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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 90, Revision 1 (FGE.90Rev1): consideration of six substances evaluated by JECFA (68th meeting) structurally related to aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in FGE.18Rev1 and FGE.75Rev1[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 of 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 six aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances evaluated by JECFA at the 68th meeting in 2007. This revision of FGE.90 is made because additional toxicity data have become available for a structurally related substance in FGE.75Rev1, anhydrolinalool oxide (5) [FL-no: 13.097]. The Panel agrees with the application of the Procedure as performed by the JECFA for four substances [FL-no: 02.018, 02.245, 02.250 and 02.251]. For two substances [FL-no: 13.076 and 13.087] it could not be concluded that they are metabolised to innocuous substances. Based on the exposure estimates (MSDI) and the no observed adverse effect level (NOAEL) from 90-day toxicity study with anhydrolinalool oxide (5), the Panel considered that the substances [FL-no: 13.076 and 13.087] were not of safety concern at the estimated levels of intake based on the maximised survey-derived daily intake (MSDI) approach. The specifications for the materials of commerce have also been considered. For substance [FL-no: 02.251] information on the stereoisomeric composition has not been specified, and for substance [FL-no: 13.087], the identity of the isomers needs to be specified. For three substances [FL-no: 02.018, 13.076 and 13.087] the modified theoretical added maximum daily intake (mTAMDI) is above the threshold of concern and therefore more reliable exposure data are required to perform a more refined exposure estimation and to judge whether a re-evaluation according to the Procedure is needed.

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[1] On request from the European Commission, Question Nos EFSA-Q-2013-00195 and EFSA-Q-2013-00196, adopted on 2 December 2015.

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KEY WORDS

food safety, tertiary alcohols, flavourings, JECFA 68th meeting, FGE.18Rev1

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 90 (FGE.90), the European Food Safety Authority (EFSA) considered six flavouring substances from a group of flavouring substances consisting of acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances evaluated by JECFA at the 68th meeting. The JECFA has evaluated a group of 15 flavouring substances consisting of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols, and structurally related substances. Two of the JECFA evaluated substances are not in the Register ((±)-ethyl 2-hydroxy-2-methylbutyrate, JECFA no: 1651 and (±)-ethyl 2-hydroxy-3-methylbutyrate, JECFA no: 1652). Seven tertiary alcohols [FL-no: 02.035, 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] have been considered in FGE.89. Therefore, this consideration only deals with six substances.

This revision of FGE.90 is made because EFSA received new toxicity data on anhydrolinalool oxide [FL-no: 13.097] from FGE.75 which support the evaluation of [FL-no: 13.076 and 13.087] in this FGE.

The Panel concluded that the six substances [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087] are structurally related to the aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in the Flavouring Group Evaluation 18, Revision 3 (FGE.18Rev3).

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for four of the six substances [FL-no: 02.018, 02.245, 02.250 and 02.251]. For the remaining two substances [FL-no: 13.076 and 13.087], no metabolism data are available, neither for the substances themselves nor for related substances. Therefore, in contrast to the JECFA, the Panel cannot conclude that these substances are metabolised to innocuous products and they should accordingly be evaluated *via* the B-side of the Procedure scheme. The present revision of FGE.90, FGE.90Rev1, includes the consideration of new available toxicity data made available since the publication of FGE.90. A no observed adverse effect level (NOAEL) of 52 mg/kg body weight (bw) was derived from a 90-day study in rats for the structurally related substance anhydrolinalool oxide. Compared with an exposure estimate of 0.12 µg */capita* per day for both [FL-no: 13.076 and 13.087], a margin of safety of 26×10^6 can be calculated.

Thus for four substances [FL-no: 02.018, 02.245, 02.250 and 13.076], the Panel agrees with the JECFA conclusion 'no safety concern at estimated level of intake as flavouring substances' based on the MSDI approach.

For the six substances, use levels have been provided by the Industry [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087]. The modified theoretical added maximum daily intake (mTAMDI) figures calculated for three of the six substances [FL-no: 02.018, 13.076 and 13.087] are above the threshold of concern for their structural classes. For these substances, more reliable exposure data are needed. On the basis of such data, the substances should be reconsidered using the Procedure.

Adequate specifications are available for four out of six materials of commerce. For substance [FL-no: 02.251] information on the stereoisomeric composition and for substance [FL-no: 13.087] the identity of the isomers and the stereoisomeric composition needs to be specified.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of flavourings is regulated under Regulation (EC) No 1334/2008 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. The list contains flavourings substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000.

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 derivatives 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. A 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.

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.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requested ESFA 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.

INTERPRETATION OF THE TERMS OF REFERENCE

The present scientific opinion FGE.90 Revision 1 covers the safety assessment of the following flavouring substances: 6-hydroxydihydrotheaspirane with [FL 13.076] and 6-acetoxydihydrotheaspirane [FL 13.087].

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 JECFA (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 higher of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case, the Panel will need EU production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach. It is noted that the JECFA, at its 65th meeting considered 'how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods' (JECFA, 2006).

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

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

Threshold of 1.5 µg / capita per Day (Step B5) Used by the JECFA

The JECFA uses the threshold of concern of 1.5 µg / capita 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 / capita 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 conditions of use result in an intake greater than 1.5 µg 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 per person per day.

Genotoxicity

As reflected in the Opinion of SCF (SCF, 1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *in vitro* will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of JECFA, 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 68th meeting, the JECFA evaluated a group of 15 flavouring substances consisting of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances. Two were not in the Register and seven tertiary alcohols [FL-no: 02.035, 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] have been considered in FGE.89 (EFSA, 2009a). The remaining six substances have originally been considered by EFSA in FGE.90 (EFSA, 2010).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.90	15 February 2010	http://www.efsa.europa.eu/en/scdocs/scdoc/1336.htm	6
FGE.90Rev1			6

The present revision of FGE.90, FGE.90Rev1 includes the consideration of additional toxicity data provided for one representative substance anhydrolinalool oxide (5) [FL-no: 13.097] to be considered in FGE.75Rev1. The data provided are a 90-day study (Bauter, 2013). The new information will support the re-evaluation of 6-hydroxydihydrotheaspirane [FL-no: 13.076] and 6-acetoxydihydrotheaspirane [FL-no: 13.087].

2. Presentation of the Substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA Status

The JECFA has evaluated a group of 15 flavouring substances consisting of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances (JECFA, 2008a).

2.1.2. EFSA Considerations

Two of the JECFA evaluated substances are not in the Register ((±)-ethyl 2-hydroxy-2-methylbutyrate, JECFA no: 1651 and (±)-ethyl 2-hydroxy-3-methylbutyrate, JECFA no: 1652). Seven tertiary alcohols [FL-no: 02.035, 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] have been considered in FGE.89. Therefore, this consideration only deals with six substances.
The Panel concluded that the six substances [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087] are structurally related to the group of aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in the Flavouring Group Evaluation 18, Revision 3 (FGE.18Rev3). The latter 2 substances [FL-no: 13.076] and [FL-no: 13.087] are also structurally related to anhydrolinalol oxide (5) [FL-no: 13.097] evaluated in FGE.75 Revision 1.

2.2. Isomers

2.2.1. Status

The following four substances [FL-no: 02.018, 02.250, 13.076 and 13.087] have a chiral centre and two substances [FL-no: 02.018 and 02.251] can exist as geometrical isomers.

2.2.2. EFSA Considerations

Information about the stereoisomeric composition has not been specified for two substances [FL-no: 13.087 and 02.251].

Adequate specifications are available for four out of six materials of commerce. For substance [FL-no: 02.251] information on the stereoisomeric composition and for substance [FL-no: 13.087] the identity of the isomers and the stereoisomeric composition needs to be specified.

2.3. Specifications

2.3.1. JECFA Status

The JECFA specifications are available for all six substances.

2.3.2. EFSA Considerations

The European Flavouring Industry has submitted specifications for all six substances commercially used in Europe. (EFFA, 2006; EFFA, 2010;). Although the JECFA specifications are available, the specifications used in this consideration are those submitted by the Industry (see Table 3).

Specifications including complete purity criteria and identity tests are available for all six substances (see Section 1.2).

3. INTAKE ESTIMATIONS

3.1. JECFA Status

For all six substances evaluated through the JECFA Procedure intake data are available for the EU.

3.2. EFSA Considerations

For the six substances [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087] normal and maximum use levels have been provided by the Flavour Industry (EFFA, 2006; EFFA, 2007; EFFA, 2010;) in accordance with the Commission Regulation (EC) No 1565/2000 , see Table 1. Based on the normal use levels, mTAMDI figures (see Table 2) can be calculated for these six substances (for calculation of mTAMDI figures, see e.g. FGE.03, Annex II (EFSA, 2004)).

Table 1: Normal and Maximum use levels (mg/kg) available for the JECFA evaluated substances in FGE.90, Revision 1

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	**02.0**	**03.0**	**04.1**	**04.2**	**05.0**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
02.018	2	-	2	-	-	200	2	2	-	-	-	-	1	-	2	30	2	-
	8	-	8	-	-	500	7	6	-	-	-	-	5	-	5	100	10	-
02.245	-	-	-	0.5	0,5	0.5	-	1	-	-	-	-	-	-	0.2	0.2	-	0.5
	-	-	-	1.5	1.5	1.5	-	3	-	-	-	-	-	-	0.5	0.5	-	1.5
02.250	0.0005	0.0005	0.005	0.005	0.005	0.05	-	0.005	0.0005	0.0005	-	-	0.0005	-	0.05	0.05	0.0005	0.0005
	0.025	0.025	0.25	0.025	0.025	2.5	-	0.25	0.025	0.025	-	-	0.025	-	2.5	2.5	0.025	0.025
02.251	0.0005	0.0005	0.005	0.005	0.005	0.05	-	0.005	0.0005	0.0005	-	-	0.0005	-	0.05	0.05	0.0005	0.0005
	0.0125	0.0125	0.125	0.0125	0.0125	1.25	-	0.125	0.0125	0.0125	-	-	0.0125	-	1.25	1.25	0.0125	0.0125
13.076	1	-	1	-	-	100	2	4	1	1	-	-	1	-	10	10	1	-
	10	-	5	-	-	1000	4	6	2	2	-	-	2	-	50	50	5	-
13.087	1	-	1	-	-	10	2	2	-	-	-	-	1	-	1	2	1	-
	8	-	80	-	-	20	7	6	-	-	-	-	10	-	5	10	5	-

Table 2: Estimated intakes based on the MSDI- and the mTAMDI approach

FL-no	EU Register name	MSDI – EU (μg /capita per day)	MSDI – USA (μg / capita per day)	mTAMDI (μg / person per day)	Structural class	Threshold of concern (μg / person per day)
02.018	Nerolidol	43	23	7000	Class I	1800
02.245	2,3,4-Trimethyl-3-pentanol	0.49	ND	220	Class I	1800
02.250	2,4,8-Trimethyl-7-nonen-2-ol	3.0	0.1	19	Class I	1800
02.251	2,4,8-Trimethyl-3,7-nonadien-2-ol	3.0	1	19	Class I	1800
13.076	6-Hydroxydihydrotheaspirane	0.12	0.05	6700	Class II	540
13.087	6-Acetoxydihydrotheaspirane	0.12	ND	940	Class II	540

ND: No intake data available

4. GENOTOXICITY DATA

4.1. Genotoxicity Studies – Text taken[4] from the JECFA (JECFA, 2008a)

JECFA did not review any genotoxicity studies related to the substances considered in this opinion. They did, however, comment on one chromosomal aberration assay on linalyl acetate [FL-no: 09.013], a supporting substance that gave negative results and concluded that this substance was not of safety concern. JECFA also commented on the closely related substance linalyl proprionate which is not in the Register, but gave negative results in an Ames test when tested at levels of up to 5,000 microgram/plate +/- S9 (JECFA, 2008a).

4.2. Genotoxicity Studies – Text taken[5] from EFSA FGE.18Rev3 (EFSA, 2015)

In vitro/in vivo

Data from *in vitro* tests are available for four candidate [FL-no: 02.052, 02.041, 02.123 and 02.168] and for eight supporting substances [FL-no: 01.002, 01.008, 02.013, 02.014, 02.015, 02.097, 09.013 and 09.830]. Data from *in vivo* tests are available for two candidate [FL-no: 02.052 and 02.123] and for three supporting substances [FL-no: 01.008, 02.013 and 02.015].

2-Methylpropan-2-ol [FL-no: 02.052] was negative in reversion tests in *Salmonella* Typhimurium TA1535, TA1537, TA98 and TA100, without and with metabolic activation by rat and hamster liver S9 (Zeiger et al., 1987). A borderline (less than two-fold) increase in revertants in strain TA1535 was observed in two other studies (Haworth et al., 1981a; Haworth et al., 1981b), which were not available for evaluation. A marginal increase in sister chromatid exchange (SCE) was reported from two studies with Chinese hamster ovary (CHO) cells, which could not be evaluated because the papers were submitted incompletely (Putman, 1985; Thilagar et al., 1981). A borderline increase in mutant frequency was observed in mouse-lymphoma TK +/- cells in a single test in the absence of metabolic activation, whereas negative results were obtained in repeated experiments with S9 (McGregor et al., 1988). Again, similar results are quoted in the summary of an unpublished study not available for evaluation (Kirby et al., 1981). Finally, a slight increase in petite (mitochondrial) mutations was reported in yeast after treatment with 2-methylpropan-2-ol (Jiménez et al., 1988), but this effect is not considered relevant for genotoxicity assessment.

In vivo, 2-methylpropan-2-ol gave clearly negative results in a rat bone marrow micronucleus test, after intraperitoneal (i.p.) administration of a range of doses (six doses from 39 to 1,250 mg/kg body weight (bw)), which reached complete lethality at the highest dose (NTP, 1997). Negative results were also obtained in the mouse peripheral blood micronucleus assay, after 13 weeks of oral exposure to 3,000–40,000 ppm in drinking water. There was no deviation in the PCE/NCE ratio in treated animals, but signs of general toxicity were observed at the two highest doses, indicating significant systemic exposure (NTP, 1995). In another study, 2-methylpropan-2-ol was negative in the mouse bone marrow micronucleus assay when given by i.p. injections at doses up to 1,250 mg/kg bw (three daily administrations) (NTP, 1996). The alleged positive result obtained with 2-methylpropan-2-ol in a rat bone marrow chromosomal aberration test after oral administration of 1/5 of the LD50 (Barilyak and Kozachuk, 1988) is considered inconclusive, because the result is not adequately supported by experimental data.

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

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

Terpineol [FL-no: 02.230] (the mixture of alpha-terpineol, beta-terpineol, delta-terpineol and gamma-terpineol)

Terpineol was tested negative in a rec assay in *Bacillus subtilis* (Oda et al., 1978).

alpha-Terpineol [FL-no: 02.014] was reported to give weakly positive results (as a dose-dependent increase in mutation frequency both with and without S9 activation with a maximum increase of 2.2-fold compared with the control) in an Ames-type mutagenicity assay in one (TA102) of four *Salmonella* Typhimurium strains tested (TA97a, TA98, TA100, TA102). alpha-Terpineol was incorporated into agar plates up to 2,500 microgram/plate, either with or without S9 metabolic activation (Gomes-Carneiro et al., 1998).

In other studies, alpha-terpineol gave consistently negative results in Ames assays in *S.* Typhimurium strains TA98, TA100, TA1535, TA1537,and TA1538, either with or without S9 metabolic activation (Heck et al., 1989; Florin et al., 1980; Lorillard, 1983).

In an *in vivo/in vitro* study designed to investigate the mutagenicity of the metabolites of beta-terpineol [FL-no: 02.097], Sprague–Dawley rats were administered a single dose of 0.5 ml (452 mg) of beta-terpineol by gavage and the urine was collected for 24 h. The urine (500 µl) was hydrolysed with beta-glucuronidase. Hydrolysed and unhydrolysed urine samples, ether extracts of the urine, and aqueous fractions of the urine–ether extracts were then separately incubated with *S.* Typhimurium strains TA98 and TA100 without S9 activation. Neither beta-terpineol, nor any of the urinary solutions isolated from the urine of rats given 452 mg doses of beta-terpineol, showed any evidence of mutagenicity in either TA98 or TA100 without metabolic activation (Rockwell and Raw, 1979).

In gene mutation tests in mouse lymphoma cells, alpha-terpineol was non-mutagenic when applied at doses up to 250 nl/ml (with S9) and 300 nl/ml (without S9) (Lorillard, 1982); negative results were also obtained in another study in which alpha-terpineol was tested up to 460 nl/ml (with S9) and 380 nl/ml (without S9) (Kirby et al., 1984). Based on the negative results obtained in gene mutation tests in mammalian cells, and in view of the sensibility of the TK +/- system to mutagens specifically active toward the *S.* Typhimurium strain TA102, the Panel concluded that alpha-terpineol does not raise concern for genotoxicity.

Overall, 2-methylpropan-2-ol provided an equivocal evidence of genotoxicity in some *in vitro* assays, whereas it was clearly negative *in vivo* in cytogenetic tests conducted up to the maximum tolerated dose. The overall weight of the experimental evidence does not raise concern for *in vivo* genotoxicity.

2-Methylbut-3-en-2-ol [FL-no: 02.123] was reported to be negative in two bacterial gene mutation tests and in an *in vivo* micronucleus test, however, the unpublished study reports are not available for re-evaluation.

For the other substances in FGE.18Rev1, the available data considered valid do not give rise to any safety concerns with respect to genotoxicity.

For a summary of *in vitro/in vivo* genotoxicity data, considered by EFSA in FGE.18Rev3 see Table 4 and Table 5.

5. A 90-Day Study for 6-acetoxydihydrotheaspirane [FL-no: 13.087]

A 90-day single dose study on [FL-no: 13.087] is available (Griffiths, 1979). The numbers of parameters examined in this study, although state of the art at that time, are, however, limited compared to modern OECD guidelines.

Griffiths (1979) did a 90-day study of 3 mg/kg per day of 6-acetoxydihydrotheaspirane by gavage in male and female Sprague–Dawley rats (n = 15 per group) of initial body weight 70–95 g (in an

aqueous solution kept at 30–35^{0}C to hold the compound in solution). The only difference between controls and treated rats was a 4.7% decrease in red bloods cells (and haemoglobin and haematocrit) in females. During the 3 months of treatment, no other changes were observed in body weight, haematology, serum chemistry and microscopy of the organs. Since an OECD guideline 90-day study in rats on a supporting compound is available, the more limited Griffith (1979) study will not be used for safety assessment.

6. A 90-Day Study on anhydrolinalool oxide [FL-no: 13.097] evaluated in FGE.75Rev1 (EFSA, 2015)

A new guideline study on a supporting substance, anhydrolinalool oxide [FL-No: 13.097] is now available. It supports the evaluation of 6-hydroxydihydrotheaspirane [FL-No: 13.076] and acetoxydihydrotheaspirane [FL-No: 13.087]. This OECD TG 408 compliant 90-day study in rats is described extensively in FGE75Rev1. A NOAEL of 52 mg/kg bw per day could be derived from the results.

6.1. EFSA Considerations

The Panel concluded that the data available do not preclude evaluation of the six substances [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087] through the Procedure.

7. Application of the Procedure

7.1. Application of the Procedure to Aliphatic, Acyclic and Alicyclic Terpenoid Tertiary Alcohols and Structurally Related Substances by JECFA (JECFA, 2008a):

According to the JECFA, four of the substances belong to structural class I and two to structural class II using the decision tree approach presented by Cramer *et al.* (1978).

The JECFA concluded all six substances at step A3 in the JECFA Procedure – meaning that the substances are expected to be metabolised to innocuous products (step 2) and concluded that the intakes for all substances are below the thresholds for their structural classes I and II (step A3).

The evaluations of the six substances are summarised in Table 7.

7.2. Application of the Procedure to Aliphatic, Alicyclic and Aromatic Saturated and Unsaturated Tertiary Alcohols, Aromatic Tertiary Alcohols and their Esters evaluated by EFSA (EFSA, 2015):

Thirty candidate substances were evaluated in FGE.18Rev3; 20 substances are classified into structural class I, 11 substances into structural class II and one candidate substance is classified into structural class III according to the decision tree approach presented by Cramer et al. (1978).

Twenty-eight substances were evaluated at step A3, i.e. the substances are expected to be metabolised to innocuous products (step 2) and the estimated daily intake is below the threshold for the structural classes I and II (step A3).

Four of the candidate substances were evaluated at step B4, but no NOAEL could be derived for any of the four candidate substances and accordingly additional data for these substances were required.

The evaluations of the 32 substances are summarised in Table 8.

7.3. EFSA Considerations

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for four of the six aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances evaluated by the JECFA [FL-no: 02.018, 02.245, 02.250 and 02.251]. For the remaining two substances [FL-no: 13.076 and 13.087], no metabolism data are available, neither for the substances themselves nor for related substances. Therefore, in contrast to the JECFA, the Panel cannot conclude that these substances are metabolised to innocuous products and they 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 for the structurally related substance anhydrolinalool oxide. Compared with an exposure estimate of 0.12 µg /capita per day for both [FL-no: 13.076 and 13.087] a margin of safety of more than 26×10^6 can be calculated. Accordingly, for these two substances the Panel concluded that they are not of safety concern at estimated level of intake as flavouring substances based on the MSDI approach.

8. CONCLUSION

The JECFA has evaluated a group of 15 flavouring substances consisting of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances.

Two of the JECFA evaluated substances are not in the Register ((±)-ethyl 2-hydroxy-2-methylbutyrate, JECFA no: 1651 and (±)-ethyl 2-hydroxy-3-methylbutyrate, JECFA no: 1652). Seven tertiary alcohols [FL-no: 02.035, 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] have been considered in FGE.89. Therefore, this consideration only deals with six substances.

The Panel concluded that the six substances [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087] are structurally related to the aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in the Flavouring Group Evaluation 18, Revision 3 (FGE.18Rev3) or FGE.75, Revision 1 (FGE.75Rev1).

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for four of the six substances [FL-no: 02.018, 02.245, 02.250 and 02.251]. For the remaining two substances [FL-no: 13.076 and 13.087], no metabolism data are available, neither for the substances themselves nor for related substances. Therefore, in contrast to the JECFA, the Panel cannot conclude that these substances are metabolised to innocuous products and they 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 for the structurally related substance anhydrolinalool oxide. Compared with an exposure estimate of 0.12 µg / capita per day for both [FL-no: 13.076 and 13.087] a margin of safety of more than 26×10^6 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. In order to determine whether the conclusion for the six JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications.

Adequate specifications are available for four out of six materials of commerce. For substance [FL-no: 02.251], information on the stereoisomeric composition has not been specified and for substance [FL-no: 13.087], the identity of the isomers needs to be specified.

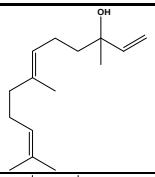
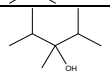
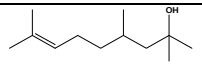
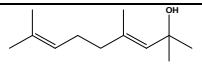
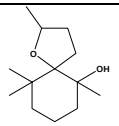
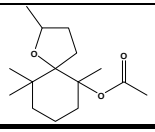
Thus, for four substances [FL-no: 02.018, 02.245, 02.250 and 13.076] the Panel agrees with the JECFA conclusion 'No safety concern at estimated level of intake as flavouring substances' based on the MSDI approach.

For the six substances, use levels have been provided by the Industry [FL-no: 02.018, 02.245, 02.250, 02.251, 13.076 and 13.087]. The mTAMDI figures calculated for three of the six substances [FL-no: 02.018, 13.076 and 13.087] are above the threshold of concern for their structural classes. For these

substances, more reliable exposure data are needed. On the basis of such data the substances should be reconsidered using the Procedure.

Thus, for two substances [FL-no: 02.251 and 13.087] the Panel has reservations (missing information on stereoisomerism and mixture of isomers).

Table 3: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic, Acyclic and Alicyclic Terpenoid Tertiary Alcohols and Structurally Related Substances (JECFA, 2008b)

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 / Reference for specifications
02.018 1646	Nerolidol		2772 67 7212-44-4	Liquid $C_{15}H_{26}O$ 222.38	Slightly soluble Soluble	276 NMR 96% to 100%	1.478-1.483 0.870-0.876	Specifications (EFFA, 2006). 34-44% Cis nerolidol. 54-64% Trans nerolidol.
02.245 1643	2,3,4-Trimethyl-3-pentanol		3903 3054-92-0	Liquid $C_8H_{18}O$ 130.23	Insoluble Soluble	156.5 IR NMR MS 97 %	1.440 0.850	Specifications (EFFA, 2010).
02.250 1644	2,4,8-Trimethyl-7-nonen-2-ol		4212 437770-28-0	Liquid $C_{12}H_{24}O$ 184.32	Insoluble Soluble	60-70 (2 hPa) IR NMR 96 %	1.448-1.456 0.845-0.855	Racemate (EFFA, 2010). Specifications ().; (EFFA. 2010).
02.251 1645	2,4,8-Trimethyl-3,7-nonadien-2-ol		4211 479547-57-4	Liquid $C_{12}H_{22}O$ 182.31	Insoluble Soluble	70-72 (2 hPa) NMR 96 %	1.463-1.471 0.857-0.867	Mixture of (Z)- and (E)-isomer (EFFA. 2010). Specifications (EFFA. 2010).
13.076 1648	6-Hydroxydihydrotheaspirane		3549 11917 65620-50-0	Liquid $C_{13}H_{24}O_2$ 212.33	Very slightly soluble Soluble	273.4 MS 97% to 100%	1.481-1.487 0.999-1.005	Specifications (EFFA, 2006; EFFA. 2010). 46-53% trans isomer (CASrn 65620-50-0), 44-51% cis isomer (CASrn 57967-68-7) , 0-2% Isospiranol (CASrn 54344-69-3).
13.087 1647	6-Acetoxydihydrotheaspirane		3651 57893-27-3	Solid $C_{15}H_{26}O_3$ 254.37	Insoluble Soluble	293.7 33-55 IR NMR 96% to 100%	n.a n.a	Specifications (EFFA, 2006; EFFA. 2010). According to EFFA Assay min is 96-100% (Sum of two isomers).

(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.

Genotoxicity Data Tables

No genotoxicity data available for the substances in this FGE.90

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.18Rev2 (EFSA, 2011). Substances listed in brackets are the JECFA evaluated supporting substances in FGE.18Rev2

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
2-Methylpropan-2-ol [02.052]	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537; TA1538	0.1, 0.5, 2.5, 5, 10 µl/plate (7800 µg/plate)	Questionable[(a)]	(Haworth et al., 1981a)	Unpublished GLP study. According to the conclusion of the report, the test substance 'did cause a weak but significant increase in TA1535 revertants per plate in both the presence and absence of rat liver microsomes'. However, this result cannot be re-evaluated because the corresponding page with results on TA1535 in Table format is lacking.
	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537; TA1538	probably 1 to 10 µl/plate (7800 µg/plate) (corresponding pages of the report are lacking)	Questionable[(a)]	(Haworth et al., 1981b)	Unpublished GLP study. According to the conclusion of the report, the test substance (purity 99.9 %) 'did not cause a significant increase in the number of revertants per plate in any of the tester strains with or without metabolic activation. It should be noted, however, that there was a slight increase in TA1535 revertants per plate observed in the presence and absence of rat liver microsomes'. However, this result cannot be re-evaluated because 15 pages with all results in Table format are lacking.
	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537	10,000 µg/plate	Negative[(a)]	(Zeiger et al., 1987)	Non-GLP study roughly in accordance with OECD guideline 471. There was a slight increase in TA1535 revertants per plate observed in the presence and absence of rat and hamster liver microsomes. This effect is dose-related only with hamster liver S9. Overall, the effects were less than twice compared to control. The study is considered valid.
	Yeast mitochondrial mutation assay	Several *Saccharomyces strains*	4%	Positive	(Jiménez et al., 1988)	This non-GLP study was not in accordance with OECD guideline No. 480 (1986), and the study protocol does not belong to standard protocols used in routine testing. However, the result is considered valid since main details of method and results are reported. Endpoint not relevant for genotoxicity.
	Forward mutation assay	Mouse lymphoma L5178Y TK +/-	0, 1000, 2000, 3000, 4000, 5000 µg/ml	Negative[(a)]	(McGregor et al., 1988)	Non-GLP study in accordance with OECD guideline 476 (1984). Study is considered valid.
	Forward mutation assay	Mouse lymphoma L5178Y TK +/-	1.3 to 100 µl/ml (78,000 µg/ml)	Negative	(Kirby et al., 1981)	Unpublished GLP study. According to the report's summary, test substance of high (99.9 %) purity did not induce any detectable increases in the mutant frequencies in the presence and absence of S9-mix. When cultures were tested in the presence of S9-mix with less pure test substance none of the cultures exhibited increases in mutant frequency. Without S9-mix this test substance did appear to induce an increase in the mutant frequency of cultures treated with the higher doses, but a dose-related response was not evident. In addition, in only one of two experiments was a greater than two-fold increase in mutant frequency observed. However, this result cannot be re-evaluated because 47 pages with all results in Table format are lacking in the report submitted.

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.18Rev2 (EFSA, 2011). Substances listed in brackets are the JECFA evaluated supporting substances in FGE.18Rev2

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Chromosomal aberration	Chinese hamster ovary cells	160 to 5000 microgram/ml	Negative	(NTP, 1984)	Limited validity. This non-GLP study was in accordance with OECD guideline No. 473 (1983) except that only a single harvest time was used, however, the study protocol does not fully meet the criteria of the revised guideline from 1997. According to the version from 1997, a single sampling time should be equivalent to about 1.5 normal cell cycle lengths, duplicate cultures should be used at each concentration and 200 metaphases should be scored per concentration.
	Sister chromatid exchange	Chinese hamster ovary cells	6 concentrations ranging from 0.625 to 20 µl/ml (15,600 µg/ml)	Negative	(Putman, 1985)	Unpublished GLP study. According to the report's summary, test substance of high (99.9 %) purity caused a significant increase in sister chromatid exchanges at the high dose only in the assay without S9 and at the two highest doses in the assay with S9, however, the test article did not meet the criteria for a positive response (at least two-fold increase or a significant positive dose-response over at least three doses). However, this result cannot be re-evaluated because pages with all results in Table format are lacking in the report submitted.
	Sister chromatid exchange	Chinese hamster ovary cells	20 µl/ml (15,600 µg/ml)	Negative	(Thilagar et al., 1981)	Unpublished GLP study is considered valid. A marginal increase in SCE frequency was observed in the tests with and without S9, while only the highest concentration without S9 resulted in a significant increase. Thus, the test article did not meet the criteria for a positive response (at least two-fold increase or a significant positive dose-response over at least three doses). (All relevant tables were submitted)
2-Methylbutan-2-ol [02.041]	Mutagenicity assays	*S.* Typhimurium TA1535; TA1537; TA1538; *S. cerevisiae*	NR	Negative	(Dow Chemical Company, 1982)	Very short abstract only.
	Sister chromatid exchange	Chinese hamster ovary cells	160, 500, 1600, 5000 µg/ml	Positive[(c)] Negative[(b)]	(NTP, 1997)	
	Sister chromatid exchange	Chinese hamster ovary cells	2000, 3000, 4000, 5000 µg/ml	Negative[(a)]	(NTP, 1997)	
2-Methylbut-3-en-2-ol [02.123]	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537	20 - 5000 µg/plate	Negative[(a)]	(BASF, 1989)	Summary in IUCLID data set only. According to this summary, the assay was not in compliance with GLP but in accordance with OECD guideline 471. The unpublished study report is not available for re-evaluation.
	Liquid suspension assay	*S.* Typhimurium TA98; TA100	20 - 5000 µg/plate	Negative[(a)]	(BASF, 1991)	Summary in IUCLID data set only. According to this summary, the assay was not in compliance with GLP but in accordance with OECD guideline 471. The unpublished study report is not available for re-evaluation.
Isophytol [02.168]	Ames test	*S.* Typhimurium TA97; TA98; TA100; TA1535	100, 333, 1000, 3333, 10000 microgram/plate	Equivocal[(a)]	(NTP, 1994)	This non-GLP study is considered valid. It is in accordance with OECD guideline No. 471 (1983). The study is published in the Web and the report contains sufficient details.
	Ames test	*S.* Typhimurium TA97, TA98, TA100, and TA1535	five doses from 100 to 10000 microgram/plate	Negative	(NTP, 2000)	This non-GLP study is considered valid. It is in accordance with OECD guideline No. 471 (1983). The study is published in the Web and the report contains sufficient details.
(Linalool [02.013])	Ames test(modified)	*S.* Typhimurium TA100	3 µl/2 ml (2610 µg/2ml) incubation volume 1 mg/plate	Negative[(a)]	(Eder et al., 1980)	

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.18Rev2 (EFSA, 2011). Substances listed in brackets are the JECFA evaluated supporting substances in FGE.18Rev2

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Ames test	*S.* Typhimurium TA92; TA94; TA98; TA100; TA1535; TA1537	(1000 µg/plate)	Negative[(a)]	(Ishidate et al., 1984)	
	Ames test	*S.* Typhimurium TA98; TA100	100 µl (87000 µg)	Negative[(a)]	(Rockwell and Raw, 1979)	
	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537; TA1538	10,000 nl/plate (8700 µg/plate)	Negative[(a)]	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Chromosomal aberration assay	Chinese hamster fibroblasts	0.25 mg/ml (250 µg/ml)	Negative[(a)]	(Ishidate et al., 1984)	
	Unscheduled DNA synthesis	Rat hepatocytes	50 nl/ml (43.6 µg/ml)	Negative	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Mutation assay	*E. coli* WP2 *uvrA*	1 mg/plate (1000 µg/plate)	Negative	(Yoo, 1986)	In Japanese (only summary and tables in English). Thus, the validity cannot be evaluated.
	Recassay	*B. subtilis* H17 (rec+); M45 (rec-)	17 µg	Negative	(Oda et al., 1979)	
	Recassay	*B. subtilis* H17 (rec+); M45 (rec-)	10 µl/disk (8700 µg/disk)	Positive	(Yoo, 1986)	In Japanese (only summary and tables in English). Thus, the validity cannot be evaluated.
	Mammalian cell mutation	Mouse Lymphoma L5178Y TK+/-	3.9 to 300 nl/ml	Negative[(b)] Positive[©]	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	1000 µM (154,250 µg)	Negative[(a, d)]	(Sasaki et al., 1989)	
(Linalyl acetate [09.013])	Ames test	*S.*Typhimurium TA98; TA100; TA1535; TA1537; TA1538	25,000 nl/plate (22575µg/plate)	Negative[(a)]	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Unscheduled DNA synthesis	Fischer or SD rat hepatocytes	300 nl/ml (271 µg/ml)	Negative	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Recassay	*B. subtilis* H17 (rec+); M45 (rec-)	18 µg	Negative	(Oda et al., 1979)	
	Chromosome aberration	Peripheral human lymphocytes	180 µg/ml	Negative[(a)]	(Bertens and van de Waart, 2000)	
(alpha-Terpineol [02.014])	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537; TA1538	10,000 µg/plate	Negative	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Ames test	*S.* Typhimurium TA97a; TA98; TA100;	2500 µg/plate	Negative	(Gomes-Carneiro et al., 1998)	The study is considered valid. A slight but dose-related response was noted with TA102 with and without the use of metabolic activation.
		TA102	2500 µg/plate	Weakly positive[(e)]		
	Ames test	*S.* Typhimurium TA98; TA100; TA1535; TA1537; TA1538	1000 µg/plate	Negative[(a)]	(National Cancer Institute, 1983)	
	Ames test	*S.*Typhimurium TA98; TA100; TA1535; TA1537; TA1538	10,000 µg/plate	Negative[(a)]	(Lorillard, 1983)	

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.18Rev2 (EFSA, 2011). Substances listed in brackets are the JECFA evaluated supporting substances in FGE.18Rev2

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Spot test	*S.* Typhimurium TA98; TA100; TA1535; TA1537	3 µmol/plate (463 µg/plate)	Negative[a]	(Florin et al., 1980)	
	Mammalian cell mutation	Mouse Lymphoma L5178Y TK +/-	0.5 µl/ml (467µg/ml) 0.75µl/ml (700 µg/ml)	Negative[c] Negative[b]	(Kirby et al., 1984)	
	Mammalian cell mutation	Mouse Lymphoma L5178Y TK +/-	300 nl/ml (280 µg/ml) 250 nl/ml (233 µg/ml)	Negative[a]	(Heck et al., 1989)	Some important details of method and results are not reported. Thus, the validity of this study cannot be evaluated.
	Mammalian cell mutation	Mouse lymphoma L5178Y TK +/-	15.6 -250 nl/ml 15.6 -300 nl/ml	Negative[b] Negative[c]	(Lorillard, 1982)	
	Recassay	*S. cerevisiae*	NR	Negative	(Oda et al., 1979)	
(Terpinyl acetate [09.830])	Rec assay	*B. subtilis* H17; M45	19 µg	Negative	(Oda et al., 1979)	
(beta-Terpineol) [02.097])	Ames	*S.* Typhimurium TA98; TA100	100 µg (93,000 µg)	Negative[a]	(Rockwell and Raw, 1979)	
	Rec assay	*S. cerevisiae*	NR	Negative[a]	(Oda et al., 1979)	Article does not specify alpha- or beta-terpineol
(1-Isopropyl-4-methylbenzene [01.002])	*In vivo/in vitro* Ames test	*S.*Typhimurium TA98 and TA100	0.5 ml (equivalent to 1,706 mg/kg bw) administered to Sprague–Dawley rats, urine collected and tested *in vitro*	Negative[e]	(Rockwell and Raw, 1979)	
(Myrcene [01.008])	Ames test	*S.* Typhimurium TA100; TA1535; TA97; TA98	0, 33, 100, 333, 1000, 3333 and 10,000 µg/plate	Negative[a]	(NTP, 1999	
	Chromosome aberration	Human lymphocytes	0, 100, 500 and 1000 µg/ml	Negative[a]	(Kauderer et al., 1991)	
	Sister chromatid exchange	Human lymphocytes	0, 100, 500 and 1000 µg/ml	Negative[a]	(Kauderer et al., 1991)	
	HPRT assay	V79 Chinese hamster cells	0, 100, 500 and 1000 µg/ml	Negative[a]	(Kauderer et al., 1991)	
	Sister chromatid exchange	V79 Chinese hamster cells	0, 100, 250 and 500 µg/ml	Negative[a]	(Röscheisen et al., 1991)	
	Sister chromatid exchange	HTC cells	0, 100, 250 and 500 µg/ml	Negative	(Röscheisen et al., 1991)	
(Menthol [02.015])	Ames test	*S* Typhimurium TA92, TA100, TA94, TA98, TA1535, TA1537	0, and 6 concentrations up to 5000 µg/plate	Negative[a]	(Ishidate et al., 1984)	d,l-Menthol was used. The study is considered valid.
	Ames test (preincubation method)	*S.* Typhimurium TA1535, TA97, TA100, TA98	3 - 666 µg/plate	Negative[a]	(Zeiger et al., 1988)	d,l-Menthol was used. The study is considered valid.
	Ames test	*S.* Typhimurium TA2637, TA100, TA98	0, 5 - 500 µg/plate	Negative[a]	(Nohmi et al., 1985)	d,l-menthol was tested. The highest concentrations were cytotoxic. The study is considered valid.
	Ames test	*S.* Typhimurium TA2637, TA100, TA98	0, 20 - 500 µg/plate	Negative[a]	(Nohmi et al., 1985)	l-menthol was tested. The highest concentrations were cytotoxic. The study is considered valid.
	Ames test	*S* Typhimurium TA1537, TA1535, TA100, TA98	0, 6.4, 32, 160, and 800 µg/plate	Negative[a]	(Andersen and Jensen, 1984)	No indication of which enantiomer was used. In the absence of metabolic activation, the highest concentration was cytotoxic. The study is considered valid.
	Ames test	*E. coli WP2 uvrA* (Trp^-)	100 - 800 µg/plate	Negative	(Yoo, 1986)	l-Menthol was used. The article is not in English. The validity of the study cannot be evaluated. It is unclear whether metabolic activation or a control group was used.

Table 4: Genotoxicity Data (*in vitro*) EFSA / FGE.18Rev2 (EFSA, 2011). Substances listed in brackets are the JECFA evaluated supporting substances in FGE.18Rev2

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Ames test	*S.* Typhimurium TA97A; TA98; TA100; TA102	0, 5 - 800 µg/plate	Negative[(a)]	(Gomes-Carneiro et al., 1998)	(-)-Menthol was used. The range of concentrations tested varied between the different strains. Cytotoxicity was observed with the highest concentrations tested with TA97A and, in the presence of metabolic activation, the highest concentration tested with TA102. The study is considered valid.
	Rec assay	*B. subtilis* H17, M45	Up to 10,000 µg/disk	Positive	(Yoo, 1986)	l-Menthol was used. Inhibition zone for rec- and rec+ was 42 and 23 mm, respectively. The article is not in English. It is not clear from the study whether metabolic activation, or a control group was used. The validity of this study cannot be assessed. The method (rec assay) has poor predictive value.
	Rec assay	*B. subtilis* H17, M45	20 µg/disk	Negative	(Oda et al., 1979)	l-Menthol was used. The article is not in English. Only one concentration level is mentioned at a table. No data on metabolic activation or control group. The validity of this study cannot be evaluated. The method (rec assay) has poor predictive value.
	Alkaline elution assay	Rat hepatocytes	0, 0.1 - 1.3 mM (203.2 µg/ml[4])	Negative	(Storer et al., 1996)	The experiment employed d-Menthol. An increase in DNA breaks was only observed at concentrations associated with cytotoxicity. The authors concluded that this was a false-positive result. The study is considered valid.
	Sister chromatid exchange	Chinese hamster ovary cells	5 – 50 amd 0, 2 – 25 µg/ml[3] 0, 16 – 167 µg/ml [2]	Negative[(a)]	(Ivett et al., 1989)	d,l-Menthol was used. The compound was tested up to toxic or nearly toxic concentration levels. The study is considered valid.
	Sister chromatid exchange	Human lymphocytes	0, 0.1, 1, 10 mM (1563 µg/ml[4])	Negative[(a)]	(Murthy et al., 1991)	The study is considered valid.
	Cytogenetic assay	Human embryonic lung cells	0, 0.1, 1, 10 µg/ml	Negative	(Food and Drug Research Laboratories, Inc., 1975)	The report does not mention exogenous metabolic activation. The study is considered valid.
	Chromosome aberration	Chinese hamster fibroblasts	0 and three concentrations up to 200 µg/ml	Negative[(c)]	(Ishidate et al., 1984)	The maximum concentration (cytotoxic) was selected by a preliminary test. The study is considered valid.
	Chromosome aberration	Chinese hamster ovary cells	0, 50 - 250 µg/ml	Negative[(a)]	(Ivett et al., 1989)	d,l-Menthol was used. The compound was tested up to toxic or nearly toxic concentration levels. The study is considered valid.
	Chromosome aberration	Human lymphocytes	0, 0.1, 1, 10 mM (1563 µg/ml[4])	Negative[(a)]	(Murthy et al., 1991)	The study is considered valid.
	Gene mutation assay	Mouse lymphoma L5178Y TK+/-cells	0, 12.5 - 200 µg/ml	Negative[(a)]	(Myhr and Caspary, 1991)	d,l-Menthol was used. The maximum concentration was selected by a preliminary test The study is considered valid.

NR = Not Reported
(a)With and without metabolic activation.
(b)With metabolic activation.
(c) Without metabolic activation.
(d) With and without pre-treatment with mitomycin C at 0.15 µM for 21 h.
(e)With and without presence of beta-glucuronidase

Table 5: Genotoxicity Data (*in vivo*) for 18Rev2 (EFSA, 2011). Substances listed in brackets are JECFA-evaluated substances

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
2-Methylpropan-2-ol [02.052]	*In vivo* Chromosomal Aberration assay	Male rats	Once *via* gavage	0.2 × LD50	Positive[1]	(Barilyak and Kozachuk, 1988)	Validity questionable. This study was not in compliance with GLP and not in accordance with OECD guideline No. 475 (1983). Some main details of method and results are not available. The authors report the results of tests on a series of monohydric alcohols (from C1 to C16, 18 compounds) in rat bone marrow cytogenetic tests. All compounds were claimed positive compared to the untreated control group, even though no statistics is shown. It is noted that a single control group, with 0.0% of cells with aberrations was used throughout the study. Lacking historical control data, it is not possible to establish whether the alleged positive results were due to and uniformly positive response elicited by all chemicals, or rather by an incidental very low frequency of aberrations in the group of rats (8 animals) used as control. In this respect, it is noted that the incidence of chromosomal aberrations observed with some 'positive' compounds, including 2-methylpropan-2-ol (1.6+/-0.5%), are close to background incidences commonly observed. Even the lack of a concurrent raise in gaps in treated animals casts doubts on an induced genotoxic effect. Moreover, the lack of a positive control group in the study is noted. For these reasons, the results of this study are considered inconclusive.
	In vivo Micronucleus assay	Mouse bone marrow erythrocytes	i.p. × 3 at 24 h intervals (=72 h)	312.5, 625, and 1250 mg/kg bw	Negative	(NTP, 1996)	This study is considered valid. It was not in compliance with GLP but in accordance with OECD guideline No. 474 (1983/1997) except that only 5 male animals were tested. The study is published in the Web and the report contains sufficient details. Due to the lack of an effect on the PCE/NCE ratio, it is unclear whether the test substance has reached the bone marrow. Relevance of the result is limited.
	In vivo micronucleus assay	Rat bone marrow cells	i.p. × 3 at 24 h intervals (=72 h)	0, 39–1250 mg/kg bw,	Negative	(NTP, 1997)	
	In vivo micronucleus assay	Mouse peripheral blood cells	Drinking water	3000–40000	Negative	(NTP, 1995)	
2-Methylbut-3-en-2-ol [02.123]	*In vivo* Micronucleus assay	Mouse bone marrow erythrocytes	Once *via* gavage	500, 1000, 1500 mg/kg	Negative	(BASF, 1992)	Summary in IUCLID data set only. According to this summary, the assay was performed in compliance with GLP and in accordance with OECD guideline 474. One thousand PCEs were counted per animal. The unpublished study report is not available for re-evaluation.
(Linalool [02.013])	*In vivo* Micronucleus assay	Mouse bone marrow erythrocytes	Once *via* gavage	1500 mg/kg	Negative	(Meerts and van de Waart, 2001)	This study is considered valid. It was in compliance with GLP and in accordance with OECD Guideline 474 (1997). However, due to the lack of an effect on the PCE/NCE ratio it is unclear whether the test substance reached the bone marrow. Thus, the relevance of the result is limited.
(Myrcene [01.008])	*In vivo* micronucleus assay	Rat bone marrow cells	Gavage	0, 100, 500 or 1000 mg/kg bw	Negative	(Zamith et al., 1993)	
	In vivo micronucleus assay	Mouse peripheral blood cells	Gavage	Up to 2000 mg/kg bw/day for 13 weeks	Negative	(NTP, 2001)	

Table 5: Genotoxicity Data (*in vivo*) for 18Rev2 (EFSA, 2011). Substances listed in brackets are JECFA-evaluated substances

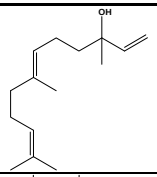
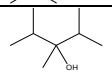
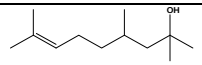
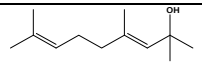
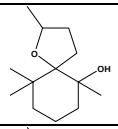
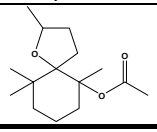
Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
(Menthol [02.015])	Host-mediated mutation assay	*S.* Typhimurium TA1530 and G46; *S. cerevisiae* D3 inoculated in mice (7–9 animals/group)	Gavage	0, 1.45 - 5000 mg/kg bw (single dose) 0, 1150 mg/kg bw/day (repeated doses)	Equivocal	(Food and Drug Research Laboratories, Inc., 1975)	Negative results, with exception of the combination *S* Typhimurium TA1530 – 5000 mg/kg bw and *S. cerevisiae* D3 – 1150 mg/kg bw/day. This study is considered valid, but the equivocal result might have low relevance as the effect was only observed at very high (lethal) dose levels.
	In vivo cytogenetic assay	Male rat bone marrow cells	Gavage	0, 1.45–3000 mg/kg bw (single dose) 0, 1150 mg/kg bw/day (repeated doses)	Negative	(Food and Drug Research Laboratories, Inc., 1975)	Oral DL_{50} was determined as 940 mg/kg bw. The study is considered valid but the negative result is of limited relevance, as no effect on mitotic index was observed. However, testing at higher dose levels may not have been possible, due to lethality.
	In vivo micronucleus assay	B6C3F1 male mouse bone marrow cells	i.p.	0, 250–1000 mg/kg bw/day, during 3 days	Negative	(Shelby et al., 1993)	d,l-Menthol was used. The study is considered valid, but the negative result is of limited relevance, as no toxicity to the bone marrow was observed. However, testing at higher dose levels was not possible, because the highest dose caused 50% lethality.
	In vivo dominant lethal assay	Male rat fertility, spermatozoa	Gavage	0, 1.45–3000 mg/kg bw (single dose) 0, 1150 mg/kg bw/day (repeated doses)	Negative	(Food and Drug Research Laboratories, Inc., 1975)	This study is considered valid.

Table 6: Subchronic and chronic toxicity studies on [FL-no: 13.097] (substance evaluated in FGE.75Rev1)

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 1189 mg/kg bw/day for males and 0, 385.5, 661.9 and 921.2 mg/kg bw/day for females	14	385.5	(Bauter, 2012)	
	Rat; M/F 20	Diet	0, 46.4, 233.4 and 452.9, 500 mg/kg bw for males and 0, 53.2, 257.3 and 506.5 mg/kg bw for females	90	105	(Bauter, 2013)	OECD (408) compliant 90-day study.
6-Acetoxydihydrotheaspirane [13.087]	Rat; M/F	Oral gavage	3.0 mg/kg bw per day	90	No NOAEL	(Griffith, 1979)	Study of limited value because parameters are missing

Summary of Safety Evaluation

Table 7: Summary of Safety Evaluation of Aliphatic, Acyclic and Alicyclic Terpenoid Tertiary Alcohols and Structurally Related Substances (JECFA, 2008a)

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
02.018 1646	Nerolidol		43 23	Class I 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.
02.245 1643	2,3,4-Trimethyl-3-pentanol		0.49 ND	Class I 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.
02.250 1644	2,4,8-Trimethyl-7-nonen-2-ol		3.0 0.1	Class I 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.
02.251 1645	2,4,8-Trimethyl-3,7-nonadien-2-ol		3.0 1	Class I A3: Intake below threshold	(d)	No safety concern at the estimated level of intake based on the MSDI approach.	Composition of stereoisomeric mixture to be specified.
13.076 1648	6-Hydroxydihydrotheaspirane		0.12 0.05	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.
13.087 1647	6-Acetoxydihydrotheaspirane		0.12 ND	Class II A3: Intake below threshold	(d)	No safety concern at the estimated level of intake based on the MSDI approach (Step B4).	According to EFFA, the commercial product is a mixture of two isomers; identity of the isomers to be specified.

(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.
ND: not determined

Table 8: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA FGE.18Rev2 and EFSA FGE.75 Rev1) (EFSA, 2011 and EFSA, 2009)

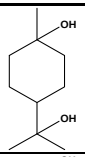
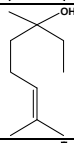
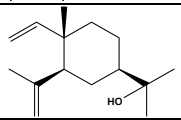
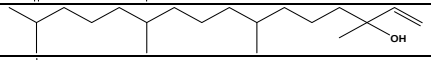
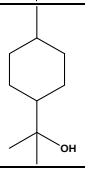
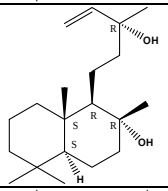
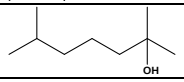
FL-no	EU Register name	Structural formula	MSDI (a) (µg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
02.054	p-Menthane-1,8-diol		11	Class I A3: Intake below threshold	4)	6)	
02.140	1,2-Dihydrolinalool		0.044	Class I A3: Intake below threshold	4)	6)	
02.149	Elemol		1.6	Class I A3: Intake below threshold	4)	6)	
02.168	Isophytol		0.037	Class I A3: Intake below threshold	4)	7)	
02.171	p-Menthan-8-ol		0.012	Class I A3: Intake below threshold	4)	6)	
02.206	Sclareol		0.67	Class I A3: Intake below threshold	4)	6)	
02.219	2,6-Dimethyl-2-heptanol		0.012	Class I A3: Intake below threshold	4)	6)	

Table 8: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA FGE.18Rev2 and EFSA FGE.75 Rev1) (EFSA, 2011 and EFSA, 2009)

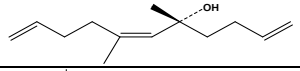
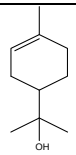
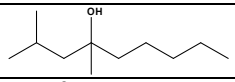
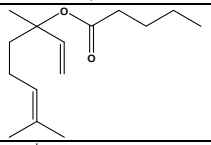
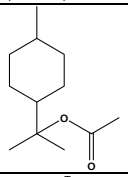
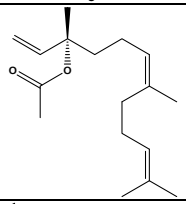
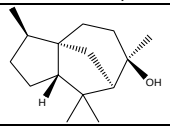
FL-no	EU Register name	Structural formula	MSDI (a) (µg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
02.226	[S-(cis)]-3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol		0.049	Class I A3: Intake below threshold	4)	8)	
02.230	Terpineol	 alfa Terpineol shown	1200	Class I A3: Intake below threshold	4)	7)	a)
02.253 1850	2,4-Dimethyl-4-Nonanol		0.24	Class I A3: Intake below threshold	4)	7)	
09.614	Linalyl valerate		0.43	Class I A3: Intake below threshold	4)	6)	
09.617	p-Menthan-8-yl acetate		0.012	Class I A3: Intake below threshold	4)	6)	
09.671	Nerolidyl acetate		0.061	Class I A3: Intake below threshold	4)	6)	
02.120	Cedrol		13	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		

Table 8: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA FGE.18Rev2 and EFSA FGE.75 Rev1) (EFSA, 2011 and EFSA, 2009)

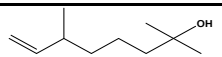
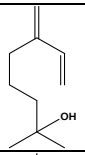
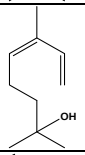
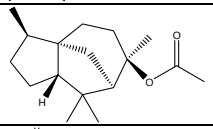
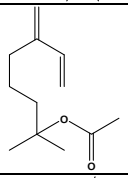
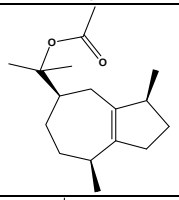
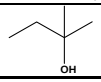
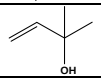
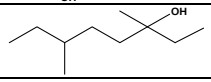
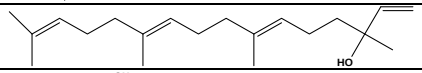
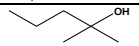
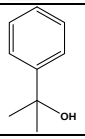
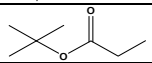
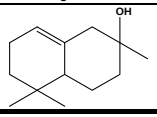
FL-no	EU Register name	Structural formula	MSDI (a) (µg/*capita* per day)	Class (b) Evaluation procedure path (c)	Outcome on the named compound [(d) or (e)]	Outcome on the material of commerce [(f), (g) or (h)]	Evaluation remarks
02.144	2,6-Dimethyloct-7-en-2-ol		0.0012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
02.185	Myrcenol		0.012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
02.191	Ocimenol		0.012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
09.171	Cedryl acetate		0.99	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
09.669	Myrcenyl acetate		8.6	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
09.808	Guaiyl acetate		0.0012	Class I B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		
02.041	2-Methylbutan-2-ol		2.7	Class II A3: Intake below threshold	(d)	(f)	

Table 8: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA FGE.18Rev2 and EFSA FGE.75 Rev1) (EFSA, 2011 and EFSA, 2009)

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
02.052	2-Methylpropan-2-ol		0.012	Class II A3: Intake below threshold	(d)	(f)	
02.123	2-Methylbut-3-en-2-ol		0.0012	Class II A3: Intake below threshold	(d)	(f)	
02.147	3,6-Dimethyloctan-3-ol		0.0012	Class II A3: Intake below threshold	(d)	(g)	
02.150	Geranyl linalool		0.026	Class II A3: Intake below threshold	(d)	(f)	
02.181	2-Methylpentan-2-ol		0.12	Class II A3: Intake below threshold	(d)	(f)	
02.184	3-Methylpentan-3-ol		0.0012	Class II A3: Intake below threshold	(d)	(f)	
02.203	2-Phenylpropan-2-ol		0.0012	Class II A3: Intake below threshold	(d)	(f)	
09.356	1,1-Dimethylethyl propionate		0.0012	Class II A3: Intake below threshold	(d)	(f)	
02.197	1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethylnaphthalen-2-ol		0.026	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		

(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 / capita 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.

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ABBREVIATIONS

CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DNA	deoxyribonucleic acid
EPA	United States Environmental Protection Agency
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
i.p.	intraperitoneal
IR	infrared spectroscopy
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MSDI	maximised survey-derived daily intake
mTAMDI	modified theoretical added maximum daily intake
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PCE	polychromatic erythrocyte
SCE	sister chromatic exchange
SCF	Scientific Committee on Food
WHO	World Health Organization