European Food Safety Authority

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Flavouring Group Evaluation 53 (FGE.53)

Consideration of phenethyl alcohol, aldehyde, acid and related acetals and esters evaluated by JECFA (59th meeting) structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14 (2005) and one phenoxyethyl ester evaluated in FGE.23 (2006)

(Commission Regulation (EC) No 1565/2000 of 18 July 2000)

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission

(Question No EFSA-Q-2008-032D)

(Adopted on 15 May 2007)

PANEL MEMBERS

Fernando Aguilar, Herman Autrup, Susan Barlow, Laurence Castle, Riccardo Crebelli, Wolfgang Dekant, Karl-Heinz Engel, Nathalie Gontard, David Gott, Sandro Grilli, Rainer Gürtler, John-Christian Larsen, Catherine Leclercq, Jean-Charles Leblanc, Xavier Malcata, Wim Mennes, Maria-Rosaria Milana, Iona Pratt, Ivonne Rietjens, Paul Tobback, Fidel Toldrá

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) is asked to advise the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular the Scientific Panel is requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The present consideration concerns 41 phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances evaluated by the JECFA (59th meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluation of 10 phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated in the Flavouring Group Evaluation 14 (FGE.14) and one phenoxyethyl ester evaluated in Flavouring Group Evaluation 23 (FGE.23).

The Panel concluded that the 41 substances in the JECFA flavouring group of 41 phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances are structurally related to the group of ten phenethyl derivatives evaluated by EFSA in FGE.14 and one phenoxyethyl ester evaluated in FGE.23.

Further two substances [FL-no: 09.704 and 09.712] were evaluated by the JECFA in this group, which may be metabolised to alpha,beta-unsaturated aldehydes and will be considered together with other alpha,beta-unsaturated compounds.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 41 phenylethyl derivatives.

For four substances [FL-no: 06.027, 09.702, 09.783 and 16.041] the JECFA evaluation is only based on Maximised Survey-derived Daily Intake (MSDI) values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances.

For all 41 substances evaluated through the Procedure use levels are needed to calculate the modified Theorical Added Maximum Daily Intake (mTAMDI) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 41 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications are available for 31 of the materials of commerce. For nine substances [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.772, 09.785, 09.791 and 16.041] information on the stereoisomeric composition is lacking and for three substances [FL-no: 06.007, 06.027 and 09.805] further information on the composition is requested.

Thus for 12 substances [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.702, 09.772, 09.783, 09.785, 09.791, 09.805 and 16.041] the Panel has reservations (only USA production volumes available and/or missing data on specifications and/or isomerism/composition). For the remaining 29 substances [FL-no: 02.019, 05.030, 05.042, 05.044, 06.006, 06.024, 08.038, 08.049, 09.031, 09.083, 09.137, 09.168, 09.261, 09.262, 09.407, 09.427, 09.466, 09.487, 09.496, 09.703, 09.707, 09.758, 09.784, 09.786, 09.787, 09.788, 09.789, 09.797 and 09.804] the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

KEYWORDS

Phenethyl, phenoxyethyl, JECFA 59th meeting, FGE.14, FGE.23.

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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 2006/252/EC (EC, 2006). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

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

Commission Regulation (EC) No1565/2000 lays down that substances that are contained in the Register and will be classified in the future by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) so as to present no safety concern at current levels of intake will be considered by the European Food Safety Authority (EFSA), who may then decide that no further evaluation is necessary.

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

TERMS OF REFERENCE

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

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000), hereafter named the “EFSA Procedure”. This Procedure is based on the opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b) hereafter named the “JECFA Procedure”. The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated

levels of intake, whether additional data are required or whether certain substances should not be put through the EFSA Procedure.

The following issues are of special importance.

Intake

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

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

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

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

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

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

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 evaluation by the Panel could lead to a different opinion than that of the JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

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

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has evaluated a group of 43 flavouring substances consisting of phenethyl alcohol, aldehyde, acid, and related acetals and esters. Two of the substances [FL-no: 09.704 and 09.712] may be metabolised to alpha,beta-unsaturated aldehydes and will be considered together with alpha,beta-unsaturated aldehydes and ketones. This consideration will therefore only deal with 41 JECFA evaluated substances.

1.1.2. EFSA Considerations

The Panel concluded that all the 41 substances in the JECFA flavouring group of phenethyl alcohol, aldehyde, acid, and related acetals and esters are structurally related to the group of ten phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in the Flavouring Group Evaluation 14 (FGE.14) and one phenoxyethyl ester evaluated in the Flavouring Group Evaluation 23 (FGE.23).

1.2. Isomers

1.2.1. JECFA Status

11 Register substances in the group of the JECFA evaluated phenethyl alcohol, aldehyde, acid, and related acetals and esters have possibility for stereoisomerism [FL-no: 06.007, 06.016, 06.027, 06.036, 09.496, 09.538, 09.772, 09.785, 09.791, 09.805 and 16.041].

1.2.2. EFSA Considerations

Information is lacking about the stereoisomerism for nine of the 11 substances [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.772, 09.785, 09.791 and 16.041].

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 41 substances (JECFA, 2001c). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate except that information on stereoisomerism is lacking for [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.772, 09.785, 09.791 and 16.041], see Section 1.2, and further information on the composition of [FL-no: 06.007, 06.027 and 09.805] is requested.

2. Intake Estimations

2.1. JECFA Status

For 37 substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining four substances production figures are only available for the USA.

2.2. EFSA Considerations

As production figures are only available for the USA for four substances, MSDI values for the EU cannot be calculated for these [FL-no: 06.027, 09.702, 09.783 and 16.041].

3. Genotoxicity Data

3.1. Genotoxicity Studies - Text Taken from the JECFA (JECFA, 2003a)

Tests for genotoxicity have been performed on seven representative phenethyl alcohol derivatives and three phenoxyethyl alcohol derivatives.

In vitro

Phenethyl alcohol [FL-no: 02.019], phenylacetaldehyde [FL-no: 05.030], phenylacetic acid [FL-no: 08.038], ethyl phenylacetate [FL-no: 09.784], isobutyl phenylacetate [FL-no: 09.788], isoamyl phenylacetate [FL-no: 09.789] and *para*-tolylacetaldehyde [FL-no: 05.042] have been tested for their ability to induce reverse mutation in various strains of *Salmonella typhimurium* (e.g., TA98, TA100, TA1535, TA1537 and TA1538) in the presence or absence of an exogenous metabolic activation system. None of the compounds was mutagenic when tested at concentrations up to 5000 µg/ml or 50 mg/plate (Oda et al., 1979; Florin et al., 1980; Rapson et al., 1980; Ishidate et al., 1984; Heck et al., 1989; Kato et al., 1989; Fujita et al., 1994). No reverse mutation was seen when various strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) were incubated with ethyl (*para*-tolyloxy)acetate [FL-no: 09.797] at up to 3600 µg per plate (Wild et al., 1983), 2-phenoxyethyl isobutyrate [FL-no: 09.487] at 3600 µg per plate (Wild et al., 1983) or sodium 2-(4-methoxyphenoxy)propanoate [FL-no: 16.041] at up to 5000 µg per plate (Varley, 1985), with or without metabolic activation.

Tests of the ability of ethyl phenylacetate [FL-no: 09.784] and isoamyl phenylacetate [FL-no: 09.789] to induce mutation in *Bacillus subtilis* H17 and M45 were inconclusive. In a study in which ethyl phenylacetate was incubated with *B. subtilis* H17 and M45 at 21 µg per disc, the difference in the zone of inhibition (0.8 mm) between the two strains indicated that it was not active (Oda et al., 1979). In a study with a lower concentration, ethyl phenylacetate was incubated at a concentration of 20 µl per disc with *B. subtilis* H17 and M45 in the same assay. The difference in the zone of inhibition (> 8 mm) between the two strains was considered to provide evidence of mutagenicity (Yoo, 1986). Contradictory data have also been reported with isoamyl phenylacetate [FL-no: 09.789]. When 20 µg per disc were incubated with *B. subtilis* H17 and M45, a weak (2–5 mm difference) positive response was reported by Oda et al. (Oda et al., 1979), while Yoo (Yoo, 1986) reported a negative response with 20 µl per disc.

Phenylacetaldehyde [FL-no: 05.030] was tested in *E. coli* strain WP2uvrA/pKM101 with preincubation (Kato et al., 1989), and *para*-tolylacetaldehyde [FL-no: 05.042] was studied in *E. coli* strain PQ37 (Ohshima et al., 1989), both at unspecified concentrations. There was no evidence of mutagenicity in either assay. In another assay, 200–1600 µg per plate of ethyl phenylacetate showed no evidence of mutagenicity when incubated with *E. coli* WP2uvrA (Yoo, 1986). The contradictory results reported by Yoo (Yoo, 1986) and Oda et al. (Oda et al., 1979), the negative result in the WP2 uvrA strain and the fact that phenethyl alcohol is bactericidal in *E. coli* (Treick & Konetzka, 1964; Brunner & Treick, 1982) support the conclusion that the results with *B. subtilis* H17 and M45 should not be used in the overall assessment of the genotoxic potential of these substances.

No increase in sister chromatid exchange frequency was observed when human whole blood lymphocyte cultures were exposed to 2-phenethyl alcohol [FL-no: 02.019] for 72 h (Norppa & Vainio, 1983). Also, no increase in unscheduled DNA synthesis was noted when rat hepatocytes were incubated with phenylacetic acid (Heck et al., 1989). Incubation of ethyl phenylacetate at 1000

µg/ml with Chinese hamster fibroblasts for 48 h caused chromosomal aberrations in 3% of cells. On the basis of a threshold of positivity of > 10%, ethyl phenylacetate gave negative results in this assay (Ishidate et al., 1984).

In vivo

The results of tests for genotoxicity *in vivo* with phenylacetate ester and 2-phenoxyethyl isobutyrate [FL-no: 09.487] and sodium 2-(4-methoxyphenoxy)propanoate [FL-no: 16.041] were negative. No significant increase in the number of micronucleated polychromatic erythrocytes was seen in mice given intraperitoneal injections of 2-phenoxyethyl isobutyrate at 620–1900 mg/kg bw (Wild et al., 1983). In another test, sodium 2-(4-methoxyphenoxy)propanoate was given to mice by gavage at doses of 500–2000 mg/kg bw. An increased frequency of micronucleated polychromatic erythrocytes was found in males at 500 mg/kg bw at 24 h (Asquith & Pickering, 1985).

A phenyl acetate ester that was not included in this group of substances, isoeugenol phenylacetate, was also tested for its ability to induce micronucleus formation. Groups of male and female NMRI mice were given the compound at doses of 1100–2800 mg/kg bw by intraperitoneal injection. After 30 h, they were killed, and the mean number of micronucleated polychromatic erythrocytes per 1000 normochromatic erythrocytes was calculated. No effect was seen at any dose. Furthermore, the frequency of sex-linked lethal mutations was not increased when *Drosophila melanogaster* were fed a solution of isoeugenol phenylacetate at 25 mmol/l for 3 days (Wild et al., 1983).

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

3.2. Genotoxicity Studies - Text Taken from EFSA (EFSA, 2005e)

In vitro / in vivo

Valid *in vitro* mutagenicity and/or genotoxicity data are available for EFSA evaluated substance [FL-no: 02.166] and for two JECFA evaluated substances [FL-no: 02.019 and 09.784]. There are neither *in vivo* mutagenicity/genotoxicity data available for the EFSA evaluated substances of the present flavouring group evaluation nor for the substances previously evaluated by the JECFA.

Valid *in vitro* and limited *in vivo* mutagenicity data are available for isoeugenyl phenylacetate, a phenyl acetate ester structurally related to the EFSA evaluated substances in this evaluation (Wild et al., 1983).

For the EFSA evaluated substance 2-(4-hydroxyphenyl)ethan-1-ol [FL-no: 02.166] there are data available from a Comet assay in oxidative stress sensitive PC human prostate cancer cells (PC3) in which the substance at any of the concentrations tested did not increase the value of oxidative DNA damage (DNA strand breaks) as compared to control cells. On the contrary, at relatively high concentrations the substance was found to decrease DNA-damage induced by hydrogen peroxide. However, results indicated that the substance induced lipid peroxidation and decreased the

antioxidant capacity of the cells. These effects on enzymes may be attributed to a pro-oxidant activity of 2-(4-hydroxyphenyl)ethan-1-ol (Quiles et al., 2002).

Data on phenethyl alcohol[1] (syn. 2-phenylethan-1-ol) [FL-no: 02.019] and ethyl phenylacetate [FL-no: 09.784][2] are considered representative for some of the EFSA evaluated substances (see footnotes). They have been tested for their ability to induce reverse mutations in various strains of *Salmonella typhimurium* (e.g. TA92, TA94, TA97, TA98, TA100, TA1535, TA1537 and TA1538) in the presence or absence of an exogenous metabolic activation system. None of the compounds was mutagenic in any of the tester strains when tested at concentrations up to 5000 microgram/plate.

There are some positive findings with two of the potential hydrolysis products of the two EFSA evaluated acetals [FL-no: 06.078 and 06.080] *in vitro* and *in vivo*, ethanol and acetaldehyde. The genotoxicity of these two compounds is well known. However, they both do occur naturally in many foods in mg amount (apart from alcoholic beverages) (TNO, 2000) and, based on the MSDI approach, the estimated intakes of EFSA evaluated flavouring substances which might be expected to be hydrolysed to the corresponding alcohols and aldehydes are much lower. Further, ethanol and acetaldehyde are endogenous. So, the daily *in vivo* formation of ethanol has been estimated to be 40-80 mg/kg body weight/day (JECFA, 1997a).

For the JECFA evaluated substances, there are *in vitro* genotoxicity studies available from test systems other than bacterial, which were reported to be negative: no increase in sister chromatid exchange frequency was reported in human whole blood lymphocyte cultures exposed to phenethyl alcohol [FL-no: 02.019] for 72 hours; and ethyl phenylacetate [FL-no: 09.784] did not cause chromosomal aberrations in Chinese hamster fibroblasts when incubated for 48 hours.

From the available *in vitro* and *in vivo* mutagenicity data on the additional structurally related substance isoeugenyl phenylacetate there is no indication of a mutagenic activity: a negative result was reported in an Ames Test in various strains of *Salmonella typhimurium* (e.g. TA98, TA100, TA1535, TA1537 and TA1538) with and without metabolic activation and the substance was reported not to induce sex-linked recessive (lethal) mutations in *Drosophila melanogaster in vivo* (Wild et al., 1983).

There are no genotoxicity studies available on 2-phenethyl acetals, neither from the group of EFSA evaluated nor of JECFA evaluated substances.

Conclusion on Genotoxicity

Overall the genotoxicity data available are not sufficient to evaluate the genotoxicity adequately, however, the data available on candidate and supporting substances do not give rise to concern with respect to genotoxicity.

[1] *JECFA-evaluated 2-(4-hydroxyphenyl)ethanol [FL-no: 02.166]*

[2] *JECFA-evaluated pentyl phenylacetate [FL-no: 09.761], menthyl phenylacetate [FL-no: 09.620], hex-2-enyl phenylacetate [FL-no: 09.400]*

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

3.3. EFSA Considerations

There are valid *in vitro* genotoxicity data available for one [FL-no: 02.166] of the ten substances evaluated in FGE.14. Valid *in vitro* and limited *in vivo* mutagenicity data are available for two of the JECFA evaluated substances and on a further structurally related substance (isoeugenyl phenylacetate). For the EFSA evaluated substance, 2-(4-hydroxyphenyl)ethan-1-ol [FL-no: 02.166], the only available study gave no indication of a genotoxic potential *in vitro*.

There are no genotoxicity studies available for the phenoxyethyl ester [FL-no: 09.687] evaluated in FGE.23.

From the various studies carried out with the JECFA evaluated substances, there is no indication of a genotoxic activity of the phenethyl alcohols, phenylacetic acids and related esters in bacterial mutation assays.

Overall the Panel concluded that the genotoxicity data available are not sufficient to evaluate the genotoxicity adequately, however, the data available do not preclude evaluation of the 41 JECFA evaluated phenetyl alcohol, aldehyde, acid and related acetals and esters through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 41 Phenylethyl Alcohol and Related Substances Evaluated by the JECFA (JECFA, 2003a)

According to the JECFA 37 of the substances belong to structural class I and four to structural class III using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded 40 of the substances at step A3 in the JECFA Procedure – i.e. the substances are expected to be metabolised to innocuous products (step 2) and the intakes for all substances are below the thresholds for their structural classes I and III (step A3).

One substance was concluded at step A5 – i.e. the intake is above the threshold for the structural class, the substance is not endogenous, but a NOAEL is available that can provide an adequate margin of safety to the estimated intake of the substance [FL-no: 09.487].

In conclusion, the JECFA evaluated all 41 substances as to be of no safety concern at the estimated levels of intakes as flavouring substances based on the MSDI approach.

The evaluations of the 41 phenetyl alcohol, aldehyde, acid and related acetals and esters are summarised in Table 3.1: Summary of Safety Evaluation of 41 Phenylethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters (JECFA, 2003a).

4.2. Application of the Procedure to Ten Phenethyl Derivatives and the Phenoxyethyl Ester by EFSA (EFSA, 2005e)

Ten candidate substances were evaluated in FGE.14. All ten substances are classified into structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The ten substances were all concluded 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 class (step A3).

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

The stepwise evaluations of the ten substances evaluated in FGE.14 and the phenoxyethyl ester evaluated in FGE.23 are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14 and One Phenoxyethyl Ester Evaluated in FGE.23).

4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 41 substances in the group of phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances.

5. Conclusion

The Panel concluded that the 41 substances in the JECFA flavouring group of 41 phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances are structurally related to the group of ten phenethyl derivatives evaluated by EFSA in FGE.14 and one phenoxyethyl ester evaluated in FGE.23.

Further two substances [FL-no: 09.704 and 09.712] were evaluated by the JECFA in this group, which may be metabolised to alpha,beta-unsaturated aldehydes and will be considered together with other alpha,beta-unsaturated compounds.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 41 phenylethyl derivatives.

For four substances [FL-no: 06.027, 09.702, 09.783 and 16.041] the JECFA evaluation is only based on MSDI values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances.

For all 41 substances evaluated through the Procedure use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 41 JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications are available for 31 of the 41 materials of commerce. For nine substances [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.772, 09.785, 09.791 and 16.041] information on the stereoisomeric composition is lacking and for three substances [FL-no: 06.007, 06.027 and 09.805] further information on the composition is requested.

Thus, for 12 substances [FL-no: 06.007, 06.016, 06.027, 06.036, 09.538, 09.702, 09.772, 09.783, 09.785, 09.791, 09.805 and 16.041] the Panel has reservations (only USA production volumes available and/or missing data on specifications and/or isomerism/composition). For the remaining 29 substances [FL-no: 02.019, 05.030, 05.042, 05.044, 06.006, 06.024, 08.038, 08.049, 09.031, 09.083, 09.137, 09.168, 09.261, 09.262, 09.407, 09.427, 09.466, 09.487, 09.496, 09.703, 09.707, 09.758, 09.784, 09.786, 09.787, 09.788, 09.789, 09.797 and 09.804] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY FOR JECFA EVALUATED SUBSTANCES IN THE PRESENT GROUP

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 41 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances

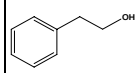
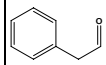
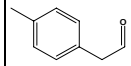
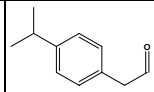
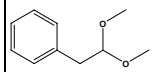
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.019 987	2-Phenylethan-1-ol		2858 68 60-12-8	Liquid $C_8H_{10}O$ 122.17	Slightly soluble 1 mL in 2 mL 50% ethanol	219-221 IR 98 %	1.529-1.535 1.017-1.020	
05.030 1002	Phenylacetaldehyde		2874 116 122-78-1	Liquid C_8H_8O 120.15	Slightly soluble 1 mL in 2 mL 80% ethanol	195 NMR 95 %	1.524-1.545 1.023-1.045	
05.042 1023	p-Tolylacetaldehyde		3071 130 104-09-6	Liquid $C_9H_{10}O$ 134.18	Insoluble Miscible	210 NMR 95 %	1.530-1.549 1.010-1.016	
05.044 1024	p-Isopropyl phenylacetaldehyde		2954 132 4395-92-0	Liquid $C_{11}H_{14}O$ 162.23	Insoluble Miscible	230-243 NMR 97 %	1.515-1.525 0.965-0.975	
06.006 1003	1,1-Dimethoxy-2-phenylethane		2876 40 101-48-4	Liquid $C_{10}H_{14}O_2$ 166.22	Insoluble 1 mL in 2 mL 70% ethanol	219 IR 95 %	1.492-1.498 1.000-1.006	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 41 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances

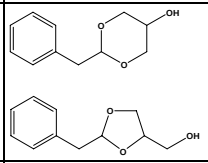
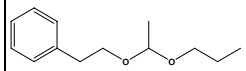
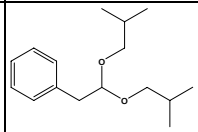
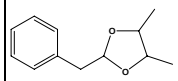
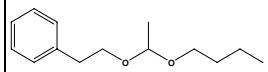
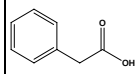
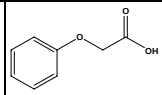
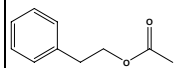
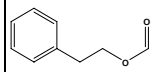
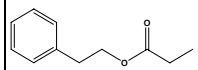
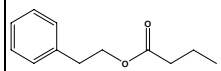
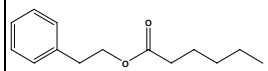
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
06.007 1004	Phenylacetaldehyde glyceryl acetal 6)		2877 41 29895-73-6	Liquid $C_{11}H_{14}O_3$ 194.23	Insoluble Miscible	358 NMR 95 %	1.524-1.536 1.158-1.168	CASrn in Register refers to named substance; "Incompletely Defined Substance".
06.016 1000	1-Phenylethoxy-1-propoxy ethane 6)		2004 511 7493-57-4	Liquid $C_{13}H_{20}O_2$ 208.30	Miscible	272 NMR 96 %	1.475-1.483 0.944-0.950	CASrn in Register refers to the racemate.
06.024 1006	1,1-Di-isobutoxy-2-phenylethane		3384 595 68345-22-2	Liquid $C_{16}H_{26}O_2$ 250.38	Insoluble Miscible	240 IR 97 %	1.468-1.476 0.928-0.936	
06.027 1005	4,5-Dimethyl-2-benzyl-1,3-dioxolan 6)		2875 669 5468-06-4	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble Miscible	118 (13 hPa) NMR 93 %	1.496-1.512 1.030-1.040	CASrn does not specify stereoisomers. According to JECFA: Min. assay value is "93%" and secondary components "butane-2,3-diol".
06.036 1001	1-Butoxy-1-(2-phenylethoxy)ethane 6)		3125 10007 64577-91-9	Liquid $C_{14}H_{22}O_2$ 222.33	Miscible	280-282 NMR 97 %	1.467-1.481 0.923-0.935	CASrn in Register refers to the racemate.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 41 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances

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
08.038 1007	Phenylacetic acid		2878 672 103-82-2	Solid $C_8H_8O_2$ 136.15	Slightly soluble Soluble	265 76-78 IR 99 %	n.a. n.a.	
08.049 1026	Phenoxyacetic acid		2872 2005 122-59-8	Solid $C_8H_8O_3$ 152.15	Slightly soluble Soluble	285 98-103 NMR 98 %	n.a. n.a.	
09.031 989	Phenethyl acetate		2857 221 103-45-7	Liquid $C_{10}H_{12}O_2$ 164.20	Insoluble 1 mL in 2 mL 70% ethanol	232 IR 98 %	1.496-1.502 1.030-1.034	
09.083 988	Phenethyl formate		2864 350 104-62-1	Liquid $C_9H_{10}O_2$ 150.18	Slightly soluble Miscible	226 NMR 96 %	1.503-1.513 1.056-1.065	
09.137 990	Phenethyl propionate		2867 418 122-70-3	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	244-245 NMR 97 %	1.489-1.499 1.010-1.021	
09.168 991	Phenethyl butyrate		2861 506 103-52-6	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble Miscible	238 NMR 97 %	1.487-1.493 0.991-0.994	
09.261 995	2-Phenethyl hexanoate		3221 10882 6290-37-5	Liquid $C_{14}H_{20}O_2$ 220.31	Insoluble Miscible	263 NMR 98 %	1.480-1.488 0.969-0.980	

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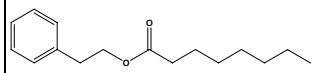
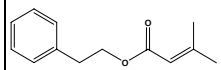
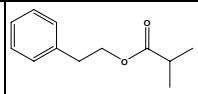
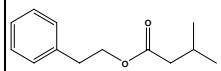
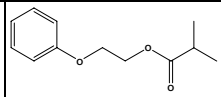
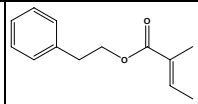
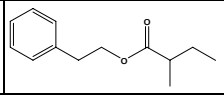
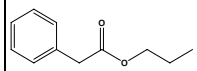
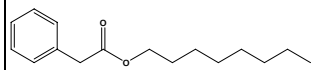
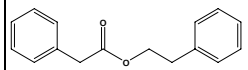
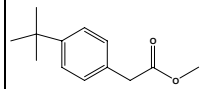
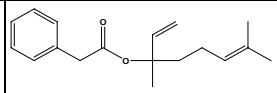
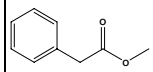
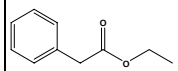
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.262 996	Phenethyl octanoate		3222 10884 5457-70-5	Liquid $C_{16}H_{24}O_2$ 248.37	Insoluble Miscible	295.5 NMR 98 %	1.479-1.486 0.973-0.977 (20°)	
09.407 998	2-Phenethyl 3-methylcrotonate		2869 246 42078-65-9	Liquid $C_{13}H_{16}O_2$ 204.27	Insoluble Miscible	285 NMR 97 %	1.514-1.520 1.011-1.019	
09.427 992	Phenethyl isobutyrate		2862 302 103-48-0	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble 1 mL in 3 Ml 80% ethanol	230 IR 98 %	1.485-1.490 0.987-0.990	
09.466 994	Phenethyl isovalerate		2871 461 140-26-1	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble 1 mL in 3 ml 80% ethanol	263 IR 97 %	1.482-1.487 0.973-0.976	
09.487 1028	2-Phenoxyethyl isobutyrate		2873 2089 103-60-6	Liquid $C_{12}H_{16}O_3$ 208.26	Insoluble 1 mL in 3 mL 70% alcohol	265 NMR 97 %	1.491-1.496 1.044-1.048	
09.496 997	Phenethyl 2-methylcrotonate		2870 2186 55719-85-2	Liquid $C_{13}H_{16}O_2$ 204.27	Insoluble Miscible	259 NMR 98 %	1.494-1.518 1.148-1.159	
09.538 993	Phenethyl 2-methylbutyrate 6)		3632 10883 24817-51-4	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble Miscible	230 NMR 95 %	1.481-1.489 0.974-0.980	CASrn in Register refers to the racemate.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 41 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances

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
09.702 1010	Propyl phenylacetate		2955 229 4606-15-9	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	253 NMR 97 %	1.489-1.497 0.985-0.995 (15.5°)	
09.703 1017	Octyl phenylacetate		2812 230 122-45-2	Liquid $C_{16}H_{24}O_2$ 248.37	Insoluble Miscible	315 NMR 98 %	1.479-1.487 0.950-0.956	
09.707 999	Phenethyl phenylacetate		2866 234 102-20-5	Solid $C_{16}H_{16}O_2$ 240.30	Insoluble 1 mL in 4 mL 90% ethanol	325 28 IR 98 %	1.545-1.551 1.079-1.082	
09.758 1025	Methyl p-tert-butylphenylacetate		2690 577 3549-23-3	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble Miscible	106 (3 hPa) NMR 97 %	1.494-1.504 0.995-1.003	
09.772 1019	Linalyl phenylacetate 6)		3501 655 7143-69-3	Liquid $C_{18}H_{24}O_2$ 272.39	Insoluble Miscible	317 NMR 95 %	1.500-1.508 0.966-0.974	CASrn in Register refers to the racemate.
09.783 1008	Methyl phenylacetate		2733 2155 101-41-7	Liquid $C_9H_{10}O_2$ 150.18	Insoluble 1 mL in 6 mL 60% ethanol	215 IR 97 %	1.504-1.510 1.061-1.067	
09.784 1009	Ethyl phenylacetate		2452 2156 101-97-3	Liquid $C_{10}H_{12}O_2$ 164.20	Insoluble 1 mL in 3 mL 70% ethanol	228 IR 97 %	1.494-1.500 1.027-1.032	

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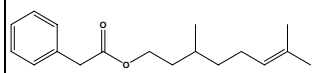
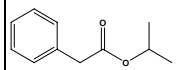
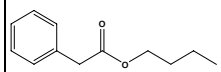
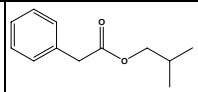
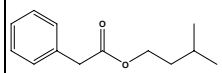
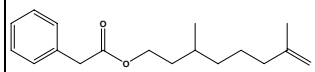
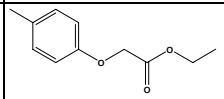
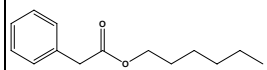
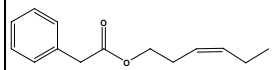
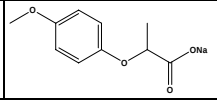
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.785 1021	Citronellyl phenylacetate 6)		2315 2157 139-70-8	Liquid $C_{18}H_{26}O_2$ 274.40	Insoluble Miscible	342 NMR 98 %	1.492-1.510 0.958-0.960	CASrn in Register refers to the racemate.
09.786 1011	Isopropyl phenylacetate		2956 2158 4861-85-2	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	238-253 NMR 97 %	1.483-1.491 1.006-1.012 (20°)	
09.787 1012	Butyl phenylacetate		2209 2159 122-43-0	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble 1 ml in 1 ml	258-260 IR 98 %	1.486-1.493 0.990-0.997	
09.788 1013	Isobutyl phenylacetate		2210 2160 102-13-6	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble 1 mL in 2 mL 80% ethanol	247 IR 98 %	1.484-1.488 0.984-0.988	
09.789 1014	3-Methylbutyl phenylacetate		2081 2161 102-19-2	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble 1 ml in 1 ml	268 IR 97%	1.483-1.490 0.975-0.981	CASrn in Register refers to 3-methylbutyl phenylacetate. According to JECFA: MIn. assay value is" 97 (sum of n-amyl and isoamyl esters)" and the composition is "65% n-amyl and 35% 3-methylbutyl phenylacetate".
09.791 1018	Rhodinyl phenylacetate 6)		2985 2163 10486-14-3	Liquid $C_{18}H_{26}O_2$ 274.40	Insoluble Miscible	340 NMR 95 %	1.494-1.505 0.965-0.972	CASrn in Register refers to to (3S)-enantiomer.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 41 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances

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
09.797 1027	Ethyl (p-tolyloxy)acetate		3157 2243 67028-40-4	Liquid $C_{11}H_{14}O_2$ 178.22	Insoluble Miscible	120-121 NMR 98 %	1.499-1.506 1.075-1.080 (20°)	
09.804 1015	Hexyl phenylacetate		3457 10694 5421-17-0	Liquid $C_{14}H_{20}O_2$ 220.31	Insoluble Miscible	262 MS 97 %	1.480-1.490 0.970-0.977	
09.805 1016	Hex-3(cis)-enyl phenylacetate		3633 10682 42436-07-7	Liquid $C_{14}H_{18}O_2$ 218.30	Insoluble Miscible	299 NMR 97 %	1.497-1.504 0.996-1.004	According to JECFA: Min. assay value is "97 %" and "predominantly (>90%) cis-isomer".
16.041 1029	Sodium 2-(4-methoxyphenoxy)propionate) 6)		3773 13794-15-5	Solid $C_{10}H_{11}O_4$,Na+ 218.19	Soluble Miscible	n.a. 190 IR 98 %	n.a. n.a.	CASrn in Register refers to the racemate.

1) Solubility in water, if not otherwise stated.

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

3) At 1013.25 hPa, if not otherwise stated.

4) At 20°C, if not otherwise stated.

5) At 25°C, if not otherwise stated.

6) Stereoisomeric composition not specified.

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (*in vitro / in vivo*) for 41 Phenetyl Alcohol, Aldehyde, Acid , and Related Acetals and Esters (JECFA, 2003a)

Table 2.1: Summary of Genotoxicity Data for 41 Phenethyl Alcohols, Aldehydes and Acids and Related Acetals and Esters (JECFA, 2003a)

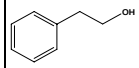
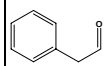
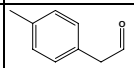
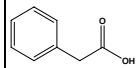
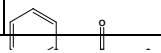
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
02.019	2-Phenylethanol		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 mmol/plate	Negative[a]	(Florin et al., 1980)
			Sister chromatid exchange	Human lymphocytes	Not specified	Negative	(Norppa & Vainio, 1983)
05.030	Phenylacetaldehyde		Reverse mutation	*S. typhimurium* TA98, TA100, TA104	Not specified	Negative[a]	(Kato et al., 1989)
			Mutation	*E. coli* WP2uvrA/pkM101	Not specified	Negative[a]	(Kato et al., 1989)
05.042	p-Tolylacetaldehyde		Reverse mutation	*S. typhimurium* TA100	0.1–1000 µg/plate	Negative	(Rapson et al., 1980)
			Mutation	*E. coli* PQ37	Not specified	Negative	(Ohshima et al., 1989)
08.038	Phenylacetic acid		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1000 mg	Negative[a]	(Heck et al., 1989)
			Unscheduled DNA synthesis	Rat hepatocytes	500 mg	Negative	(Heck et al., 1989)
			Mutation	Mouse lymphoma L5178Y $Tk^{+/-}$ cells	1500 mg	Negative[a]	(Heck et al., 1989)
09.784	Ethyl phenylacetate		Mutation	*B. subtilis* H17 (rec^{+}) and M45 (rec^{-})	21 mg/disc	Negative	(Oda et al., 1979)

Table 2.1: Summary of Genotoxicity Data for 41 Phenethyl Alcohols, Aldehydes and Acids and Related Acetals and Esters (JECFA, 2003a)

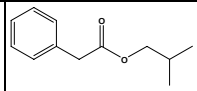
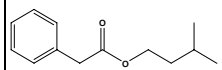
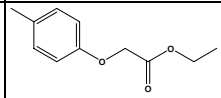
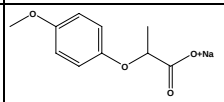
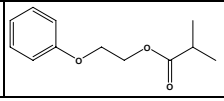
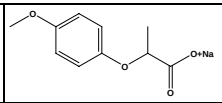
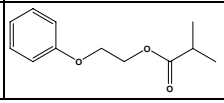
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
			Mutation	*B. subtilis* H17 (rec^+) and M45 (rec^-)	20 ml/disc	Positive[b]	(Yoo, 1986)
			Reverse mutation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	5 mg	Negative[a]	(Ishidate et al., 1984)
			Chromosomal abberation	Chinese hamster fibroblast cells	1 mg/ml	Negative[a]	(Ishidate et al., 1984)
			Mutation	*E. coli* WP2uvrA (trp^-)	200–1600 µg/plate	Negative[b]	(Yoo, 1986)
09.788	Isobutyl phenylacetate		Reverse mutation	*S. typhimurium* TA97, TA102	0–0.1 mg/plate	Negative[a]	(Fujita et al., 1994)
09.789	3-Methylbutyl phenylacetate		Mutation	*B. subtilis* H17 (rec^+) and M45 (rec^-)	20 mg/disc	Positive[b]	(Oda et al., 1979)
			Mutation	*B. subtilis* H17 (rec^+) and M45 (rec^-)	20 ml/disc	Negative[b]	(Yoo, 1986)
			Reverse mutation	*S. typhimurium* TA98, TA100	10 mg/plate	Negative[a]	(Oda et al., 1979)
					50 mg/plate	Lethal[a,b]	
09.797	Ethyl (p-tolyloxy)acetate		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA100, TA98	3600 µg/plate	Negative[a]	(Wild et al., 1983)
16.041	Sodium 2-(4-methoxyphenoxy)propionate		Reverse mutation	*S. typhimurium* TA1535, TA98, TA100, TA1537	5000 µg/plate	Negative[a]	(Varley, 1985)
09.487	2-Phenoxyethyl isobutyrate		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA100, TA98	3600 µg/plate	Negative[a]	(Wild et al., 1983)

Table 2.1: Summary of Genotoxicity Data for 41 Phenethyl Alcohols, Aldehydes and Acids and Related Acetals and Esters (JECFA, 2003a)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vivo							
16.041	Sodium 2-(4-methoxyphenoxy)propionate		Micronucleus formation	Mouse bone marrow cells	2000 mg/kg/bw	Negative[c]	(Asquith, 1985)
09.487	2-Phenoxyethyl isobutyrate		Micronucleus formation	Mouse bone marrow cells	1900 mg/kg/bw	Negative[b]	(Wild et al., 1983)

[a] *With and without metabolic activation.*

[b] *Administered intraperitoneally.*

c Information reported in the table are not consistent with the text (see section 3.1 – in vivo*): however the results are considered negative – the substance could not be identified as the study report only containea a code number and not the substance name (unpublished data submitted from EFFA).*

Table 2.2: Genotoxicity (*in vitro*) EFSA / FGE.14

Substances listed in brackets are JECFA evaluated supporting substances in FGE.14.

Table 2.2: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.14

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
(2-Phenylethan-1-ol [02.019])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol/plate (366 µg/plate)[8]	Negative[1]	(Florin et al., 1980)	Published non-GLP study. Limited report of study details. No results reported. Validity of the study cannot be evaluated.
	Ames reverse mutation assay	*S. typhimurium* TA100, TA1535, TA1538	0 - 99.6 µmol/plate (0 – 12200 µg/plate)[8]	Negative[2, 3]	(Zeiger & Pagano, 1984)	Spot-Test on inhibition of reversion induced by known mutagens. Published non-GLP study of acceptable quality. Limited report of study details and results. Overall, study and results are considered valid.
	Mutation Assay	*Saccharomyces saké* strain Kyokai no. 7	0.1, 0.15, 0.20% (1000, 1500, 2000 µg/ml)	Negative	(Kojima et al., 1976)	Published study in Japanese (summary and tables with results in English). Validity of the study cannot be evaluated.
	Sister chromatid exchange	Human lymphocytes	0.1 - 10 mM (12.2 to 1220 µg/ml)[8]	Negative[4]	(Norppa & Vainio, 1983)	Published non-GLP study of acceptable quality.
2-(4-Hydroxyphenyl)ethan-1-ol [02.166]	Comet assay	PC human prostate cancer cells	0, 10, 50, 100, 250 µM (0, 1.4, 7, 14, 35 µg/ml)[9]	Negative[5]	(Quiles et al., 2002)	Published non-GLP study of acceptable quality. Study is considered valid.
(Phenylacetaldehyde [05.030])	Ames reverse mutation assay (preincubation)	*S. typhimurium* TA98, TA100, TA104 *E. coli* WP2*uvr*A/ pKM101	Not specified	Negative[1]	(Kato et al., 1989)	Only abstract reported. Validity of the study cannot be evaluated.
(Phenylacetic acid [08.038])	Ames reverse mutation assay	*S. typhimurium* TA98, A100, TA1535, TA1537, TA1538	1000 µg/plate[7]	Negative[1]	(Heck et al., 1989)	Published non-GLP study. No details of study design and results reported. Validity of the study cannot be evaluated.
	Unscheduled DNA synthesis	Rat hepatocytes	500 µg/ml[7]	Negative	(Heck et al., 1989)	Published non-GLP study. No details of study design and results reported. Validity of the study cannot be evaluated.
	Forward mutation assay	Mouse lymphoma L5178Y TK+/- cells	1000, 1500 µg/ml[7]	Negative[1]	(Heck et al., 1989)	Published non-GLP study. No details of study design and results reported. Validity of the study cannot be evaluated. It has to be noted, that there was some activity observed in the study even for GRAS substances (for which a negative result was found in the Ames test by the same authors), for which effects of nonphysiological medium conditions on the outcome of the study might be responsible for this. Therefore the validity of the study is questionable.
(Ethyl phenylacetate [09.784])	Ames reverse mutation assay	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	up to 5000 µg/plate[10]	Negative[1]	(Ishidate et al., 1984)	Published non-GLP study of acceptable quality.
	Chromosomal aberration assay	Chinese hamster fibroblast cells	up to 1000 µg/ml[11]	Negative	(Ishidate et al., 1984)	Published non-GLP study of acceptable quality.
	Rec assay	*B. subtilis* H17 (rec +) and M45 (rec-)	21 µg/disk	Negative	(Oda et al., 1979)	Study published in Japanese with no English abstract. Data extracted from tables only. Validity of the study cannot be evaluated.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.14

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
	Rec assay	*B. subtilis* H17 (rec+) and M45 (rec-)	20 µg/disk	Positive	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Mutation assay	*E. coli* WP2*uvr*A (trp-)	200 - 1600 µg/plate	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
(Isobutyl phenylacetate [09.788])	Ames reverse mutation assay	*S. typhimurium* TA97, TA102	1, 5, 10, 50 and 100 µg/plate	Negative[1]	(Fujita et al., 1994)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
(3-Methylbutyl phenylacetate [09.789])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100	10 µg/plate 50 µg/plate	Negative[1] Cytotoxic[1]	(Oda et al., 1979)	Study published in Japanese with no English abstract. Data extracted from tables only. Validity of the study cannot be evaluated.
	Rec assay	*B. subtilis* H17 (rec+) and M45 (rec-)	20 µg/disk	Positive	(Oda et al., 1979)	Study published in Japanese with no English abstract. Data extracted from tables only. Validity of the study cannot be evaluated.
	Rec assay	*B. subtilis* H17 (rec+) and M45 (rec-)	20 µg/disk	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
(*p*-Tolyacetaldehyde [05.042])	Ames reverse mutation assay	*S. typhimurium* TA100	0.1, 1, 10, 100, 1000 µg/plate	Negative	(Rapson et al., 1980)	Published non-GLP study. Study design and results insufficiently reported. Validity of the study cannot be evaluated.
	SOS Chromtest	*E. coli* PQ37	Not specified	Negative[4]	(Ohshima et al., 1989)	Published non-GLP. p-Tolylacetaldehyde has not been analysed per se but after nitrosation (it is unclear to the rapporteur whether the substance has been assayed at all in the study). Due to limited report of experimental details and results the validity of the study cannot be evaluated.
(Isoeugenyl phenylacetate[6] [09.710])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	up to 3600 µg/plate[12]	Negative[1]	(Wild et al., 1983)	Published non-GLP study. No detailed results reported. However, as experimental details and evaluation criteria including results of positive controls are sufficiently reported the study is considered valid.

[1] *With and without S9 metabolic activation.*

[2] *With S9 metabolic activation.*

[3] *Toxic at concentrations from 91.3 µmol/plate.*

[4] *Without S9 metabolic activation.*

[5] *At the two highest dose levels evaluated 2-(4-hydroxyphenyl)ethan-1-ol reduced the DNA damage of H_2O_2 treated cells (by 23% at 100 µM and by 40%, at 250 µM).*

[6] *A phenyl acetate ester structurally related to the EFSA evaluated chemicals and JECFA evaluated chemicals, phenethyl alcohol, aldehyde, acid, and related acetals and esters and related substances JECFA (JECFA, 2004a).*

[7] *Highest inactive dose tested.*

[8] *Calculated based on molecular weight = 122.16.*

[9] *Calculated based on molecular weight = 138.17.*

[10] *Six different concentrations used (single concentrations not reported).*

[11] *Three different doses used (single doses not reported).*

[12] *Five different concentrations used (single concentrations not reported).*

Table 2.3: Genotoxicity (*in vivo*) EFSA / FGE.14

Substances listed in brackets are JECFA evaluated supporting substances in FGE.14.

Table 2.3: Summary of Genotoxicity Data (*in vivo*) EFSA / FGE.14

Chemical Name	Test System	Test Object	Route	Dose	Result	Reference	Comments
(Isoeugenyl phenylacetate[1] [09.710])	Micronucleus formation assay	Mouse bone marrow cells	i.p.	0, 564, 987 or 1410 mg/kg bw (two applications)	Negative	(Wild et al., 1983)	Published non-GLP study. Details of study protocol and results insufficiently reported. Effect on PCE/NCE ratio not reported. No positive control. Validity of the study cannot be evaluated.
	Sex-linked recessive mutation	*D. melanogaster*	NR	25 mM	Negative	(Wild et al., 1983)	Published non-GLP study. Details of study protocol reported elsewhere. Study is considered valid.

NR=Not Reported

[1]*A phenyl acetate ester structurally related to the EFSA evaluated substances and JECFA evaluated substances, phenethyl alcohol, aldehyde, acid, and related acetals and esters and related substances JECFA (JECFA, 2004a).*

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 41 Phenylethyl Alcohol, Aldehyde, Acid, and Related Acetals and Esters (JECFA, 2003a)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

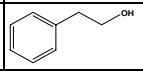
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.019 987	2-Phenylethan-1-ol		1200 330	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

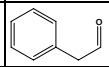
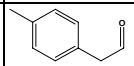
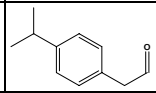
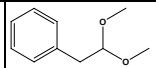
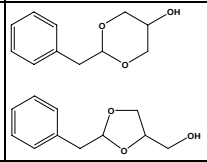
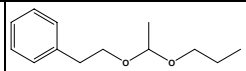
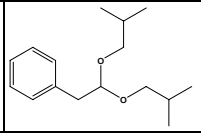
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
05.030 1002	Phenylacetaldehyde		37 60	Class I A3: Intake below threshold	4)	6)	6)
05.042 1023	p-Tolylacetaldehyde		5.5 3	Class I A3: Intake below threshold	4)	6)	6)
05.044 1024	p-Isopropyl phenylacetaldehyde		0.061 0.01	Class I A3: Intake below threshold	4)	6)	6)
06.006 1003	1,1-Dimethoxy-2-phenylethane		17 40	Class I A3: Intake below threshold	4)	6)	6)
06.007 1004	Phenylacetaldehyde glyceryl acetal		0.12 1	Class I A3: Intake below threshold	4)	6)	CASrn in Register refers to named substance; "Incompletely Defined Substance". Stereoisomeric composition and composition of mixture to be specified.
06.016 1000	1-Phenylethoxy-1-propoxy ethane		0.12 6	Class I A3: Intake below threshold	4)	6)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified.
06.024 1006	1,1-Di-isobutoxy-2-phenylethane		27 0.4	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

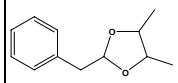
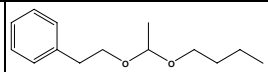
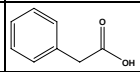
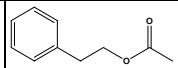
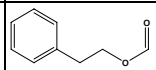
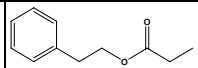
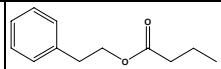
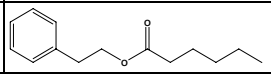
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
06.027 1005	4,5-Dimethyl-2-benzyl-1,3-dioxolan		ND 1	Class I A3: Intake below threshold	4)	7)	CASrn does not specify stereoisomers, according to JECFA: Min. assay value is "93%" and secondary components "butane-2,3-diol", stereoisomeric composition and composition of mixture to be specified. 7)
06.036 1001	1-Butoxy-1-(2-phenylethoxy)ethane		0.012 ND	Class I A3: Intake below threshold	4)	6)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified.
08.038 1007	Phenylacetic acid		240 60	Class I A3: Intake below threshold	4)	6)	6)
09.031 989	Phenethyl acetate		89 60	Class I A3: Intake below threshold	4)	6)	6)
09.083 988	Phenethyl formate		2.1 30	Class I A3: Intake below threshold	4)	6)	6)
09.137 990	Phenethyl propionate		0.97 3	Class I A3: Intake below threshold	4)	6)	6)
09.168 991	Phenethyl butyrate		28 30	Class I A3: Intake below threshold	4)	6)	6)
09.261 995	2-Phenethyl hexanoate		12 2	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

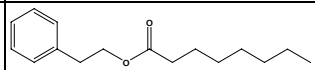
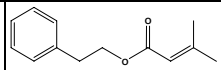
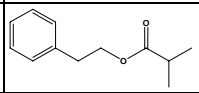
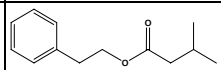
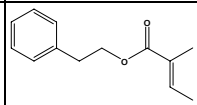
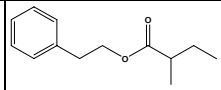
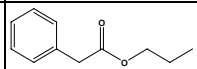
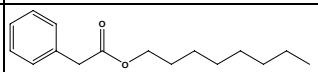
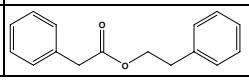
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.262 996	Phenethyl octanoate		23 0.1	Class I A3: Intake below threshold	4)	6)	6)
09.407 998	2-Phenethyl 3-methylcrotonate		1.3 ND	Class I A3: Intake below threshold	4)	6)	6)
09.427 992	Phenethyl isobutyrate		19 60	Class I A3: Intake below threshold	4)	6)	6)
09.466 994	Phenethyl isovalerate		81 30	Class I A3: Intake below threshold	4)	6)	6)
09.496 997	Phenethyl 2-methylcrotonate		0.24 1	Class I A3: Intake below threshold	4)	6)	6)
09.538 993	Phenethyl 2-methylbutyrate		0.37 ND	Class I A3: Intake below threshold	4)	6)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified.
09.702 1010	Propyl phenylacetate		ND 0.3	Class I A3: Intake below threshold	4)	7)	7)
09.703 1017	Octyl phenylacetate		0.0037 0.006	Class I A3: Intake below threshold	4)	6)	6)
09.707 999	Phenethyl phenylacetate		33 80	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

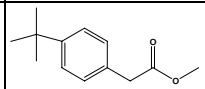
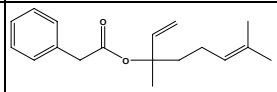
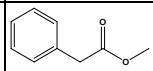
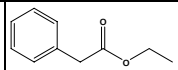
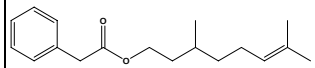
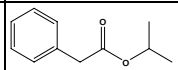
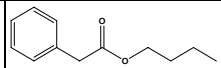
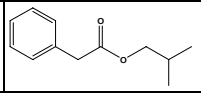
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.758 1025	Methyl p-tert-butylphenylacetate		17 20	Class I A3: Intake below threshold	4)	6)	6)
09.772 1019	Linalyl phenylacetate		0.073 ND	Class I A3: Intake below threshold	4)	6)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified.
09.783 1008	Methyl phenylacetate		ND 20	Class I A3: Intake below threshold	4)	7)	7)
09.784 1009	Ethyl phenylacetate		110 20	Class I A3: Intake below threshold	4)	6)	6)
09.785 1021	Citronellyl phenylacetate		1.2 2	Class I A3: Intake below threshold	4)	6)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified.
09.786 1011	Isopropyl phenylacetate		0.061 ND	Class I A3: Intake below threshold	4)	6)	6)
09.787 1012	Butyl phenylacetate		2.4 3	Class I A3: Intake below threshold	4)	6)	6)
09.788 1013	Isobutyl phenylacetate		18 20	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

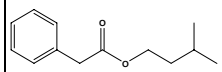
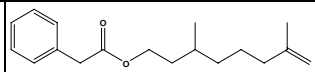
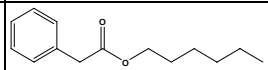
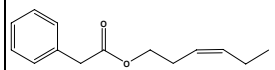
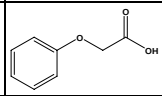
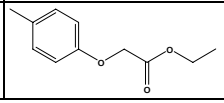
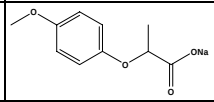
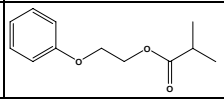
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.789 1014	3-Methylbutyl phenylacetate		28 30	Class I A3: Intake below threshold	4)	6)	CASrn in Register refers to 3-methylbutyl phenylacetate. According to JECFA: MIn. assay value is" 97 (sum of n-amyl and isoamyl esters)" and the composition is "65% n-amyl and 35% 3-methylbutyl phenylacetate". 6)
09.791 1018	Rhodinyl phenylacetate		0.0012 ND	Class I A3: Intake below threshold	4)	6)	CASrn refers to to (3S)-enantiomer Stereoisomeric composition to be specified.
09.804 1015	Hexyl phenylacetate		6.9 ND	Class I A3: Intake below threshold	4)	6)	6)
09.805 1016	Hex-3(cis)-enyl phenylacetate		0.73 0.05	Class I A3: Intake below threshold	4)	6)	According to JECFA: Min. assay value is "97 %" and "predominantly (>90%) cis-isomer". Composition of mixture to be specified.
08.049 1026	Phenoxyacetic acid		30 0.1	Class III A3: Intake below threshold	4)	6)	6)
09.797 1027	Ethyl (p-tolyloxy)acetate		0.12 ND	Class III A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 41 JECFA Evaluated Substances (JECFA, 2003a)

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
16.041 1029	Sodium 2-(4-methoxyphenoxy)propanoate		ND 6	Class III A3: Intake below threshold	4)	7)	CASrn reported refers to the racemate. Stereoisomeric composition to be specified. 7)
09.487 1028	2-Phenoxyethyl isobutyrate		1.7 110	Class III A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	6)	6)

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

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

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

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

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

6) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

7) MSDI based on USA production figure.

ND: Not determined

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14 and One Phenoxyethyl Ester Evaluated in FGE.23)

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

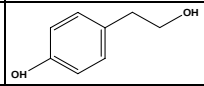
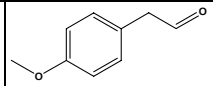
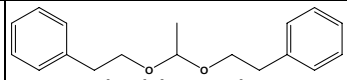
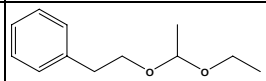
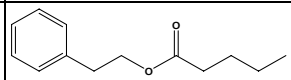
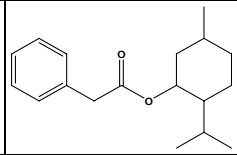
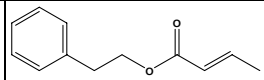
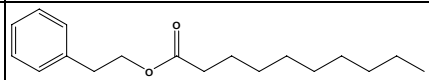
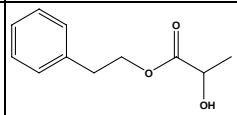
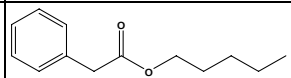
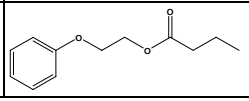
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.166	2-(4-Hydroxyphenyl)ethan-1-ol		0.12	Class I A3: Intake below threshold	4)	6)	
05.159	p-Methoxyphenylacetaldehyde		0.037	Class I A3: Intake below threshold	4)	6)	
06.078	1,1-Diphenethoxyethane	 2-Phenethyl structure shown	0.012	Class I A3: Intake below threshold	4)	7)	
06.080	1-Ethoxy-1-(2-phenylethoxy)ethane		0.012	Class I A3: Intake below threshold	4)	6)	
09.201	Phenethyl valerate	 2-Phenethyl structure shown	0.012	Class I A3: Intake below threshold	4)	7)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.620	Menthyl phenylacetate		1.5	Class I A3: Intake below threshold	4)	7)	
09.684	Phenethyl crotonate	 2-Phenethyl structure shown	0.73	Class I A3: Intake below threshold	4)	7)	
09.685	2-Phenethyl decanoate		0.037	Class I A3: Intake below threshold	4)	6)	
09.686	Phenethyl lactate	 2-Phenethyl structure shown	0.24	Class I A3: Intake below threshold	4)	7)	
09.761	Pentyl phenylacetate		1.9	Class I A3: Intake below threshold	4)	6)	
09.687	2-Phenoxyethyl butyrate		0.085	Class III A3: Intake below threshold	4)	6)	

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

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

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

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

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

6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).

7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce.

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

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SCIENTIFIC PANEL MEMBERS

Fernando Aguilar, Herman Nybro Autrup, Susan Barlow, Laurence Castle, Riccardo Crebelli, Wolfgang Dekant, Karl-Heinz Engel, Nathalie Gontard, David Michael Gott, Sandro Grilli, Rainer Gürtler, John Chr. Larsen, Catherine Leclercq, Jean-Charles Leblanc, F. Xavier Malcata, Wim Mennes, Maria Rosaria Milana, Iona Pratt, Ivonne Magdalena Catharina Maria Rietjens, Paul P. Tobback, Fidel Toldrá.

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