives are summarised in Table 3.1: Summary of Safety Evaluation of 11 tetrahydrofuran derivatives (JECFA, 2006a).

4.2. Application of the Procedure to Six Tetrahydrofuran Derivatives Evaluated by EFSA in FGE.33:

Step 1

All candidate substances are classified according to the decision tree approach by Cramer et al. (1978) into structural class III.

Step 2

Four of the candidate substances [FL-no: 13.120, 13.167, 13.189 and 13.198] can be concluded to be metabolised to innocuous substances and will therefore proceed along the A-side of the Procedure.

Two of the substances cannot be anticipated to be metabolised to innocuous products and proceeds via the B-side of the Procedure [FL-no: 13.182 and 16.054].

Step A3

The MSDI of the four candidate substances [FL-no: 13.120, 13.167, 13.189 and 13.198] were estimated to be in the range 0.0012 to 3.0 microgram/capita/day, which are below the threshold of concern for structural class III of 90 microgram/person/day. Therefore, it can be concluded that these substances would not be expected to be of safety concern.

Step B3

The MSDI of the two candidate substances [FL-no: 13.182 and 16.054] proceeding via the B-side were estimated to be 0.011 and 0.65 microgram/capita/day, respectively, which are below the threshold of concern for structural class III of 90 microgram/person/day. Therefore, these substances can proceed to step B4 of the Procedure.

Step B4

For the two candidate substances [FL-no: 13.182 and 16.054] a NOAEL could not be provided for the substances or for structurally related substances and accordingly additional data are required for these substances.
Accordingly, four substances [FL-no: 13.120, 13.167, 13.189 and 13.198] do not pose a safety concern based on the MSDI approach, whereas for two substances [FL-no: 13.182 and 16.054] additional data are required.

The stepwise evaluation of the six substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.33).

4.3. **EFSA Considerations**

The JECFA concluded all the 11 tetrahydrofuran derivatives at step A3. The Panel agrees with the application of the Procedure as performed by the JECFA for 10 of the 11 substances. For the remaining substance [FL-no: 13.097] the Panel did not find that the substance could be metabolised to innocuous products and should accordingly be evaluated via the B-side of the Procedure scheme. A NOAEL could not be identified for the substance or for structurally related substances and accordingly, additional data are required for this substance.

For one substance [FL-no: 13.060] no European production figures were available and consequently no European exposure estimate could be calculated. Accordingly, the safety in use in Europe could not be assessed using the Procedure for this substance.

5. **Conclusion**

The Panel has considered 11 substances in the JECFA flavouring group of tetrahydrofuran and furanone derivatives. The Panel concluded that the 11 substances evaluated by the JECFA were structurally related to the six tetrahydrofuran derivatives evaluated by EFSA in Flavouring Group Evaluation (FGE.33).

Seven other substances were also evaluated by the JECFA in this group, but two are not in the Register [2-hexyl-4-acetoxytetrahydrofuran (JECFA-no: 1440) and (+/-)-2-(5-methyl-5-vinyltetrahydrofuran-2-yl)propionaldehyde (JECFA-no: 1457)] and five are alpha,beta-unsaturated ketones. These five substances will be evaluated together with other alpha,beta-unsaturated ketones and aldehydes.

The JECFA concluded all the 11 tetrahydrofuran derivatives at step A3. The Panel agrees with the application of the Procedure as performed by the JECFA for 10 of the 11 substances. For the remaining substance [FL-no: 13.097] the Panel did not find that it could be metabolised to innocuous products and should accordingly be evaluated via the B-side of the Procedure scheme. A NOAEL could not be identified for the substance or for structurally related substances and accordingly, additional data are required for this substance.

For one substance [FL-no: 13.060] the JECFA evaluation is based on a MSDI derived from an production figure from the USA. An EU production figure is needed in order to finalise the evaluation of this substance.

For all 11 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 11 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:
The available specifications for all 11 substances are not fully complete as information on stereoisomerism is lacking for all the substances [FL-no: 13.007, 13.020, 13.042, 13.048, 13.049, 13.060, 13.090, 13.095, 13.097, 13.140 and 13.166] (See section 1.2). In addition to this solubility data are lacking for three substances [FL-no: 13.042, 13.097 and 13.140].

Thus, for all 11 substances [FL-no: 13.007, 13.020, 13.042, 13.048, 13.049, 13.060, 13.090, 13.095, 13.097, 13.140, 13.166] the Panel has reservations (no European production volumes available, preventing them from being evaluated using the Procedure and/or, missing information on stereoisomerism and solubility, and/or additional toxicity data required).
**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 4)</th>
<th>ID test Assay minimum</th>
<th>Refrac. Index 4)</th>
<th>Spec. gravity 5)</th>
<th>EFSA comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.007</td>
<td>1441</td>
<td>2-(3-Phenylpropyl)tetrahydrofuran 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>2898</td>
<td>489</td>
<td>5208-40-0</td>
<td>Liquid</td>
<td>C13H18O</td>
<td>190.28</td>
<td>Very slightly soluble</td>
<td>Soluble</td>
<td>105-107 (1 hPa)</td>
<td>NMR 98 %</td>
<td>1.511-1.516</td>
<td>0.975-0.983</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.020</td>
<td>1443</td>
<td>Tetrahydrofurfuryl alcohol 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3056</td>
<td>2029</td>
<td>97-99-4</td>
<td>Liquid</td>
<td>C6H10O</td>
<td>102.15</td>
<td>Soluble</td>
<td>Soluble</td>
<td>178-179</td>
<td>NMR 100 %</td>
<td>1.449-1.455</td>
<td>1.050-1.052</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.042</td>
<td>1448</td>
<td>4,5-Dihydro-2-methylfuran-3(2H)-one 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3373</td>
<td>2338</td>
<td>3188-00-9</td>
<td>Liquid</td>
<td>C5H8O2</td>
<td>100.12</td>
<td>Soluble</td>
<td>Soluble</td>
<td>139</td>
<td>NMR 97 %</td>
<td>1.534-1.537</td>
<td>1.180-1.185</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.048</td>
<td>1444</td>
<td>Tetrahydrofurfuryl butyrate 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3057</td>
<td>11841</td>
<td>2217-33-6</td>
<td>Liquid</td>
<td>C6H10O3</td>
<td>172.23</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>227</td>
<td>NMR 97 %</td>
<td>1.446-1.452</td>
<td>1.007-1.013</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.049</td>
<td>1445</td>
<td>Tetrahydrofurfuryl propionate 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3058</td>
<td>11843</td>
<td>637-65-0</td>
<td>Liquid</td>
<td>C6H10O3</td>
<td>158.20</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>207</td>
<td>NMR 97 %</td>
<td>1.435-1.441</td>
<td>1.037-1.043</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.060</td>
<td>1447</td>
<td>Tetrahydrofurfuryl cinnamate 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3320</td>
<td>11821</td>
<td>65505-25-1</td>
<td>Liquid</td>
<td>C13H16O3</td>
<td>232.28</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>&gt;300</td>
<td>NMR 95 %</td>
<td>1.593-1.600</td>
<td>1.107-1.113</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.090</td>
<td>1452</td>
<td>2,2-Dimethyl-5-(1-methylprop-1-enyl)tetrahydrofuran 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3665</td>
<td>10937</td>
<td>7416-35-5</td>
<td>Liquid</td>
<td>C10H14O</td>
<td>154.24</td>
<td>Slightly soluble</td>
<td>Soluble</td>
<td>65 (13 hPa)</td>
<td>NMR 98 %</td>
<td>1.446-1.451</td>
<td>0.858-0.865</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.095</td>
<td>1453</td>
<td>2,5-Diethyltetrahydrofuran 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3743</td>
<td>11882</td>
<td>41239-48-9</td>
<td>Liquid</td>
<td>C8H14O</td>
<td>128.22</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>116</td>
<td>NMR 97 %</td>
<td>1.403-1.407</td>
<td>0.827-0.833</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>FL-no</td>
<td>JECFA-no</td>
<td>EU Register name</td>
<td>Structural formula</td>
<td>FEMA no</td>
<td>CoE no</td>
<td>CAS no</td>
<td>Phys. form</td>
<td>Mol. formula</td>
<td>Mol. weight</td>
<td>Solubility 1)</td>
<td>Solubility in ethanol 2)</td>
<td>Boiling point, °C 3)</td>
<td>Melting point, °C</td>
<td>ID test</td>
<td>Assay minimum</td>
<td>Refrac. Index 4)</td>
<td>Spec. gravity 5)</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>------------------</td>
<td>--------------------</td>
<td>---------</td>
<td>--------</td>
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<td>------------</td>
<td>----------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>13.097</td>
<td>1455</td>
<td>Anhydrolinalool oxide (5) 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3759</td>
<td>11944</td>
<td>13679-86-2</td>
<td>Liquid</td>
<td>C_{10}H_{16}O</td>
<td>152.24</td>
<td>Soluble</td>
<td>Soluble</td>
<td>58 (17 kPa)</td>
<td>NMR 97 %</td>
<td>1.449-1.454</td>
<td>0.874-0.878</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.140</td>
<td>1454</td>
<td>Linalool oxide (5-ring) 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3746</td>
<td>11876</td>
<td>1365-19-1</td>
<td>Liquid</td>
<td>C_{10}H_{18}O_{2}</td>
<td>170.25</td>
<td>Soluble</td>
<td>Soluble</td>
<td>188</td>
<td>NMR 95 %</td>
<td>1.451-1.456</td>
<td>0.932-0.942</td>
<td>CASrn in Register does not specify stereoisomers.</td>
<td></td>
</tr>
<tr>
<td>13.166</td>
<td>1442</td>
<td>Tetrahydrofurfuryl acetate 6)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>3055</td>
<td>2069</td>
<td>637-64-9</td>
<td>Liquid</td>
<td>C_{7}H_{12}O_{3}</td>
<td>144.20</td>
<td>Soluble</td>
<td>Soluble</td>
<td>194-195(979hPa)</td>
<td>NMR 97 %</td>
<td>1.435-1.440</td>
<td>1.058-1.064</td>
<td>CASrn in Register does not specify stereoisomers.</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 kPa, 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.
# Table 2: Genotoxicity Data

Table 2.1: Genotoxicity Data (*in vitro*/*in vivo*) for 11 Tetrahydrofuran Derivatives (JECFA, 2006a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>JECFA-no</th>
<th>EU Register name</th>
<th>JECFA name</th>
<th>Structural formula</th>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.007</td>
<td>1441</td>
<td>2-(3-Phenylpropyl)tetrahydrofuran</td>
<td></td>
<td></td>
<td>Reverse Mutation</td>
<td><em>S. typhimurium</em> TA1535, TA1537, TA1538, TA100 and TA98</td>
<td>≤3 600 µg/plate</td>
<td>Negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(Wild et al., 1983).</td>
</tr>
<tr>
<td>13.020</td>
<td>1443</td>
<td>Tetrahydrofurfuryl alcohol</td>
<td></td>
<td></td>
<td>Reverse Mutation</td>
<td><em>S. typhimurium</em> TA100 TA102 and TA98</td>
<td>1–102100 µg/plate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Negative&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(Aeschbacher et al., 1989).</td>
</tr>
<tr>
<td>13.049</td>
<td>1445</td>
<td>Tetrahydrofurfuryl propionate</td>
<td></td>
<td></td>
<td>Reverse Mutation</td>
<td><em>S. typhimurium</em> TA1535 TA1537, TA1538, TA100</td>
<td>≤3 600 µg/plate</td>
<td>Negative&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(Wild et al., 1983).</td>
</tr>
</tbody>
</table>

### In vivo

<table>
<thead>
<tr>
<th>FL-no</th>
<th>JECFA-no</th>
<th>EU Register name</th>
<th>JECFA name</th>
<th>Structural formula</th>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.049</td>
<td>1445</td>
<td>Tetrahydrofurfuryl propionate</td>
<td></td>
<td></td>
<td>Micronucleus formation</td>
<td>Male and female mouse bone marrow&lt;sup&gt;e&lt;/sup&gt;</td>
<td>316, 632, 949 mg/kg bw</td>
<td>Negative</td>
<td>(Wild et al., 1983).</td>
</tr>
</tbody>
</table>

<sup>a</sup> With or without metabolic activation provided by S9 (9000 x g supernatant from rodent liver).

<sup>b</sup> Calculated based on the relative molecular mass of tetrahydrofurfuryl alcohol = 102.1.

<sup>c</sup> Modified pre-incubation method.

<sup>d</sup> Without metabolic activation.

<sup>e</sup> Administered intraperitoneally.
Table 2.2: Genotoxicity \textit{(in vitro)} EFSA / FGE.33
Substances listed in brackets are JECFA evaluated substances

<table>
<thead>
<tr>
<th>Chemical Name [FL-no]</th>
<th>Test System</th>
<th>Test Object</th>
<th>Concentration</th>
<th>Result</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2-(3-Phenylpropyl)tetrahydrofuran [13.007])</td>
<td>Reverse mutation</td>
<td>S. typhimurium TA1535, TA1537, TA1538, TA100 and TA98</td>
<td>Up to 3600 µg/plate</td>
<td>Negative</td>
<td>(Wild et al., 1983)</td>
<td></td>
</tr>
<tr>
<td>(Tetrahydrofurfuryl alcohol [13.020])</td>
<td>Reverse mutation</td>
<td>S. typhimurium TA100 TA102 and TA98</td>
<td>1–102100 µg/plate</td>
<td>Negative(^1) (^2)</td>
<td>(Aeschbacher et al., 1989)</td>
<td></td>
</tr>
<tr>
<td>(Tetrahydrofurfuryl propionate [13.049])</td>
<td>Reverse mutation</td>
<td>S. typhimurium TA1535 TA1537, TA1538, TA100</td>
<td>Up to 3600 µg/plate</td>
<td>Negative</td>
<td>(Wild et al., 1983)</td>
<td></td>
</tr>
<tr>
<td>3,6-Dimethyl-2,3,3a,4,5,7a-hexahydro-benzofuran [13.198]</td>
<td>Reverse mutation</td>
<td>S. typhimurium TA1535, TA1537, TA102, TA100 and TA98</td>
<td>0, 3.16, 10, 31.6, 100, 316 microg/plate</td>
<td>Negative(^3) (^4)</td>
<td>(Stien, 2005a)</td>
<td></td>
</tr>
<tr>
<td>(1,8-Cineole [03.001])</td>
<td>Reverse mutation</td>
<td>S. typhimurium TA100, TA102, TA98 and TA97</td>
<td>250-2500 microg/plate</td>
<td>Negative(^1)</td>
<td>(Gomes-Carneiro et al., 1998)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA1535, TA1537, TA100 and TA98</td>
<td>3.3-3333 microg/plate</td>
<td>Negative(^1) (^2)</td>
<td>(Haworth et al., 1983)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary cells</td>
<td>50-500 microg/ml 600-800 microg/ml</td>
<td>Positive(^1) (^2) Negative(^4)</td>
<td>(Galloway et al., 1987)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary cells K-1</td>
<td>10, 33.3 and 100 micromol/l (1.5, 5.1 and 15.4 microg/ml)</td>
<td>Negative(^1)</td>
<td>(Sasaki et al., 1989)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chromosomal aberrations</td>
<td>Chinese hamster ovary cells</td>
<td>479-663 microg/ml 630-810 microg/ml</td>
<td>Negative(^1) (^2)</td>
<td>(Galloway et al., 1987)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA repair</td>
<td>Bacillus subtilis H17 (rec+) and M45 (rec-)</td>
<td>18 microg/disk</td>
<td>Negative</td>
<td>(Oda et al., 1979)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA repair</td>
<td>Bacillus subtilis H17 (rec+) and M45 (rec-)</td>
<td>&gt; 20 microg/disk (20000 microg/disk)</td>
<td>Negative</td>
<td>(Yoo, 1986)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) With or without metabolic activation
\(^2\) Modified pre-incubation method.
\(^3\) Without metabolic activation
\(^4\) With metabolic activation

Table 2.3: Genotoxicity \textit{(in vivo)} EFSA / FGE.33
Substances listed in brackets are JECFA evaluated substances

<table>
<thead>
<tr>
<th>Chemical Name [FL-no]</th>
<th>Test System</th>
<th>Test Object</th>
<th>Route</th>
<th>Dose</th>
<th>Result</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tetrahydrofurfuryl propionate [13.049])</td>
<td>Micronucleus formation</td>
<td>Male and female mouse bone marrow</td>
<td>Intraperitoneal</td>
<td>316, 632, 949 mg/kg bw</td>
<td>Negative</td>
<td>(Wild et al., 1983)</td>
<td>Study not considered valid. One time point only is used, no PCE/NCE ratio is provided, no positive control.</td>
</tr>
</tbody>
</table>
## TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 11 Tetrahydrofuran Derivatives (JECFA, 2006a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>EU MSDI 1) US MSDI (g/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>13.042 1448</td>
<td>4,5-Dihydro-2-methylfuran-3(2H)-one</td>
<td><img src="image" alt="Structural formula" /></td>
<td>20.5 9</td>
<td>Class II 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 does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
</tr>
<tr>
<td>13.090 1452</td>
<td>2,2-Dimethyl-5-(1-methylprop-1-enyl)tetrahydrofuran</td>
<td><img src="image" alt="Structural formula" /></td>
<td>9.4 0.04</td>
<td>Class II 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 does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
</tr>
<tr>
<td>13.095 1453</td>
<td>2,5-Diethyltetrahydrofuran</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.009 0.09</td>
<td>Class II 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 does not specify stereoisomers. Stereoisomeric composition and composition to be specified.</td>
<td></td>
</tr>
<tr>
<td>13.097 1455</td>
<td>Anhydroinalool oxide (5)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.9 0.03</td>
<td>Class II A3: Intake below threshold</td>
<td>4) Additional data required.</td>
<td>CASrn in Register does not specify stereoisomers. Stereoisomeric composition and composition to be specified.</td>
<td></td>
</tr>
<tr>
<td>13.140 1454</td>
<td>Linalool oxide (5-ring)</td>
<td><img src="image" alt="Structural formula" /></td>
<td>72.5 14</td>
<td>Class II 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 does not specify stereoisomers. Stereoisomeric composition and composition to be specified.</td>
<td></td>
</tr>
<tr>
<td>13.007 1441</td>
<td>2-(3-Phenylpropyl)tetrahydrofuran</td>
<td><img src="image" alt="Structural formula" /></td>
<td>0.0009 0.7</td>
<td>Class III 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 does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3.1: Summary of safety evaluation of 11 tetrahydrofuran derivatives (JECFA, 2006a)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>JECFA-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>13.020</td>
<td>1443</td>
<td>Tetrahydrofurfuryl alcohol</td>
<td><img src="image" alt="Structure" /></td>
<td>33 22</td>
<td>Class III A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach. CASrn in Register does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.048</td>
<td>1444</td>
<td>Tetrahydrofurfuryl butyrate</td>
<td><img src="image" alt="Structure" /></td>
<td>0.009 0.2</td>
<td>Class III A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach. CASrn in Register does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.049</td>
<td>1445</td>
<td>Tetrahydrofurfuryl propionate</td>
<td><img src="image" alt="Structure" /></td>
<td>0.051 5</td>
<td>Class III A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach. CASrn in Register does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.060</td>
<td>1447</td>
<td>Tetrahydrofurfuryl cinnamate</td>
<td><img src="image" alt="Structure" /></td>
<td>ND 0.01</td>
<td>Class III A3: Intake below threshold</td>
<td>4) MSDI based on USA production figure. CASrn in Register does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.166</td>
<td>1442</td>
<td>Tetrahydrofurfuryl acetate</td>
<td><img src="image" alt="Structure" /></td>
<td>0.6 8</td>
<td>Class III A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach. CASrn in Register does not specify stereoisomers. Stereoisomeric composition to be specified.</td>
<td></td>
<td></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.33)

<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>13.120</td>
<td>2,5-Dimethyltetrahydrofuran</td>
<td><img src="image" alt="Structure" /></td>
<td>0.0012</td>
<td>Class III A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>13.167</td>
<td>Tetrahydrofuryl phenylacetate</td>
<td><img src="image" alt="Structure" /></td>
<td>0.12</td>
<td>Class III A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>13.189</td>
<td>Linalool oxide(5) acetate</td>
<td><img src="image" alt="Structure" /></td>
<td>0.012</td>
<td>Class III A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>13.198</td>
<td>3,6-Dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran</td>
<td><img src="image" alt="Structure" /></td>
<td>3.0</td>
<td>Class III A3: Intake below threshold</td>
<td>4)</td>
<td>7)</td>
<td></td>
</tr>
<tr>
<td>13.182</td>
<td>2-Methyl-3-thioacetoxytetrahydrofuran</td>
<td><img src="image" alt="Structure" /></td>
<td>0.011</td>
<td>Class III A3: Intake below threshold, B4: No adequate NOAEL</td>
<td></td>
<td></td>
<td>Additional data required</td>
</tr>
<tr>
<td>16.054</td>
<td>6-Methylene-2,10,10-trimethyl-1-oxaspiro[4,5]dec-7-ene</td>
<td><img src="image" alt="Structure" /></td>
<td>0.65</td>
<td>Class III A3: Intake below threshold, B4: No adequate NOAEL</td>
<td></td>
<td></td>
<td>Additional data required</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.
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 and/or information on stereoisomerism.
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.
REFERENCES:


SCIENTIFIC PANEL MEMBERS

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