EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2016 Scientific Opinion on Flavouring Group Evaluation 75, Revision 1 (FGE.75Rev1): Consideration of tetrahydrofuran derivatives evaluated by JECFA (63rd meeting) structurally related to tetrahydrofuran derivatives evaluated by EFSA in FGE.33 (2008)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 75, Revision 1 (FGE.75Rev1): Consideration of tetrahydrofuran derivatives evaluated by JECFA (63rd meeting) structurally related to tetrahydrofuran derivatives evaluated by EFSA in FGE.33 (2008)[1]

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

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ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) of the EFSA 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 10 tetrahydrofuran derivatives and one furanone derivative evaluated by the JECFA at the 63rd meeting in 2004. This revision is made due to additional toxicity data have become available for anhydrolinalool oxide (5) [FL-no: 13.097]. 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 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) of 52 mg/kg body weight was derived from a 90-day study in rats and compared with an exposure estimate of 0.9 µg/ capita / per day for anhydrolinalool oxide a margin of safety of 3.5×10^6 was calculated. Accordingly, the Panel agrees with the JECFA conclusion 'No safety concern at estimated level of intake as flavouring substances' based on the maximised survey-derived daily intake (MSDI) approach. The specifications for the materials of commerce have also been considered and for all 11 substances, the information is adequate.

KEY WORDS

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[1] On request from the European Commission, Question No EFSA-Q-2013-00194, adopted on 2 December 2015.

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tetrahydrofuran derivatives, furanone derivatives, food safety, JECFA, 63rd meeting, FGE.33

SUMMARY

Following a request from the European Commission, the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was asked to deliver a scientific opinion to provide 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 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 Flavouring Group Evaluation 75 (FGE.75), the European Food Safety Authority (EFSA) 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). This revision of FGE.75 (FGE.75Rev1) is made because EFSA received additional toxicity data for the candidate substance anhydrolinalool oxide [FL-no: 13.097].

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 substances [FL-no: 13.010, 13.084, 13.085, 13.089 and 13.099] are α,β-unsaturated furanone and will be considered together with other α,β-unsaturated aldehydes and ketones in a separate FGE (EFSA CEF Panel, 2015). This consideration will, therefore, only deal with 11 JECFA-evaluated substances.

The JECFA reached a conclusion for all 11 substances at step A3 of their procedure. 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) of 52 mg/kg body weight (bw) was derived from a 90-day study in rats and compared with an exposure estimate of 0.9 µg/capita per day for anhydrolinalool oxide a margin of safety of 3.5×10^6 can be calculated. Accordingly, the Panel agrees with the JECFA conclusion 'No safety concern at estimated level of intake as flavouring substances' based on the maximised survey-derived daily intake (MSDI) approach.

For all 11 substances, the JECFA evaluation is based on MSDI values derived from production figures from the European Union (EU).

In order to determine whether the conclusion for the 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 are available for all 11 JECFA-evaluated substances.

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 and 13.166], the Panel agrees with the JECFA conclusion 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach

For all substances, evaluated through the Procedure, use levels are needed to calculate the modified theoretical added maximum daily intake (mTAMDIs) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of flavourings is regulated under Regulation (EC) No 1334/2008[4] of the European Parliament and the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of Article 9(a) of this Regulation, an evaluation and approval are required for flavouring substances.

The Union list of flavourings and source materials was established by Commission Implementing Regulation (EC) No 872/2012.[5] The list contains flavourings substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000.[6]

The European Food Safety Authority (EFSA) has considered the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluation of 11 tetrahydrofuran and furanone derivative in the flavouring group evaluation 75 (FGE.75). The opinion was adopted on 1 April 2008.

EFSA concluded in its opinion that for anhydrolinalool oxide (5) [FL-no 13.097] it did not find that it could be metabolised to innocuous products and should accordingly be evaluated via the B-side of the Procedure scheme. No observed adverse effect level (NOAEL) could not be identified for the substance itself or for structurally related substances, and accordingly, additional data are required for this substance.

EFSA has considered the JECFA evaluation of 15 flavouring substances consisting of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances in the flavouring group evaluation 90 (FGE.90). The opinion was adopted in 24 September 2009.[7]

EFSA concluded in its opinion that for the 6-hydroxydihydrotheaspirane [FL-no 13.076] and 6-acetoxydihydrotheaspirane [FL-no 13.087] no metabolism data are available, neither for the substances themselves nor for the related substances. Therefore, in contrast to the JECFA, EFSA cannot conclude that these substances are metabolised to innocuous products and they should accordingly be evaluated via the B-side of the Procedure scheme. NOAEL could not be identified for these two substances or for structurally related substances, and accordingly, additional data are required.

The requested information on one representative material, anhydrolinalool oxide (5) [FL-no 13.097] has now been submitted by the European Flavour Association. This information is intended to cover the re-evaluation of this substance and of the two substances 6-hydroxydihydrotheaspirane [FL-no 13.076] and 6-acetoxydihydrotheaspirane [FL-no 13.087].

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

[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.

[7] EFSA Journal 2010;8(2):1336

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requested EFSA to carry out a safety assessment on the following three flavouring substances: anhydrolinalool oxide (5) [FL-no 13.097], 6-hydroxydihydrotheaspirane [FL-no: 13.076] and 6-Acetoxydihydrotheaspirane [FL-no: 13.087] in accordance with Commission Regulation (EC) No 1565/2000.

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, 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, 2006b).

In the absence of more accurate information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a 'modified theoretical added maximum daily intake' (mTAMDI) approach based on the normal use levels reported by Industry.

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 µg/person per day (step B5) used by the JECFA

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

'The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 µg/person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting 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, 1999).

Consistent with the opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 µg/person per day.

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, as 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

At its 63rd meeting, the JECFA evaluated a group of 18 flavouring substances consisting of tetrahydrofuran and furanone derivatives. Two substances were not in the Register, and five are α,β-unsaturated ketones and these have to be considered together with other α,β-unsaturated substances. The remaining 11 flavouring substances have originally been considered by EFSA in FGE.75 (EFSA, 2008b).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.75	1 April 2008	http://www.efsa.europa.eu/en/efsajournal/pub/917.htm	11
FGE.75Rev1			11

The present revision of FGE.75, FGE.75Rev1 includes the consideration of additional toxicity data provided for one representative substance anhydrolinalool oxide (5) [FL-no: 13.097]. The data provided are a 90-day study (Bauter, 2013). The new information on [FL-no: 13.097] is described in Section 5.

As the publication of FGE.75, new information on the stereoisomeric composition has been provided for the 11 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], solubility data for three substances [FL-no: 13.042, 13.097 and 13.140] and poundage data on one substance [FL-no: 13.060] (EFFA, 2010).

2. Presentation of the substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA status

The JECFA has at the 63rd meeting evaluated a group of 18 flavouring substances consisting of tetrahydrofuran and furanone derivatives (JECFA, 2006a).

2.1.2. EFSA considerations

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 five substances [FL-no: 13.010, 13.084, 13.085, 13.089 and 13.099] are α,β-unsaturated ketones and will be considered together with other α,β-unsaturated aldehydes and ketones (EFSA, 2015). This consideration will therefore only deal with 11 JECFA-evaluated substances.

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).

2.2. Isomers

2.2.1. Status

All substances in the JECFA evaluated group of tetrahydrofuran derivatives have one or more chiral centres.

2.2.2. EFSA considerations

Adequate information on isomeric composition is available for all the substances in FGE.75Rev1.

2.3. Specifications

2.3.1. JECFA status

JECFA specifications are available for all substances (JECFA, 2005) (see Table 1).

2.3.2. EFSA considerations

The available specifications are considered adequate for all substances in FGE.75Rev1 (see Section 2.2 and Table 1).

3. Intake estimations

3.1. JECFA status

For all substances evaluated through the JECFA Procedure intake data are available for the EU (see Table 6).

3.2. EFSA considerations

Annual production volumes as provided by industry (EFFA, 2010; EFFA, 2012a) can be used to calculate MSDIs for EU. For all substances normal and maximum use levels are needed to calculate the mTAMDIs.

4. Genotoxicity data

4.1. Genotoxicity studies – Text taken[8] 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 tetrahydrofurfuryl alcohol (1–102,100 µg/plate) [FL-no: 13.020], tetrahydrofurfuryl propionate (≤3,600 µg/plate) [FL-no: 13.049] or 2-(3-phenylpropyl)tetrahydrofuran (≤3,600 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 JECFA, see Table 2.

4.2. Genotoxicity studies – Text taken[9] from FGE.33 (EFSA, 2008a)

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 µg/plate (Stien, 2005).

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 3,600 µg/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).

[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.

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 µg/ml, which induced cell cycle delay and therefore was 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, 2003).

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 body weight (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 3 and 4.

4.3. 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.

5. 14-day and 90-day toxicity studies on anhydrolinalool oxide (5) [FL-no: 13.097]

A 90-day study requested in the previous version of this FGE were submitted for [FL-no: 13.097] by the Industry (Bauter, 2013) along with a 14-day study (Bauter, 2012).

5.1. 14-day toxicity study on anhydrolinalool oxide (5) [FL-no: 13.097]

In a 14-day dietary study (Bauter, 2012), groups (3/sex per dietary intake level) of male and female Hsd:SD® rats were fed a diet designed to provide 0 (dietary control), 4,500, 9,000 and 18,000 ppm of anhydrolinalool oxide daily. The feed concentrations correspond to intakes of 362, 633 and 1,189 mg/kg bw/day for males and 386, 662 and 921 mg/kg bw/day for females according to the study report based on measured feed intake and initial concentration of the substance in the feed. The Panel noted that the actual exposure was lower because of loss of the candidate substance from the feed during the week of exposure (see 90-day study below). Clinical observations were recorded daily and body weights and food consumption observations were made on days 0, 7 and 14. No mortality was observed throughout the course of the study and the general condition of the rats was unremarkable with exception of one 18,000 ppm female which showed a moderate hunched posture, slight to moderate piloerection and slight to moderate emaciation during days 7–14. There were statistically significant reductions in body weight gain and food consumption and efficiency for both sexes of the 9,000 and 18,000 ppm groups. No gross pathology was related to the test substance in the diet. There were incidental findings in one female each in the 9,000 and 18,000 ppm groups, which had fluid-

filled uteri and oviducts. Two females in the mid-dose group had uterine cysts but this was not attributed to the test material.

5.2. 90-day toxicity study on anhydrolinalool oxide [FL-no: 13.097]

In an OECD TG 408 compliant 90-day study, four groups of rats (10/sex per group) of male and female CRL Sprague–Dawley CD®IGS rats were fed a diet designed to provide 0 (dietary control), 700 (low dose), 3,500 (mid dose) and 7,000 (high dose) mg of anhydrolinalool oxide per kg feed daily (Bauter, 2013). Dose selection was based on the findings in the 14-day study presented in above. These dietary levels correspond to the estimated daily intake of 0, 46, 233 and 453 mg/kg body weight for males and 0, 53, 257 and 506 mg/kg bw for females, respectively. The diets were replaced once a week. At the end of the first week, the concentrations of the test substance in the diet had decreased to 27, 22 and 23% of the targeted levels, respectively. Therefore, the Panel decided to use intake levels adjusted to the concentrations determined at the end of this first week, corresponding to daily intakes of 12.5, 52 and 105 mg/kg bw, respectively, for males and 14.5, 57 and 118 mg/kg bw, respectively, for females over the entire study duration.

Clinical observations of toxicity were performed on day 0 and weekly until sacrifice. Animals were weighed on day 0 at the start of the study and weekly thereafter. Food consumption and efficiency were measured and calculated weekly. Blood chemistry and haematology were performed on blood drawn via sublingual bleed during week 12 after overnight fast. Urine was collected during the 15 hours prior to the blood draw. At termination of the study, all survivors were sacrificed and subject to full necropsy. Tissues were weighed wet and analysed according to guidelines.

There were no mortalities, clinical or ophthalmological changes associated with anhydrolinalool oxide in the diet. There was a concentration-dependent, statistically significant reduction in mean body weight for both males and females in the dietary exposure groups. At the end of the study, body weights were 100 (low dose), 91 (mid dose) and 83% (high dose) for males and 101, 92 and 89% for females, as compared to the average body weights of the animals in the control group. For males and females, the mid and high intake levels were reported to show concentration-dependent decreases in food consumption. The relative food consumptions for days 0–91 were 97 (low dose), 90 (mid dose) and 82% (high dose) for males and 97, 86 and 82% for females. Based on food consumption and body weight gain data, the food efficiency (i.e. the amount of food needed for one gram of body weight increase) was calculated. For the males treated with the high dose the average food efficiencies were significantly decreased by approximately 12% for the entire duration of the study (i.e. total increase in body weight/total food consumption, as compared to the males in the control group). The food efficiencies in the other dose groups (males as well as females) were not affected. According to the study authors, the reduction in body weight is likely to be related to these reduced food consumptions.

Haematology parameters of note were reduced haematocrit levels in the high intake group males and increased platelet counts for the middle and high intake group of males. Neither of these differences occurred with a macroscopic or histopathology correlate and were considered incidental. All female test groups were comparable to concurrent controls with respect to haematology parameters. Males in the high dietary level group were reported to show increased blood urea nitrogen and creatinine levels which are most likely related to nephropathy discussed below. Males also were reported to show decreased serum triglyceride levels which was small in magnitude with no pathology correlate and considered incidental. Females were reported to show increased serum cholesterol levels in the high intake group but there was no associated pathology so this was considered incidental and not directly related to the test material in the diet. A statistically significant decrease in prothrombin time was reported for the high intake males but it was within historical control levels. At necropsy, gross findings in male and female test and control groups were reported to be sporadic, spontaneous and considered unrelated to anhydrolinalool oxide in the diet.

Pronounced toxicity was observed in male rat kidneys. Microscopic observations attributed to test substance administration included: Kidney nephropathy in 2/10 control males, 9/10 low-dose males,

10/10 mid-dose males and 10/10 high-dose males characterised microscopically by regeneration of proximal cortical tubules with thickened basement membranes, mononuclear cell infiltrates and/or tubular casts. The intensity of the nephropathy was minimal in 2/2 control males, 9/9 low-dose males, 5/10 mid-dose males and 4/10 high-dose male findings. The intensity of the nephropathy was slight in 5/10 mid-dose males and 6/10 high-dose males. Eosinophilic cytoplasmic droplets of minimal degree were noted in proximal tubules of 6/10 low-dose males, 6/10 mid-dose males and 6/10 high-dose males. The morphologic appearance of nephropathy along with the presence of cytoplasmic droplets in proximal tubules was, according to Bauter et al (2015), consistent with alpha-2-microglobulin nephropathy syndrome. This was further confirmed by staining with the Mallory–Heidenhain method: a dose-dependent increase in staining intensity of positive cytoplasmatic droplets in the proximal convoluted tubules was observed in male rats. In female rats, no such kidney toxicity was observed, and the Mallory–Heidenhain staining was negative in the microscopic slides from female kidneys at the highest dose.

Although no specific immunohistochemical staining of α2u globulin has been done to confirm the presence of this protein, the Panel considers the evidence sufficient to conclude that this kidney toxicity in male rats exclusively is not relevant for humans (Capen et al. 1999).

The Panel considers that the decreases in final body weights in the high dose females may be attributed to the reduced food consumption and to some also in the high dose males. However, the change in food efficiency, which was observed for the males in the high dose group, may indicate an adverse effect on the animal physiology. Since there is insufficient information to attribute this effect to the renal changes (see above) the reduced food efficiency cannot be disregarded with respect to relevance for humans. In addition, the reduced food efficiency in the high dose group males is not caused by reduced food efficiency in individuals with nephropathy. Therefore, in contrast with the study authors, the Panel considered that the NOAEL from this study is the mid dose administered to the males i.e. 52 mg/kg bw per day.

For a summary of subchronic and chronic toxicity data considered by EFSA, see Table 5.

6. Application of the procedure

6.1. Application of the procedure to 10 tetrahydrofuran derivatives and a furanone derivative 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. (Cramer et al., 1978).

The JECFA concluded all the 11 substances 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 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 substances are summarised in Table 6.

6.2. Application of the procedure to six tetrahydrofuran derivatives evaluated by EFSA in FGE.33: (EFSA, 2008a)

Step 1

All candidate substances are classified according to the decision tree approach by Cramer et al. (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 from 0.0012 to 3.0 µg/*capita* per day, which are below the threshold of concern for structural class III of 90 µg/person per 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 µg/*capita* per day, respectively, which are below the threshold of concern for structural class III of 90 µg/person per 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 7.

6.3. EFSA Considerations

The JECFA reached its conclusions for all 11 tetrahydrofuran derivatives and the furanone derivative at step A3. The Panel agrees with the application of the Procedure as performed by the JECFA for 10 of the 11 substances in accordance with the approach applied in FGE.33. 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 of 52 mg/kg bw was derived from a 90-day study in rats and compared with an exposure estimate of 0.9 µg/capita per day for anhydrolinalool oxide a margin of safety of 3.5×10^6 can be calculated. Accordingly, the Panel agrees with the JECFA conclusion 'No safety concern at estimated level of intake as flavouring substances' based on the MSDI approach.

7. Conclusion

The Panel has considered 10 tetrahydrofuran derivatives and a furanone derivative previously evaluated by JECFA . 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 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 substances [FL-no: 13.010, 13.084, 13.085, 13.089 and 13.099] are α,β-unsaturated furanones and will be considered together with other α,β-unsaturated aldehydes and ketones in a separate FGE (EFSA CEF Panel, 2015). This consideration will therefore only deal with 11 JECFA-evaluated substances.

The JECFA concluded all 11 substances 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 of 52 mg/kg bw was derived from a 90-day study in rats and compared with an exposure estimate of 0.9 µg/capita per day for anhydrolinalool oxide a margin of safety of 3.5×10^6 can be calculated. Accordingly, the Panel agrees with the JECFA conclusion 'No safety concern at estimated level of intake as flavouring substances' based on the MSDI approach..

For all 11 substances, the JECFA evaluation is based on MSDI values derived from production figures from the EU.

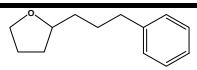
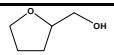
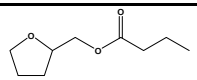
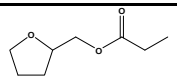
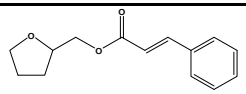
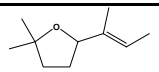
In order to determine whether the conclusion for the JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

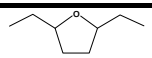
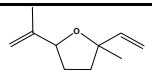
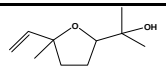
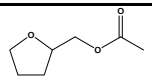
Adequate specifications including complete purity criteria and identity are available for all 20 JECFA-evaluated substances (see Section 1.2).

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 and 13.166], the Panel agrees with the JECFA conclusion 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach.

For all 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.

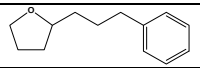
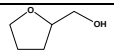
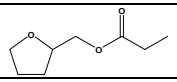
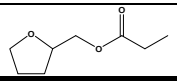
Table 1: Specification summary of the substances in the JECFA Flavouring Group of tetrahydrofuran derivatives (JECFA, 2006a)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [a] Solubility in ethanol [b]	Boiling point, °C [c] Melting point, °C ID test Assay minimum	Refrac. Index [d] Spec.gravity [e]	EFSA comments
13.007 1441	2-(3-Phenylpropyl)tetrahydrofuran		2898 489 3208-40-0	Liquid $C_{13}H_{18}O$ 190.28	Very slightly soluble Soluble	105–107 (1 hPa) NMR 98%	1.511–1.516 0.975–0.983	Racemate (EFFA, 2010).
13.020 1443	Tetrahydrofurfuryl alcohol		3056 2029 97-99-4	Liquid $C_5H_{10}O_2$ 102.15	Soluble Soluble	178–179 IR 99%	1.449–1.455 1.050–1.052	Racemate (EFFA, 2010).
13.042 1448	4,5-Dihydro-2-methylfuran-3(2*H*)-one		3373 2338 3188-00-9	Liquid $C_5H_8O_2$ 100.12	Insoluble Soluble	139 NMR 97%	1.534–1.537 1.180–1.185	Change the entry in the Union List to : 2-methyltetrahydrofuran-3-one Racemate (EFFA, 2010).
13.048 1444	Tetrahydrofurfuryl butyrate		3057 11841 2217-33-6	Liquid $C_9H_{16}O_3$ 172.23	Insoluble Soluble	227 NMR 97%	1.446–1.452 1.007–1.013	Racemate (EFFA, 2010).
13.049 1445	Tetrahydrofurfuryl propionate		3058 11843 637-65-0	Liquid $C_8H_{14}O_3$ 158.20	Insoluble Soluble	207 NMR 97%	1.435–1.441 1.037–1.043	Racemate (EFFA, 2010).
13.060 1447	Tetrahydrofurfuryl cinnamate		3320 11821 65505-25-1	Liquid $C_{14}H_{16}O_3$ 232.28	Insoluble Soluble	>300 NMR 95%	1.593–1.600 1.107–1.113	Racemate of mixture of (Z)- and (E)-isomer (EFFA, 2010). 70-95 % E-form and 5-30 % Z-form (EFFA, 2012b).
13.090 1452	2,2-Dimethyl-5-(1-methylprop-1-enyl)tetrahydrofuran		3665 10937 7416-35-5	Liquid $C_{10}H_{18}O$ 154.25	Slightly soluble Soluble	65 (13 hPa) IR NMR MS 98%	1.446–1.451 0.858–0.865	Racemate of mixture of (Z)- and (E)-isomer (EFFA, 2010). 50-80 % E-form and 20-50 % Z-form (EFFA, 2012b).

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility [a] Solubility in ethanol [b]	Boiling point, °C [c] Melting point, °C ID test Assay minimum	Refrac. Index [d] Spec.gravity [e]	EFSA comments
13.095 1453	2,5-Diethyltetrahydrofuran		3743 11882 41239-48-9	Liquid $C_8H_{16}O$ 128.22	Insoluble Soluble	116 NMR 97%	1.401–1.407 0.827–0.833	Mixture of stereoisomers (EFFA, 2010). cis (R,S) = (S,R) (50 %), trans (R,R) (25 %) and trans (S,S) (25 %) (EFFA, 2012b).
13.097 1455	Anhydrolinalool oxide (5)		3759 11944 13679-86-2	Liquid $C_{10}H_{16}O$ 152.24	Slightly soluble Soluble	58 (17 hPa) IR NMR 97%	1.449–1.454 0.874–0.878	Name in Union List to be changed to anhydrolinalool oxide (5-ring) Mixture of enantiomers (EFFA, 2010). 25% of each (EFFA, 2012b).
13.140 1454	Linalool oxide (5-ring)		3746 11876 1365-19-1	Liquid $C_{10}H_{18}O_2$ 170.25	Slightly soluble Soluble	188 NMR 95%	1.451–1.456 0.932–0.942	Mixture of enantiomers (EFFA, 2010). 25% of each (EFFA, 2012b).
13.166 1442	Tetrahydrofurfuryl acetate		3055 2069 637-64-9	Liquid $C_7H_{12}O_3$ 144.20	Soluble Soluble	194-195(979hPa) NMR 97%	1.435–1.440 1.058–1.064	Racemate (EFFA, 2010).

(a) Solubility in water, if not otherwise stated.
(b) Solubility in 95% ethanol, if not otherwise stated.
(c) At 1013.25 hPa, if not otherwise stated.
(d) At 20°C, if not otherwise stated.
(e) At 25°C, if not otherwise stated.

Table 2: Summary of genotoxicity data of tetrahydrofuran derivatives evaluated by the JECFA (JECFA, 2006a)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
13.007 1441	2-(3-Phenylpropyl)tetrahydrofuran		Reverse mutation	*S.* Typhimurium TA1535, TA1537, TA1538, TA100 and TA98	≤3,600 µg/plate	Negative[(a)]	(Wild et al., 1983).
13.020 1443	Tetrahydrofurfuryl alcohol		Reverse mutation	*S.* Typhimurium TA100 TA102 and TA98	1–102,100 µg/plate[(b)]	Negative[(a,c)]	(Aeschbacher et al., 1989)
13.049 1445	Tetrahydrofurfuryl propionate		Reverse mutation	*S.* Typhimurium TA1535 TA1537, TA1538, TA100	≤3,600 µg/plate	Negative[(d)]	(Wild et al., 1983)
In vivo							
13.049 1445	Tetrahydrofurfuryl propionate		Micronucleus formation	Male and female mouse bone marrow[(e)]	316, 632, 949 mg/kg bw	Negative	(Wild et al., 1983)

(a) With or without metabolic activation provided by S9 (9,000 × g supernatant from rodent liver).
(b) Calculated based on the relative molecular mass of tetrahydrofurfuryl alcohol = 102.1.
(c) Modified pre-incubation method.
(d) Without metabolic activation.
(e) Administered intraperitoneally.

Table 3: Genotoxicity (*in vitro*) EFSA/FGE.33 (EFSA, 2008a) (substances in brackets are JECFA-evaluated substances)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(2-(3-Phenylpropyl)tetrahydrofuran [13.007])	Reverse mutation	*S.* Typhimurium TA1535, TA1537, TA1538, TA100 and TA98	Up to 3,600 µg/plate	Negative[(a)]	(Wild et al., 1983)	
(Tetrahydrofurfuryl alcohol [13.020])	Reverse mutation	*S.* Typhimurium TA100, TA102 and TA98	1–102,100 µg/plate	Negative[(a,b)]	(Aeschbacher et al., 1989)	
(Tetrahydrofurfuryl propionate [13.049])	Reverse mutation	*S.* Typhimurium TA1535, TA1537, TA1538, TA100	Up to 3,600 µg/plate	Negative[(c)]	(Wild et al., 1983)	
3,6- Dimethyl-2,3,3a,4,5,7a-hexahydro-benzofuran [13.198]	Reverse mutation	*S.* Typhimurium TA1535, TA1537, TA102, TA100 and TA98	0, 3.16, 10, 31.6, 100, 316 µg /plate	Negative[(a)]	(Stien, 2005)	
(1,8-Cineole [03.001])	Reverse mutation	*S.* Typhimurium TA100, TA102, TA98 and TA97	250–2,500 µg/plate	Negative[(a)]	(Gomes-Carneiro et al., 1998)	
	Reverse mutation	*S.* Typhimurium TA1535, TA1537, TA100 and TA98	3.3–3,333 µg/plate	Negative[(a, b)]	(Haworth et al., 1983)	
	Sister chromatid exchange	Chinese hamster ovary cells	50–500 µg/ml 600–800 µg/ml	Positive[(c)] Negative[(d)]	(Galloway et al., 1987)	
	Sister chromatid exchange	Chinese hamster ovary cells K-1	10, 33.3 and 100 µmol/l (1.5, 5.1 and 15.4 µg/ml)	Negative[(c)]	(Sasaki et al., 1989)	
	Chromosomal aberrations	Chinese hamster ovary cells	479–663 µg/ml 630–810 µg/ml	Negative[(c)] Negative[(d)]	(Galloway et al., 1987)	
	DNA repair	*Bacillus subtilis* H17 (rec+) and M45 (rec-)	18 µg/disk	Negative	(Oda et al., 1979)	
	DNA repair	*Bacillus subtilis* H17 (rec+) and M45 (rec-)	< 20 µl/disk (20,000 µg/disk)	Negative	(Yoo, 1986)	

(a) With or without metabolic activation
(b) Modified pre-incubation method.
(c) Without metabolic activation
(d) With metabolic activation.

Table 4: Genotoxicity (*in vivo*) EFSA/FGE.33 (EFSA, 2008a) (substances in brackets are JECFA-evaluated substances)

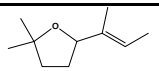
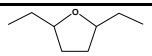
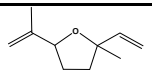
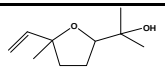
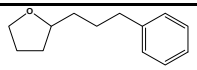
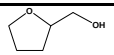
Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
(Tetrahydrofurfuryl propionate [13.049])	Micronucleus formation	Male and female mouse bone marrow	Intraperitoneal	316, 632, 949 mg/kg bw	Negative	(Wild et al., 1983)	Study not considered valid. One time point only is used, no PCE/NCE ratio is provided, no positive control.

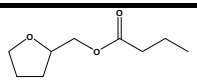
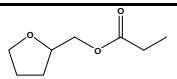
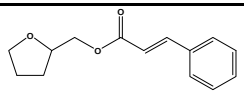
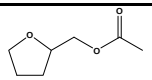
Table 5: Subchronic and chronic toxicity studies on [FL-no: 13.097]

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration (days)	NOAEL (mg/kg bw/day)	Reference	Comments
Anhydrolinalool oxide (5) [13.097]	Rat; M/F 6	Diet	0, 362.1, 633.4 and 1,189 mg/kg bw/day for males and 0, 385.5, 661.9 and 921.2 mg/kg bw/day for females	14	-	(Bauter, 2012)	
	Rat; M/F 20	Diet	0, 12.5, 52 and 105 mg/kg bw for males and 0, 14.5, 57 and 118 mg/kg bw for females	90	52	(Bauter, 2013)	OECD (408) compliant 90-day study. Dose levels have bben corrected for loss from the feed.

Summary of safety evaluations

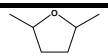
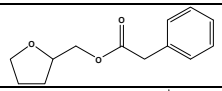
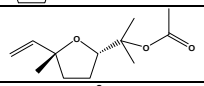
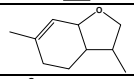
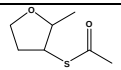
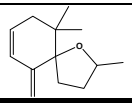
Table 6: Summary of safety evaluation of 11 tetrahydrofuran derivatives (JECFA, 2006a)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI (a) US MSDI (μg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
13.042 1448	4,5-Dihydro-2-methylfuran-3(2*H*)-one		20.5 9	Class II A3: Intake below threshold	(d)	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.
13.090 1452	2,2-Dimethyl-5-(1-methylprop-1-enyl)tetrahydrofuran		9.4 0.04	Class II A3: Intake below threshold	(d)	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.
13.095 1453	2,5-Diethyltetrahydrofuran		0.009 0.09	Class II A3: Intake below threshold	(d)	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.
13.097 1455	Anhydrolinalool oxide (5)		0.9 0.03	Class II A3: Intake below threshold	(d)	No safety concern at the estimated level of intake based on the MSDI approach (Step B4)	No safety concern at the estimated level of intake based on the MSDI approach.
13.140 1454	Linalool oxide (5-ring)		72.5 14	Class II A3: Intake below threshold	(d)	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.
13.007 1441	2-(3-Phenylpropyl)tetrahydrofuran		0.0009 0.7	Class III A3: Intake below threshold	(d)	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.
13.020 1443	Tetrahydrofurfuryl alcohol		33 22	Class III A3: Intake below threshold	(d)	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.

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI (a) US MSDI (µg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
13.048 1444	Tetrahydrofurfuryl butyrate		0.009 0.2	Class III A3: Intake below threshold	(d)	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.
13.049 1445	Tetrahydrofurfuryl propionate		0.051 5	Class III A3: Intake below threshold	(d)	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.
13.060 1447	Tetrahydrofurfuryl cinnamate		0.012 0.01	Class III A3: Intake below threshold	(d)	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.
13.166 1442	Tetrahydrofurfuryl acetate		0.6 8	Class III A3: Intake below threshold	(d)	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.

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

Table 7: Summary of safety evaluations applying the procedure (based on intakes calculated by the MSDI approach) (EFSA/FGE.33)

FL-no	EU Register name	Structural formula	MSDI (a) (µg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g), or (h)]	Evaluation remarks
13.120	2,5-Dimethyltetrahydrofuran		0.0012	Class III A3: Intake below threshold	(d)	(g)	
13.167	Tetrahydrofuryl phenylacetate		0.12	Class III A3: Intake below threshold	(d)	(g)	
13.189	Linalool oxide(5) acetate		0.012	Class III A3: Intake below threshold	(d)	(g)	
13.198	3,6-Dimethyl-2,3,3a,4,5,7a-hexahydro-benzofuran		3.0	Class III A3: Intake below threshold	(d)	(g)	
13.182	2-Methyl-3-thioacetoxytetrahydrofuran		0.011	Class III B3: Intake below threshold, B4: No adequate NOAEL	Additional data required	(g)	
16.054	6-Methylene-2,10,10-trimethyl-1-oxaspiro[4.5]dec-7-ene		0.65	Class III B3: Intake below threshold, B4: No adequate NOAEL	Additional data required	(g)	

(a) EU MSDI: Amount added to food as flavour in (kg/year) × 10E9 / (0.1 × population in Europe (= 375 × 10E6) × 0.6 × 365) = µg/capita per day
(b) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person per day
(c) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(d) No safety concern based on intake calculated by the MSDI approach of the named compound.
(e) Data must be available on the substance or closely related substances to perform a safety evaluation.
(f) 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).
(g) 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.
(h) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

DOCUMENTATION PROVIDED TO EFSA

1. Bauter MR, 2012. Anhydrolinalool oxide: palatability/toxicity study: a 14-day dietary study in rats. Product Safety Labs. Study no. 33068. February 8, 2012. Unpublished report submitted by EFFA to FLAVIS Secretariat.

2. Bauter MR, 2013. Anhydrolinalool oxide: a 90-day dietary study in rats. Product Safety Labs. Study no. 33452. January 14, 2013. Unpublished report submitted by EFFA to FLAVIS Secretariat.

3. Bauter MR, 2015. Anhydrolinalool oxide: a 90-day dietary study in rats. Product Safety Labs. Study no. 33452. January 14, 2013; amended on April 24, 2015. Unpublished report submitted by EFFA to FLAVIS Secretariat.

4. EFFA (European Flavour and Fragrance Association), 2010. EFFA Letters to EFSA for clarification of specifications and isomerism for which data were requested in published FGEs.

5. EFFA (European Flavour and Fragrance Association), 2012a. E-mail from EFFA to FLAVIS Secretariat, Danish Food Institute, Technical University of Denmark. Dated 26 January 2012. Tonnage data FGE.75.Rev1: [FL-no: 13.099]. FLAVIS/8.141.

6. EFFA (European Flavour and Fragrance Association), 2012b. E-mail from EFFA to EFSA/CEF Secretariat, dated 7 May 2012. Information on isomerism of five substances evaluated in FGE.75 [FL-no: 13.060, 13.090, 13.095, 13.097 and 13.140]. FLAVIS/8.151.

7. Stien J, 2005a. Mutagenicity study of dill-ether in the salmonella typhimurium reverse mutation assay (in vitro). Laboratory of pharmacology and toxicology kg (LPT). Report no. 18432/10/04. 24/08/05. Unpublished report submitted by EFFA to FLAVIS Secretariat.

REFERENCES

Aeschbacher HU, Wolleb U, Loliger J, Spadone JC and Liardon R, 1989. Contribution of coffee aroma constituents to the mutagenicity of coffee. Food and Chemical Toxicology 27(4), 227-232.

Capen CC, Dybing E, Rice JM and Wilbourn JD, 1999. Species differences in thyroid, kidney and urinary bladder carcinogensis. IARC Scientific Publications 147, 1-14.

CCRIS, 2002. CCRIS database. Salmonella study on 2-Methyltetrahydrofuran. [Online] http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+96-47-9

Cramer GM, Ford RA and Hall RL, 1978. Estimation of toxic hazard - a decision tree approach. Food and Cosmetics Toxicology 16(3), 255-276.

EFSA (European Food Safety Authority), 2008a. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with food on a request from the Commission related to Flavouring Group Evaluation 33: Six tetrahydrofuran derivatives from chemical groups 13, 14, 16 and 26 (Commission Regulation (EC) No 1565/2000 of 18 July 2000). The EFSA Journal 2008, 916. doi:10.2903/j.efsa.2008.916

EFSA (European Food Safety Authority), 2008b. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with food on a request from the Commission related to Flavouring Group Evaluation 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) (Commission Regulation (EC) No 1565/2000 of 18 July 2000). The EFSA Journal 2008, 917. doi:10.2903/j.efsa.2008.917

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2015. Scientific Opinion on Flavouring Group Evaluation 220 Revision 3 (FGE.220Rev3): Consideration of genotoxic potential for α,β-unsaturated 3(2H)-Furanones from subgroup 4.4 of FGE.19 by EFSA. EFSA Journal 2015;13(5):4117, 37 pp. doi:10.2903/j.efsa.2015.4117

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B and Zeiger E, 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environmental and Molecular Mutagenesis 10(Suppl. 10), 1–175.

Gomes-Carneiro MR, Felzenszwalb I and Paumgartten FJ, 1998. Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. Mutation Research 416, 129–136.

Haworth S, Lawlor T, Mortelmans K, Speck W and Zeiger E, 1983. Salmonella mutagenicity test results for 250 chemicals. Environmental Mutagenesis 5(Suppl. 1), 3–142.

JECFA (The Joint FAO/WHO Expert Committee on Food Additives), 1995. Evaluation of certain food additives and contaminants. Forty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives. 14-23 February 1995. WHO Technical Report Series, no. 859. Geneva.

JECFA (The Joint FAO/WHO Expert Committee on Food Additives), 1996. Toxicological evaluation of certain food additives. Forty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives and contaminants. WHO Food Additives Series: 35. IPCS, WHO, Geneva.

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

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

JECFA (The Joint FAO/WHO Expert Committee on Food Additives), 2005. Compendium of food additive specifications. Addendum 12. Joint FAO/WHO Expert Committee of Food Additives 63rd session. Rome, 8-17 June 2004. FAO Food and Nutrition paper 52 Add. 12.

JECFA, 2006a. Safety evaluation of certain food additives and contaminants. Sixty-third Meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 54. IPCS, WHO, Geneva.

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

National Toxicology Program (NTP), 2003g. Salmonella Study (2-Methyltetrahydrofuran) Study no A41442.

Oda Y, Hamono Y, Inoue K, Yamamoto H, Niihara T and Kunita N, 1979. [Mutagenicity of food flavors in bacteria]. Osaka Furitsu Koshu Eisei Kenkyusho kenkyu hokoku. Shokuhin eisei hen 9, 177–181. (In Japanese)

Sasaki YF, Imanishi H, Ohta T and Yasuhiko S, 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutation Research 226, 103–110.

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

Wild D, King MT, Gocke E and Eckhard K, 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, BASC and micronucleus tests. Food and Chemical Toxicology 21(6), 707–719.

Yoo YS, 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka City Medical Journal 34(3-4), 267–288.

ABBREVIATIONS

bw	body weight
CAS	Chemical Abstract Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
DNA	deoxyribonucleic acid
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 practise
ID	identity
IR	infrared spectroscopy
JECFA	the Joint FAO/WHO Expert Committee on Food Additives
MSDI	maximised survey-derived daily intake
mTAMDI	modified theoretical added maximum daily intake
NCE	normochromatic erythrocyte
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PCE	polychromatic erythrocyte
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
WHO	World Health Organization