European Food Safety Authority

The EFSA Journal (2009) 1033, 1-19

SCIENTIFIC OPINION

Flavouring Group Evaluation 89 (FGE.89):

Consideration of phenyl-substituted aliphatic tertiary alcohols and related aldehydes and esters evaluated by JECFA (63rd and 68th meetings) structurally related to aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in FGE.18Rev1 (2009)

Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

(Question No EFSA-Q-2008-309)

ADOPTED ON 26 MARCH 2009

PANEL MEMBERS

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SUMMARY

The Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) was asked 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.

The Panel concluded that the three substances in the JECFA flavouring group of phenyl-substituted aliphatic alcohols and related aldehydes and esters from their 63rd meeting and the seven substances in the JECFA flavouring group of aliphatic acyclic and alicyclic terpenoid tertairy alcohols and

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structurally related substances from their 68th meeting are structurally related to one substance in the group of aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by the European Food Safety Authority (EFSA) in the Flavouring Group Evaluation 18, Revision 1 (FGE.18Rev1).

Further 19 substances were evaluated by the JECFA at their 63rd meeting. These substances are considered in FGE.55: "Consideration of phenyl-substituted aliphatic alcohols and related aldehydes and esters". Further eight substances were evaluated by the JECFA at their 68th meeting. These substances do not contain a phenyl group.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 10 substances considered in this FGE. For all 10 substances European production figures were available and the European exposure estimates could be calculated based on Maximised Survey-derived Daily Intake (MSDI), which for all substances were below the threshold of concern for structural class I.

For six substances [FL-no: 02.037, 2.042, 09.086, 09.227, 09.232 and 09.509], use levels have been provided by the Industry. The modified Theoretical Added Maximum Daily Intake (mTAMDI) figures calculated were above the threshold of concern for structural class I. For these six substances more reliable exposure data are needed. On the basis on such additional data these flavouring substances should be reconsidered using the Procedure. For the remaining four substances [FL-no: 02.035, 02.108, 09.029 and 09.484] use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 10 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including purity and identity are available for all the 10 JECFA evaluated substances.

For the 10 JECFA evaluated phenyl-substituted aliphatic alcohols and related esters [FL-no: 02.035, 02.037, 02.042, 02.108, 09.029, 09.086, 09.227, 09.232, 09.484 and 09.509], the Panel agrees with the JECFA conclusion "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

KEYWORDS

Flavourings, safety, JECFA, 63rd meeting, 68th meeting, phenyl-substituted aliphatic tertiary alcohols and related aldehydes and esters.

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2009/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

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

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

In the period 2000 – 2008, during its 55th, 57th, 59th, 61st, 63rd, 65th, 68th and 69th meetings, the JECFA evaluated about 1000 substances which are in the EU Register.

TERMS OF REFERENCE

EFSA is requested to consider the JECFA evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a). These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC (EC, 1999a) and its consecutive amendments.

ACKNOWLEDGEMENT

European Food Safety Authority wishes to thank the members of the Working Groups on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Wilfried Bursch, Angelo Carere, Riccardo Crebelli, Karl-Heinz Engel, Henrik Frandsen, Jørn Gry, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Catherine Leclercq, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Gerard Pascal, Iona Pratt, Gerrit Speijers, Harriet Wallin.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the "JECFA Procedure". The Scientific Panel on Food 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 considerations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance.

Intake

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

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only 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, 2006c).

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

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

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

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

"The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 microgram per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 microgram per day?") (JECFA, 1999b).

In line with the Opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 microgram per person per day.

Genotoxicity

As reflected in the Opinion of SCF (SCF, 1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *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 consideration by the Panel could lead to a different opinion than that of the JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

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

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

At their 63rd meeting, the JECFA has evaluated a group of 22 flavouring substances consisting of phenyl-substituted aliphatic alcohols and related aldehydes and esters. Nineteen of these are secondary alcohols and have been considered in FGE.55. This consideration will therefore only deal with the remaining three JECFA evaluated substances from their 63rd meeting.

At their 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. Eight of these substances do not contain a phenyl group and will be considered in another FGE. This consideration will therefore only deal with seven JECFA evaluated flavouring substances consisting

of phenyl-substituted aliphatic tertiary alcohols and related aldehydes and esters from their 68th meeting.

1.1.2. EFSA Considerations

In this FGE, the Panel considered a total of 10 JECFA evaluated substances, one tertiary alcohol [FL-no: 02.108] and two esters of tertiary alcohols [FL-no: 09.029 and 09.484] evaluated by the JECFA at their 63rd meeting and three tertiary alcohols [FL-no: 02.035, 02.037 and 02.042] and four esters of tertiary alcohols [FL-no: 09.086, 09.227, 09.232 and 09.509] evaluated by the JECFA at their 68th meeting. The Panel concluded that all 10 substances in the two JECFA groups were structurally related to a tertiary aromatic alcohol [FL-no: 02.203] evaluated by EFSA in FGE.18Rev1. Consequently, data in FGE.18Rev1 are used to support the current consideration.

1.2. Isomers

1.2.1. JECFA Status

One flavouring substance [FL-no: 02.037] has a chiral centre.

1.2.2. EFSA Considerations

The CAS register number (CASrn) specifies the stereoisomerism.

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 10 substances (JECFA, 2005b; JECFA, 2008c) (see Table 1).

1.3.2. EFSA Considerations

The available specifications are considered adequate for all ten substances. According to the JECFA the minimum assay value is 90 % for 2-(4-methylphenyl)propan-2-ol [FL-no: 02.042] with 9-11 % of the secondary component, isopropenyltoluene [FL-no: 01.010] (1-isopropenyl-4-methylbenzene), and the minimum assay value is 93 % for 2-methyl-1-phenyl-2-propyl formate [FL-no: 09.086] with 5-7 % of alpha,alpha-dimethylphenethyl alcohol [FL-no: 02.035] (2-methyl-1-phenylpropan-2-ol). The Panel does not find that this will give rise to concern.

2. Intake Estimations

2.1. JECFA Status

For all 10 substances evaluated through the JECFA Procedure intake data are available for the EU.

2.2. EFSA Considerations

For six of the 10 JECFA evaluated substances normal and maximum use levels have been provided by the Flavour Industy [FL-no: 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] (EFFA, 2006k; EFFA, 2006q; EFFA, 2007a) (see Table 2.1.1). Based on these normal use levels, mTAMDI figures (see Table 2.2.2) can be calculated (EC, 2000a; EFSA, 2004d).

Table 2.1.1 Normal and Maximum use levels (mg/kg) available for the JECFA evaluated substances in FGE.89

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
02.037	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
02.042	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.086	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.227	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.232	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.509	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25

Table 2.2.2 Estimated intakes based on the MSDI and the mTAMDI approach

FL-no	EU Register name	MSDI – EU (µg/capita/day)	MSDI – USA (µg/capita/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.035	2-Methyl-1-phenylpropan-2-ol	19	12		Class I	1800
02.037	3-Methyl-1-phenylpentan-3-ol	0.012	0.1	3900	Class I	1800
02.042	2-(4-Methylphenyl)propan-2-ol	9.6	0.01	3900	Class I	1800
02.108	2-Methyl-4-phenylbutan-2-ol	3.4	0.01		Class I	1800
09.029	1,1-Dimethyl-3-phenylpropyl acetate	0.34	0.04		Class I	1800
09.086	2-Methyl-1-phenyl-2-propyl formate	0.12	0.4	3900	Class I	1800
09.227	1,1-Dimethyl-2-phenethyl acetate	47	574	3900	Class I	1800
09.232	1,1-Dimethyl-2-phenethyl butyrate	110	1020	3900	Class I	1800
09.484	1,1-Dimethyl-3-phenylpropyl isobutyrate	1.5	1		Class I	1800
09.509	1-Methyl-1-phenethyl isobutyrate	0.012	ND	3900	Class I	1800

3. Genotoxicity Data

No relevant genotoxicity data were available for the three substances under consideration evaluated by the JECFA at the 63rd meeting (JECFA, 2006a). For the seven substances under consideration evaluated by the JECFA at the 68th meeting the following data are available.

3.1. Genotoxicity Studies – Text Taken[1] from the JECFA 68th Meeting (JECFA, 2008b)

(i) In vitro

Negative results were reported in the Ames assay for 1-phenyl-3-methyl-3-pentanol [FL-no: 02.037] and alpha,alpha-dimethylphenethyl formate [FL-no: 09.086] tested at concentrations of up to 3.6 and 1.0 mg/plate, respectively, with and without metabolic activation in several strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) (Wild et al., 1983; Asquith, 1989a).

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

The absence of mutagenic activity related to terpenoids is further supported by the negative results reported for two structurally similar flavouring agents, linalyl acetate [FL-no: 09.013] and linalyl propionate [FL-no: 09.130], which have been previously evaluated by the Committee. No mutagenic potential was observed when *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 were incubated with 0, 33, 100, 333, 1000 or 5000 microgram linalyl propionate/plate in the presence or absence of metabolic activation (Sololowski, 2004). No chromosomal aberrations were observed when linalyl acetate at 0, 10, 33, 56, 100, 130 or 180 microgram/ml was incubated with human peripheral lymphocytes for 3 h with 24- and 48-h fixation times, with or without metabolic activation (Bertens, 2000).

(ii) In vivo

The potential of 1-phenyl-3-methyl-3-pentanol [FL-no: 02.037] to induce sex-linked recessive lethal mutations in adult *Drosophila melanogaster* was studied in the Basc test. Mutation frequency was unaffected when flies were exposed to a 0 or 20 mmol/l (3565 microgram/ml) solution of 1-phenyl-3-methyl-3-pentanol for 3 days (Wild et al., 1983).

In a micronucleus test, groups of four male and female NMRI mice (number per sex not reported), administered single intraperitoneal doses of 0, 357, 624, 891 or 1416 mg 1-phenyl-3-methyl-3-pentanol [FL-no: 02.037]/kg bw, demonstrated no increase in micronucleated erythrocytes in bone marrow samples obtained 30 h post-administration (Wild et al., 1983).

(iii) Conclusion on genotoxicity

The testing of these representative materials *in vitro* in bacterial test systems (Ames assay) and *in vivo* in mammalian (micronucleus test) systems showed no evidence of mutagenic or genotoxic potential. These results are further supported by the lack of positive findings in the Basc test.

3.2. Genotoxicity Considerations for the One Supporting Substance in FGE.18Rev1 (EFSA, 2009a)

For the supporting substance 2-phenylpropan-2-ol [FL-no: 02.203] from FGE.18Rev1 no relevant genotoxicity data are available. However, for the other tertiary alcohols in FGE.18Rev1 the genotoxicity data available considered valid do not give rise to any safety concern with respect to genotoxicity and in addition the Panel in its evaluation of FGE.18Rev1 anticipated that the candidate substances would be metabolised to innocous products and accordingly were evaluated via the A-side of the Procedure.

3.3. EFSA Considerations

The Panel agrees with the JECFA that the seven tertiary alcohols and related esters evaluated at the 68th JECFA meeting [FL-no: 02.035, 02.037, 02.042, 09.086, 09.227, 09.232 and 09.509] do not show evidence of genotoxic potential. The same is anticipated to apply to the three tertiary alchols and related esters evaluated at the 63rd JECFA meeting [FL-no: 02.108, 09.029 and 09.484] for which no genotoxicity data are available.

4. Application of the Procedure

4.1. Application of the Procedure to Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters by the JECFA (JECFA, 2006a):

According to the JECFA the three substances evaluated at the 63rd meeting and the seven substances evaluated at the 68th meeting all belong to structural class I using the decision tree approach presented by Cramer et al. (1978).

The JECFA concluded all 10 tertiary alcohols and related esters of tertiary alcohols 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 the substances are below the thresholds for their structural class I (step A3).

In conclusion, the JECFA evaluated all 10 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 tertiary alcohols and the esters of tertiary alcohols are summarised in Table 3.1.

4.2. Application of the Procedure to the Group of Structurally Related Substances Evaluated by EFSA (EFSA, 2009a)

The structurally related substance from FGE.18Rev1, 2-phenylpropan-2-ol [FL-no: 02.203], was classified into structural class II using the decision tree approach presented by Cramer et al. (1978).

It was concluded at step A3 that the substance is expected to be metabolised to innocuous products and the estimated daily intake is below the threshold of concern for its stuctural class.

The Panel concluded that this substance is of no safety concern at the estimated level of intake of the flavouring substance, based on the MSDI approach.

4.3. EFSA Considerations

The Panel considers that the candidate and supporting tertiary aromatic alcohols in this group of flavouring agents and those formed via hydrolysis will be metabolised to innocous products via direct conjugation of the hydroxyl group with glucuronic acid and accordingly these substances are evaluated via the A-side of the Procedure. In rabbits administered dimethylphenylcarbinol, a structurally similar compound, 85 % of the original dose was excreted in the urine as the corresponding glucuronic acid conjugate (Robinson et al., 1955).

The Panel agrees with the JECFA in the evaluation of the 10 tertiary alcohols and esters through the Procedure.

5. Conclusion

The Panel concluded that three of the 22 substances evaluated by the JECFA at their 63rd meeting in the flavouring group of phenyl-substituted aliphatic alcohols and related aldehydes and esters as well as seven of the 15 substances evaluated by the JECFA at their 68th meeting in the flavouring group of aliphatic, acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances are structurally related and will be considered together in this FGE.

The 10 substances are structurally related to 2-phenylpropan-2-ol [FL-no: 02.203] evaluated by EFSA in the Flavouring Group Evaluation 18, Revision 1 (FGE.18Rev1; aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters) (EFSA, 2009a). Consequently, data in FGE.18Rev1 are used to support the current consideration.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 10 substances considered in this FGE. For all 10 substances European production figures were available and the European exposure estimates could be calculated based on Maximised Survey-derived Daily Intake (MSDI), which for all substances were below the threshold of concern for structural class I.

For six substances, use levels have been provided by the Industry [FL-no: 02.037, 2.042, 09.086, 09.227, 09.232 and 09.509]. The mTAMDI figures calculated were above the threshold of concern for structural class I. For these six substances more reliable exposure data are needed. On the basis on such additional data these flavouring substances should be reconsidered using the Procedure. For the remaining four substances [FL-no: 02.035, 02.108, 09.029 and 09.484] use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 10 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including purity and identity are available for all the JECFA evaluated substances.

For the 10 JECFA evaluated phenyl-substituted aliphatic alcohols and related esters [FL-no: 02.035, 02.037, 02.042, 02.108, 09.029, 09.086, 09.227, 09.232, 09.484 and 09.509], the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY FOR JECFA EVALUATED SUBSTANCES IN THE PRESENT GROUP (JECFA, 2005B; JECFA, 2008C)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of phenyl-substituted aliphatic tertiary alcohols andrelated aldehydes and esters (JECFA, 2005b; JECFA, 2008c)

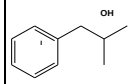
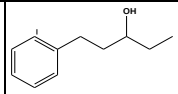
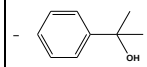
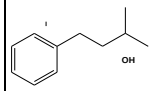
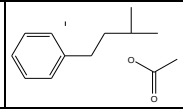
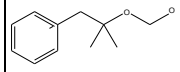
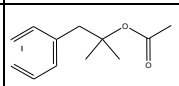
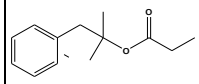
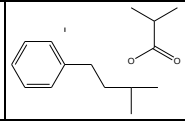
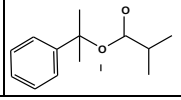
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.035 1653	2-Methyl-1-phenylpropan-2-ol		2393 84 100-86-7	Solid $C_{10}H_{14}O$ 150.22	Practically insoluble or insoluble 1 ml in 1 ml	216 24 IR NMR MS 97 %	n.a. n.a.	
02.037 1649	3-Methyl-1-phenylpentan-3-ol		2883 86 10415-87-9	Liquid $C_{12}H_{18}O$ 178.28	Slightly soluble 1 ml in 1 ml	255 IR MS 98 %	1.508-1.514 0.936-0.940	Racemate.
02.042 1650	2-(4-Methylphenyl)propan-2-ol		3242 530 1197-01-9	Liquid $C_{10}H_{14}O$ 150.22	Slightly soluble 1 ml in 1 ml	64 (0.07 hPa) NMR 90 %	1.516-1.520 0.974-0.980	According to the JECFA: Min. assay value is 90 % and secondary component 9-11 % p-isopropenyltoluene.
02.108 1477	2-Methyl-4-phenylbutan-2-ol		3629 10281 103-05-9	Liquid $C_{11}H_{16}O$ 164.25	Slightly soluble Soluble	144 (111 hPa) NMR 97 %	1.506-1.512 0.960-0.966	
09.029 1460	1,1-Dimethyl-3-phenylpropyl acetate		2735 219 103-07-1	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble Soluble	244 NMR 97 %	1.488-1.490 0.986-0.990 (15°)	
09.086 1654	2-Methyl-1-phenyl-2-propyl formate		2395 353 10058-43-2	Liquid $C_{11}H_{14}O_2$ 178.23	Practically insoluble or insoluble 1 ml in 1 ml	222 NMR 93 %	1.499-1.502 1.024-1.032	According to the JECFA: Min. assay value is 93 % and secondary component 5-7 % alpha,alpha-dimethylphenethyl alcohol.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of phenyl-substituted aliphatic tertiary alcohols andrelated aldehydes and esters (JECFA, 2005b; JECFA, 2008c)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.227 1655	1,1-Dimethyl-2-phenethyl acetate		2392 2077 151-05-3	Solid $C_{12}H_{16}O_2$ 192.26	Practically insoluble or insoluble 1 ml in 1 ml	250 30 NMR 98 %	1.490-1.495 0.995-1.002	
09.232 1656	1,1-Dimethyl-2-phenethyl butyrate		2394 2084 10094-34-5	Liquid $C_{14}H_{20}O_2$ 220.31	Practically insoluble or insoluble 1 ml in 1 ml	255 NMR 95 %	1.484-1.489 0.960-0.981	
09.484 1461	1,1-Dimethyl-3-phenylpropyl isobutyrate		2736 2086 10031-71-7	Liquid $C_{15}H_{22}O_2$ 234.34	Insoluble Soluble	250 NMR 96 %	1.475-1.485 0.949-0.959	
09.509 1657	1-Methyl-1-phenethyl isobutyrate		2388 11828 7774-60-9	Solid $C_{13}H_{18}O_2$ 206.29	Practically insoluble or insoluble 1 ml in 1 ml	 72 NMR 95 %	n.a. n.a.	

1) Solubility in water, if not otherwise stated.

2) Solubility in 95% ethanol, if not otherwise stated.

3) At 1013.25 hPa, if not otherwise stated.

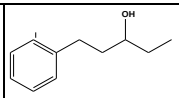
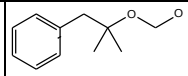
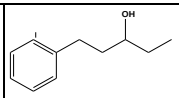
4) At 20°C, if not otherwise stated.

5) At 25°C, if not otherwise stated.

n.a. not appplicable.

TABLE 2: GENOTOXICITY DATA

Table 2: Genotoxicity Data (*in vitro / in vivo*) JECFA

Table 2: Summary of Genotoxicity Data for the 10 Phenyl-substituted Aliphatic Tertiary Alcohols and Related Aldehydes and Esters (JECFA, 2006a; JECFA, 2008b)							
FL-no JECFA-no	**EU Register name JECFA name**	**Structural formula**	**End-point**	**Test system**	**Concentration**	**Results**	**Reference**
In vitro							
02.037 1649	3-Methyl-1-phenylpentan-3-ol 1-Phenyl-3-methyl-3-pentanol		Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538	Up to 3600 microg/ plate	Negative[a]	(Wild et al., 1983)
09.086 1654	2-Methyl-1-phenyl-2-propyl formate Alpha, alpha-Dimethylphenethyl formate		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535 and TA1537	Up to 1000 microg/ plate	Negative[a]	Asquith (1989)
In vivo							
02.037 1649	3-Methyl-1-phenylpentan-3-ol 1-Phenyl-3-methyl-3-pentanol		Sex-linked recessive lethal mutation (Basc test)	*Drosophila melanogaster*	0 or 20 mmol/l (3565 microg/ml)[b]	Negative	(Wild et al., 1983)
			Micronucleus induction	NMRI mice	0, 357, 624, 891 or 1416 mg/kg bw	Negative	(Wild et al., 1983)

[a] *With and without metabolic activation.*

[b] *Calculated using molecular weight of 1-phenyl-3-methyl-3-pentanol = 178.28.*

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of Phenyl-substituted Aliphatic Tertiary Alcohols and Related Aldehydes and Esters (JECFA, 2006a; JECFA, 2008b)

Table 3.1: Summary of safety evaluation of 10 JECFA-evaluated substances (JECFA, 2006a; JECFA, 2008b)

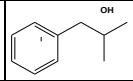
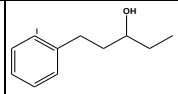
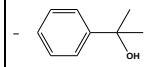
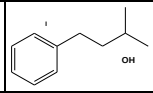
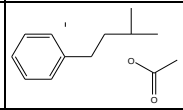
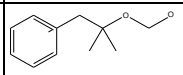
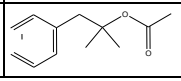
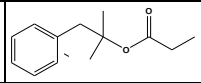
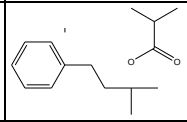
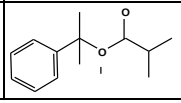
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.035 1653	2-Methyl-1-phenylpropan-2-ol		19 12	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
02.037 1649	3-Methyl-1-phenylpentan-3-ol		0.012 0.1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	Racemate No safety concern at the estimated level of intake as flavouring substance.
02.042 1650	2-(4-Methylphenyl)propan-2-ol		9.6 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
02.108 1477	2-Methyl-4-phenylbutan-2-ol		3.4 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
09.029 1460	1,1-Dimethyl-3-phenylpropyl acetate		0.34 0.04	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
09.086 1654	2-Methyl-1-phenyl-2-propyl formate		0.12 0.4	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
09.227 1655	1,1-Dimethyl-2-phenethyl acetate		47 574	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.

Table 3.1: Summary of safety evaluation of 10 JECFA-evaluated substances (JECFA, 2006a; JECFA, 2008b)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.232 1656	1,1-Dimethyl-2-phenethyl butyrate		110 1020	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
09.484 1461	1,1-Dimethyl-3-phenylpropyl isobutyrate		1.5 1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.
09.509 1657	1-Methyl-1-phenethyl isobutyrate		0.012 ND	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance.	No safety concern at the estimated level of intake as flavouring substance.

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.

2) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day.

3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.

4) No safety concern based on intake calculated by the MSDI approach of the named compound.

5) Data must be available on the substance or closely related substances to perform a safety evaluation.

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ABBREVIATIONS – TO BE CHECKED

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
DTU-NFI	Danish Technical University – National Food Institute
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practise
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
ISS	Istituto Superiore di Sanita
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
No	Number
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
PCE	Polychromatic erythrocyte
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation