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Flavouring Group Evaluation 55 (FGE.55): Consideration of phenyl-substituted aliphatic alcohols and related aldehydes and esters evaluated by JECFA (63rd meeting) structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14 (2005) and aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in FGE.15 (2005)
(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-2008-032F)

(Adopted on 16 May 2007)

PANEL MEMBERS

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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 15 phenyl-substituted aliphatic alcohols and related aldehydes and esters evaluated by the JECFA (63rd meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluation of ten phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in Flavouring Group Evaluation 14 (FGE.14) and eight aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in Flavouring Group Evaluation 15 (FGE.15).

The Panel concluded that the 15 substances in the JECFA flavouring group of phenyl-substituted aliphatic alcohols and related aldehydes and esters are structurally related to the ten phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in the Flavouring Group Evaluation 14 (FGE.14) and structurally related to the eight aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in the Flavouring Group Evaluation 15 (FGE.15).

Further seven substances were evaluated by the JECFA in this group, one of these is not in the Register (sodium 2-oxo-3-phenylpropionate), three are tertiary alcohols (or esters of tertiary alcohols) [FL-no: 02.108, 09.029 and 09.484], which will be considered together in a separate group as tertiary alcohols are not covered by the substances in FGE.14 and FGE.15, and three are alpha,beta-unsaturated aldehydes [FL-no: 05.062, 05.099 and 05.100] and will be evaluated together with other alpha,beta-unsaturated aldehydes and ketones.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 substances considered in this FGE.

For five substances [FL-no: 05.097, 08.109, 09.728, 09.729 and 09.802] the JECFA evaluation is only based on Maximised Survey-derived Daily Intake (MSDI) values derived from production figures from the USA. European production figures are needed in order to finalise the evaluation of these substances.

For all 15 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 assessments and to finalise the evaluation.

In order to determine whether the conclusion for the 15 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications including complete purity criteria and identity are available for three of the 15 JECFA evaluated substances. For 12 substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 09.057, 09.485 and 09.802] information on the isomeric composition is lacking and for [FL-no: 05.045] further information on the composition is requested.

Thus for all of the 15 evaluated substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 08.109, 09.057, 09.485, 09.728, 09.729 and 09.802] the Panel has reservations (only USA production volumes are available and/or missing data on specifications and/or isomerism/composition).

KEYWORDS

phenyl-substituted aliphatic alcohols and related aldehydes and esters, JECFA, phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters, aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives, FGE.14, FGE.15.

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

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

TERMS OF REFERENCE

EFSA is requested to consider the JECFA's 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 22 flavouring substances consisting of phenyl-substituted aliphatic alcohols and related aldehydes and esters.

One of these is not in the Register (sodium 2-oxo-3-phenylpropionate), three tertiary alcohols (or esters of tertiary alcohols) [FL-no: 02.108, 09.029 and 09.484] will be considered together in a separate group as tertiary alcohols are not covered by the substances in FGE.14 and FGE.15, and three alpha,beta-unsaturated aldehydes [FL-no: 05.062, 05.099 and 05.100] will be evaluated together with other alpha,beta-unsaturated aldehydes and ketones. This consideration will therefore only deal with 15 JECFA evaluated substances.

1.1.2. EFSA Considerations

The Panel concluded that all the 15 substances in the JECFA flavouring group of phenyl-substituted aliphatic alcohols and related aldehydes 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 structurally related to a group of eight aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in the Flavouring Group Evaluation 15 (FGE.15).

The substances in FGE.55 are primary alcohols, aldehydes or carboxylic acids and derivatives thereof, which bear a phenyl ring. These aromatic rings are attached either to a terminal carbon atom or to a carbon atom in an alkyl chain. These alkyl chains contain three or more carbon atoms. With respect to chain-length, the candidate substances in FGE.55 are similar to the substances evaluated in FGE.15. The major metabolic pathway for the substances in FGE.15 is beta-oxidation and subsequent conjugation of the residual phenylcarboxylic fragment. However, for the candidate substances in FGE.55 with the phenyl ring connected to the middle part of the alkyl chain steric

hindrance may inhibit beta-oxidation. For these substances, the phenylethyl substances evaluated in FGE.14, which cannot be metabolised via beta-oxidation either, but rather via amino acid conjugation, are more representative with respect to metabolism. Therefore, for FGE.55, both FGE.14 and FGE.15 are included as structurally related FGEs.

1.2. Isomers

1.2.1. JECFA Status

The following 12 Register substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 09.057, 09.485 and 09.802] in the group of the JECFA evaluated phenyl substituted aliphatic alcohols and related aldehydes and esters have a chiral centre.

1.2.2. EFSA Considerations

Information is lacking about the stereoisomerism for the 12 JECFA-evaluated substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 09.057, 09.485 and 09.802].

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 15 substances (JECFA, 2005b). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate except that information on stereoisomerism is lacking for [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 09.057, 09.485 and 09.802] (See Section 1.2) and further information on the composition of [FL-no: 05.045] is requested.

2. Intake Estimations

2.1. JECFA Status

For ten substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining five substances [FL-no: 05.097, 08.109, 09.728, 09.729 and 09.802] production figures are only available for the USA.

2.2. EFSA Considerations

As production figures are only available for the USA for five substances, MSDI values for the EU cannot be calculated for these [FL-no: 05.097, 08.109, 09.728, 09.729 and 09.802].

3. Genotoxicity Data

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

In vitro

Testing for genotoxicity *in vitro* has been performed for four [FL-no: 02.073, 05.038, 06.030 and 09.485] representative members of this group of phenyl-substituted aliphatic alcohols and related aldehydes and esters used as flavouring agents.

In standard assays for mutagenicity in *Salmonella typhimurium*, beta-methylphenethyl alcohol [FL-no: 02.073], 2-phenylpropionaldehyde [FL-no: 05.038], 2-phenylpropionaldehyde dimethyl acetal [FL-no: 06.030] and 2-phenylpropyl isobutyrate [FL-no: 09.485] were not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 when tested at concentrations of up to 3600 µg/plate, with and without metabolic activation (Wild et al., 1983).

In vivo

The potential of 2-phenylpropionaldehyde [FL-no: 05.038] and 2-phenylpropionaldehyde dimethyl acetal [FL-no: 06.030] to induce sex-linked recessive lethal mutations in adult *Drosophila melanogaster* were studied in the Basc test. The frequency of mutation was unaffected when solutions of 2-phenylpropionaldehyde and 2-phenylpropionaldehyde dimethyl acetal at a concentration of 10 and 5 mmol/l, respectively (1341 and 901 microgram/ml, respectively) were fed to the flies for 3 days (Wild et al., 1983).

In a test for micronucleus formation, groups of four male and four female NMRI mice given 2-phenylpropionaldehyde as a single intraperitoneal dose at 134, 402, or 670 mg/kg bw or 2-phenylpropionaldehyde dimethyl acetal as a single intraperitoneal dose at 360, 630, or 900 mg/kg bw, demonstrated no increase in micronucleated erythrocytes in samples of bone marrow obtained 30 h after administration (Wild et al., 1983).

Conclusion on genotoxicity

The testing of these representative 2-phenylpropanol derivatives in bacterial test systems *in vitro* (Ames assay) and in mammalian systems (test for micronucleus formation) *in vivo* showed no evidence of genotoxic potential. These results are further supported by the lack of positive findings in the Basc test. By analogy to structurally related cinnamyl derivatives, 2-phenylpent-4-enal [FL-no: 05.115] presents no evidence of genotoxicity in bacterial test systems (Ames assay) *in vitro* and in mammalian systems *in vivo* (tests for unscheduled DNA synthesis and for micronucleus formation).

For a summary of *in vitro / in vivo* genotoxicity data considered by 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 one 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 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 candidate nor of supporting substances.

[1] *JECFA-evaluated 2-(4-hydroxyphenyl)ethan-1-ol [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]*

Conclusion on genotoxicity

There are valid *in vitro* genotoxicity data available for one of the ten candidate substances [FL-no: 02.166] in this flavouring group evaluation. Valid *in vitro* and limited *in vivo* mutagenicity data are available for two of the supporting substances and on a further structurally related substance.

For the candidate substance 2-(4-hydroxyphenyl)ethan-1-ol [FL-no: 02.166], the only available study gave no indication of a genotoxic potential *in vitro*, but disclosed a possible pro-oxidant activity of the substance.

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

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 of the ten candidate substances in this flavouring group evaluation.

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

3.3. Genotoxicity Studies - Text Taken from EFSA (EFSA, 2005f)

In vitro / in vivo

Limited *in vitro* genotoxicity data are available for only two candidate [FL-no: 08.088 and 08.089] and for six supporting substances [FL-no: 05.080, 08.022, 09.730, 09.738, 09.740 and 09.744].

The mutagenicity studies available on the candidate substances 4-hydroxy-3,5-dimethoxycinnamic acid [FL-no: 08.088] and 4-hydroxy-3-methoxycinnamic acid [FL-no: 08.089] are considered to provide little useful information regarding the genotoxicity of the candidate substances.

4-Hydroxy-3-methoxycinnamic acid [FL-no: 08.089] was tested for its influence on spontaneous and induced sister chromatid exchange (SCE) in cultured Chinese hamster ovary (CHO) cells only in the absence of metabolic activation. The result was negative.

The six supporting substances [FL-no: 05.080, 08.022, 09.730, 09.738, 09.740 and 09.744] have been tested for their ability to induce mutations in various strains of *Salmonella typhimurium* (e.g. TA92, TA94, 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 microgram/plate. Four of the substances, cinnamic acid [FL-no: 08.022], methyl cinnamate [FL-no: 09.740], ethyl cinnamate [FL-no: 09.730] and 3-phenylpropionaldehyde [FL-no: 05.080] were tested for induction of spontaneous SCEs in cultured CHO cells only in the absence of metabolic activation. For all the four substances no influence on cell cycle and SCE was observed. Ethyl cinnamate [FL-no: 09.730] in a study carried out in the absence of S9 activation did not induce chromosomal aberrations in Chinese hamster fibroblasts.

There are no *in vivo* genotoxicity data available for the candidate and supporting substances in the present flavouring group evaluation.

Conclusion on genotoxicity

Overall, the data available are not sufficient to evaluate the genotoxicity adequately and no *in vivo* genotoxicity data are available for the candidate or for the supporting substances.

However, the various studies carried out with supporting substances give no indication of a mutagenic activity in bacterial cells or of a direct clastogenic effect on mammalian cells. Therefore, the limited available data as well as the chemical structures of the candidate substances do not give rise to concern with respect to genotoxicity of the eight candidate substances in this flavouring group evaluation.

For a summary of *in vitro / in vivo* genotoxicity data considered by EFSA see Table 2.4 and Table 2.5.

3.4. EFSA Considerations

The Panel concluded that the data available do not preclude evaluation of the15 JECFA evaluated phenyl-substituted aliphatic alcohols and related aldehydes and esters through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters by JECFA (JECFA, 2006a):

According to the JECFA the 15 substances belong to structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded all 15 substances at step A3 in the JECFA Procedure – i.e. the substances are expected to be metabolised to innocuous products (step 2) and concluded that the intakes for all substances are below the thresholds for their structural class I (step A3).

In conclusion, the JECFA evaluated all 15 substances as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 15 phenyl-substituted aliphatic alcohols and related aldehydes and esters are summarised in Table 3.1: Summary of Safety Evaluation of 15 Phenyl Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a).

4.2. Application of the Procedure to Ten Phenethyl Alcohol, Aldehyde, Esters and Related Phenylacetic Acid Esters 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 are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14).

4.3. Application of the Procedure to Eight Aryl-Substituted Saturated and Unsaturated Primary Alcohol/Aldehyde/Acid/Ester Derivatives by EFSA (EFSA, 2005f):

Eight candidate substances were evaluated in FGE.15. All eight substances are classified into structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The eight substances were 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 eight 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 eight substances are summarised in Table 3.3: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.15).

4.4. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA of the 15 phenyl-substituted aliphatic alcohols and related aldehydes and esters.

5. Conclusion

The Panel concluded that the 15 substances in the JECFA flavouring group of phenyl-substituted aliphatic alcohols and related aldehydes and esters are structurally related to the ten phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in the Flavouring Group Evaluation 14 (FGE.14) and structurally related to the eight aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in the Flavouring Group Evaluation 15 (FGE.15).

Further seven substances were evaluated by the JECFA in this group, one of these is not in the Register (sodium 2-oxo-3-phenylpropionate), three are tertiary alcohols (or esters of tertiary alcohols) [FL-no: 02.108, 09.029 and 09.484], which will be considered together in a separate group as tertiary alcohols are not covered by the substances in FGE.14 and FGE.15, and three are alpha,beta-unsaturated aldehydes [FL-no: 05.062, 05.099 and 05.100] and will be evaluated together with other alpha,beta-unsaturated aldehydes and ketones.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 substances considered in this FGE.

For five substances [FL-no: 05.097, 08.109, 09.728, 09.729 and 09.802] the JECFA evaluation is only based on MSDI values derived from production figures from the USA. European production figures are needed in order to finalise the evaluation of these substances.

For all 15 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 assessments and to finalise the evaluation.

In order to determine whether the conclusion for the 15 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications including complete purity criteria and identity are available for three of the 15 JECFA evaluated substances. For 12 substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 09.057, 09.485 and 09.802] information on the isomeric composition is lacking and for [FL-no: 05.045] further information on the composition is requested.

Thus for all of the 15 evaluated substances [FL-no: 02.073, 05.038, 05.043, 05.045, 05.046, 05.052, 05.097, 05.115, 06.030, 08.109, 09.057, 09.485, 09.728, 09.729 and 09.802] the Panel has reservations (only USA production volumes are available and/or missing data on specifications and/or isomerism/composition).

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 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters

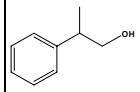
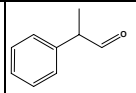
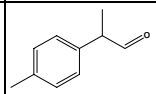
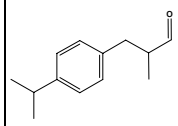
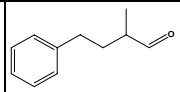
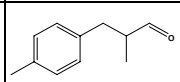
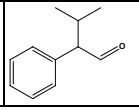
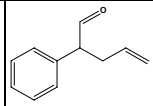
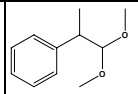
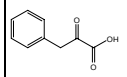
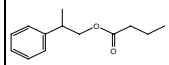
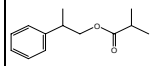
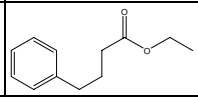
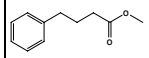
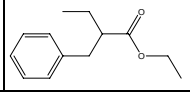
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
02.073 1459	2-Phenylpropan-1-ol 6)		2732 2257 1123-85-9	Liquid $C_9H_{12}O$ 136.19	Slightly soluble Soluble	219 NMR 98 %	1.523-1.530 0.971-0.978	CASrn refers to the racemate.
05.038 1467	2-Phenylpropanal 6)		2886 126 93-53-8	Liquid $C_9H_{10}O$ 134.18	Soluble	202-205 IR 95 %	1.515-1.520 0.998-1.006	CASrn refers to the racemate.
05.043 1471	2-(p-Tolyl)propionaldehyde 6)		3078 131 99-72-9	Liquid $C_{10}H_{12}O$ 148.21	Insoluble Soluble	222-224 NMR 95 %	1.513-1.517 0.979-0.985	CASrn refers to the racemate.
05.045 1465	3-(p-Cumenyl)-2-methylpropionaldehyde 6) 7)		2743 133 103-95-7	Liquid $C_{13}H_{18}O$ 190.29	Insoluble Soluble	270 IR 90 %	1.503-1.508 0.946-0.952	CASrn refers to the racemate According to JECFA: Min. assay value is "90%" and secondary components "3-5% 2-Methyl-3-(p-isopropylphenyl)propionic acid".
05.046 1462	2-Methyl-4-phenylbutyraldehyde 6)		2737 134 40654-82-8	Liquid $C_{11}H_{14}O$ 162.23	Insoluble Soluble	253 NMR 95 %	1.506-1.510 0.968-0.975	CASrn refers to the racemate.
05.052 1466	2-Methyl-3-(p-tolyl)propionaldehyde 6)		2748 587 41496-43-9	Liquid $C_{11}H_{14}O$ 162.23	Slightly soluble Soluble	232-239 NMR 95 %	1.519-1.525 0.991-0.997	CASrn refers to the racemate.
05.097 1463	3-Methyl-2-phenylbutyraldehyde 6)		2738 135 2439-44-3	Liquid $C_{11}H_{14}O$ 162.23	Insoluble Soluble	238 NMR 97 %	1.495-1.501 0.972-0.982	CASrn refers to the racemate.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters

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
05.115 1476	2-Phenylpent-4-enal 6)		3519 10377 24401-36-3	Liquid $C_{11}H_{12}O$ 160.22	Insoluble Soluble	95 (4 hPa) NMR 99 %	1.524-1.529 0.999-1.006	CASrn refers to the racemate.
06.030 1468	1,1-Dimethoxy-2-phenylpropane 6)		2888 2017 90-87-9	Liquid $C_{11}H_{16}O_2$ 180.25	Insoluble Soluble	240-241 IR 95 %	1.492-1.497 0.989-0.994	CASrn refers to the racemate.
08.109 1478	3-Phenylpyruvic acid		3892 156-06-9	Solid $C_9H_8O_3$ 164.16	Soluble Soluble	 158-160 NMR 98 %	n.a. n.a.	
09.057 1469	2-Phenylpropyl butyrate 6)		2891 285 80866-83-7	Liquid $C_{13}H_{18}O_2$ 206.29	Slightly soluble Soluble	268-272 NMR 98 %	1.485-1.491 0.988-0.994	CASrn refers to the racemate.
09.485 1470	2-Phenylpropyl isobutyrate 6)		2892 2087 65813-53-8	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble Soluble	258 NMR 97 %	1.482-1.488 0.971-0.977	CASrn refers to the racemate.
09.728 1458	Ethyl 4-phenylbutyrate		2453 307 10031-93-3	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble Soluble	141-144 (16hPa) NMR 97 %	1.489-1.495 0.986-0.992	
09.729 1464	Methyl 4-phenylbutyrate		2739 308 2046-17-5	Liquid $C_{11}H_{14}O_2$ 178.23	Slightly soluble Soluble	149-151 (13hPa) NMR 97 %	1.483-1.489 0.996-1.002	
09.802 1475	Ethyl 2-ethyl-3-phenylpropionate 6)		3341 10587 2983-36-0	Liquid $C_{13}H_{18}O_2$ 206.29	Insoluble Soluble	72 (0.1 hPa) IR 99 %	1.483-1.489 0.972-0.979	CASrn 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.

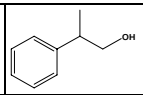
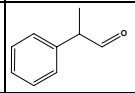
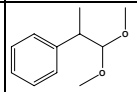
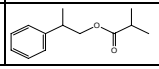
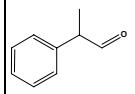
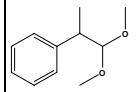
6) Stereoisomeric composition not specified.

7) Composition of mixture not specified.

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (*in vitro / in vivo*) for 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a)

Table 2.1: Summary of Genotoxicity Data of 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
02.073	2-Phenylpropan-1-ol		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	≤3600 µg/plate	Negative[a]	(Wild et al., 1983).
05.038	2-Phenylpropanal		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	≤3600 µg/plate	Negative[a]	(Wild et al., 1983).
06.030	1,1-Dimethoxy-2-phenylpropane		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	≤3600 µg/plate	Negative[a]	(Wild et al., 1983).
09.485	2-Phenylpropyl isobutyrate		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	≤3600 µg/plate	Negative[a]	(Wild et al., 1983).
In vivo							
05.038	2-Phenylpropanal		Sex-linked recessive lethal mutation(Basc test)	D. melanogaster	10 mmol/l (1341 µg/ml)	Negative	(Wild et al., 1983).
			Micronucleus formation	NMRI mice	134, 402, or 670 mg/kg bw	Negative	(Wild et al., 1983).
06.030	1,1-Dimethoxy-2-phenylpropane		Sex-linked recessive lethal mutation(Basc test)	D. melanogaster	5 mmol/l (901 µg/ml)	Negative	(Wild et al., 1983).
			Micronucleus formation	NMRI mice	360, 630, or 900 mg/kg bw	Negative	(Wild et al., 1983).

[a] *With and without metabolic activation.*

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

Substances listed in brackets are the JECFA evaluated substances

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

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
(Phenethyl alcohol [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. This bacterial DNA-repair test system is of low predictive value for genotoxicity.
	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. This bacterial DNA-repair test system is of low predictive value for genotoxicity.
	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.

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

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
(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.
(Isoamyl 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. This bacterial DNA-repair test system is of low predictive value for genotoxicity.
	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 the JECFA evaluated substances

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 2.4: Genotoxicity (in vitro) EFSA / FGE.15

Substances listed in brackets are JECFA evaluated substances

Table 2.4: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.15

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(3-Phenylpropionaldehyde [05.080]) syn. 3-Phenylpropanal	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmoles/plate (403 µg/plate)	Negative[1]	REF :102	Published non-GLP study. Qualitative screening in a spot-test only. Precipitates of substance reported. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study not considered adequate for the evaluation of mutagenic activity.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100µM (0, 0.134, 0.443, 1.34, 4.43, 13.4 µg/ml)[6]	Negative[2, 7, 10]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Cinnamic acid [08.022])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1-1000 µg	Negative[1]	(Lijinsky & Andrews, 1980)	Published non-GLP study of acceptable quality. Limited report of detailed results (for controls only).
	Rec assay	*B. subtilis* M45 (rec-), H17 (rec+)	25 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Rec assay	*B. subtilis* M45 (rec-), H17 (rec+)	2.0 mg/plate (2000 µg/plate)	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100 µM (0, 0.148, 0.489, 1.482, 4.933, 14.82 µg/ml)[6]	Negative[2, 7, 8]	REF :1312	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
4-Hydroxy-3,5-dimethoxycinnamic acid [08.088]	Mutation assay	*E. coli* B/r WP2	1000 µg/plate	Negative[2, 4]	(Shimoi et al., 1985)	Published non-GLP study. Study designed for the determination of effects on UV-induced mutagenesis. Experimental details of the assessment of direct mutagenic activity not reported and results not shown. Thus, the validity of these data cannot be evaluated.
4-Hydroxy-3-methoxycinnamic acid [08.089]	Ames reverse mutation assay	*S. typhimurium* TA98, TA100	NR[5]	Negative[1, 3]	(Matsuda et al., 1992)	Published non-GLP study. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study designed for the determination of ozonation products of 4-hydroxy-3-methoxy-cinnamic acid (and other structural components of humic substances). Thus only results of negative control (not ozonated) are of relevance in this evaluation.
	Mutation assay	*E. coli* B/r WP2	1000 µg/plate	Negative[2, 4]	(Shimoi et al., 1985)	Published non-GLP study. Study designed for the determination of effects on UV-induced mutagenesis. Experimental details of the

Table 2.4: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.15

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
						assessment of direct mutagenic activity not reported and results not shown. Thus, the validity of these data cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 3.3, 10, 33.3, 100, 333 µM (0, 0.641, 1.94, 6.41, 19.4, 64.1 µg/ml)[6]	Negative[2, 7, 8, 9]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-, UV- and X-ray-induced SCEs.
(Ethyl cinnamate [09.730])	Ames reverse mutation assay (preincubation method)	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537,	up to 5000 µg/plate[11]	Negative[1]	(Ishidate et al., 1984)	Published non-GLP study of acceptable quality.
	Chromosomal aberration assay	Chinese hamster fibroblasts	up to 63 µg/ml[12]	Equivocal[2, 13] Negative[2, 13]	(Ishidate et al., 1984)	Published non-GLP study of limited quality.
	Rec assay	*B. subtilis* M45 (rec^-), H17 (rec^+)	20 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3 µM (0, 0.176, 0.581, 1.76, 5.81 µg/ml)[6]	Negative[2, 7, 8]	REF :1312	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Benzyl cinnamate [09.738])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmoles/plate (715 µg/plate)	Negative[1]	(Florin et al., 1980)	Published non-GLP study. Qualitative screening in a spot-test only. Precipitates of substance reported. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study not considered adequate for the evaluation of mutagenic activity.
	Rec assay	*B. subtilis* M45 (rec^-), H17 (rec^+)	1.0 mg/disk (1000 µg/plate)	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
(Methyl cinnamate [09.740])	Rec assay	*B. subtilis* M45 (rec^-), H17 (rec^+)	20 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100 µM (0, 0.162, 0.535, 1.62, 5.40, 16.2 µg/ml)[6]	Negative[2, 7, 8]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Cyclohexyl cinnamate [09.744])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	up to 3600 µg/plate[14]	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.

NR = Not reported

1 With and without S9 metabolic activation.

2 Without S9 metabolic activation.

3 Ozonated samples gave a positive result (more than three times compared to spontaneous mutation) with tester strain TA100 with metabolic activation and weakly positive result (1.5-3 times) without metabolic activation possibly due to formed ozonation products (aldehydes, ketones and carboxylic acids such as formaldehyde, acetaldehyde, glyoxal and methylglyoxal as identified in the same study after ozonation of p-hydroxybenzaldehyde).

4 Negative result reported for both direct mutagenic activitäy and enhancement of UV-induced mutagenesis.

5 Unquantified samples of 4-hydroxy-3-methoxy-cinnamic acid were ozonated at a ratio of sample to ozone of 1:0 (control), 1:0.5, 1:1 and 1:6 (by weight) and then tested for mutagenicity.

6 The highest concentration was reported to be toxic.

7 The substance did not influence cell cycle (data not shown) and spontaneous SCEs at the concentrations used.

8 Posttreatment of mitomycin-treated cells with the substance increased the frequency of induced SCEs in a dose-related manner. The effect was statistically significant ($p<0.001$) at the two highest nontoxic concentrations.

9 The frequency of SCEs induced by UV was significantly increased by treatment with 4-hydroxy-3-methoxy-cinnamic acid at 10 ($0.001<p<0.01$), 33.3 and 100 μM ($p<0.001$) in a dose-related manner. On the contrary, X-ray induced SCEs were significantly reduced by treatment with 4-hydroxy-3-methoxy-cinnamic acid at 10 ($0.01<p<0.05$), 33.3 and 100 μM ($p<0.001$). The effect was also dose-related.

10 Posttreatment of mitomycin-treated cells with the substance did not influence the frequency of induced SCEs.

11 Six different concentrations used (single concentrations not reported).

12 Three different doses used (single doses not reported).

13 Negative result with respect to chromosomal aberrations; equivocal result considering the observed polyploidization effect.

14 Five different concentrations used (single concentrations not reported).

Table 2.5: Genotoxicity (*in vivo*) EFSA / FGE.15

No data were available for any of the substances considered in FGE.15.

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 15 Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a)

Table 3.1: Summary of safety evaluation of 15 JECFA Evaluated Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a)

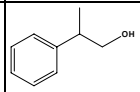
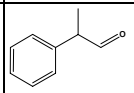
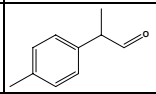
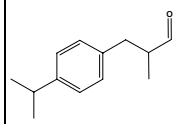
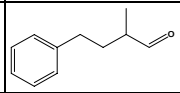
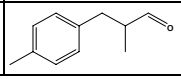
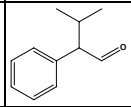
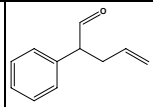
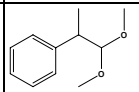
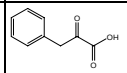
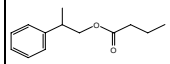
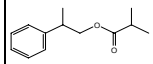
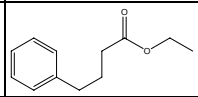
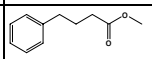
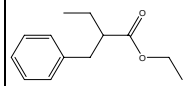
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.073 1459	2-Phenylpropan-1-ol		0.09 0.01	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
05.038 1467	2-Phenylpropanal		110 6	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
05.043 1471	2-(p-Tolyl)propionaldehyde		0.034 0.01	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
05.045 1465	3-(p-Cumenyl)-2-methylpropionaldehyde		18 343	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate According to JECFA: Min. assay value is "90%" and secondary components "3-5% 2-Methyl-3-(p-isopropylphenyl)propionic acid". Composition of stereoisomers and mixture to be specified.
05.046 1462	2-Methyl-4-phenylbutyraldehyde		0.34 0.4	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
05.052 1466	2-Methyl-3-(p-tolyl)propionaldehyde		0.51 27	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.

Table 3.1: Summary of safety evaluation of 15 JECFA Evaluated Phenyl-Substituted Aliphatic Alcohols and Related Aldehydes and Esters (JECFA, 2006a)

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
05.097 1463	3-Methyl-2-phenylbutyraldehyde		ND 0.07	Class I A3: Intake below threshold	4)	7)	CASrn refers to the racemate Composition of stereoisomers to be specified. 7)
05.115 1476	2-Phenylpent-4-enal		0.026 0.04	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
06.030 1468	1,1-Dimethoxy-2-phenylpropane		4.3 3	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
08.109 1478	3-Phenylpyruvic acid		ND 0.09 8)	Class I A3: Intake below threshold	4)	7)	7) 9)
09.057 1469	2-Phenylpropyl butyrate		0.0034 0.5	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
09.485 1470	2-Phenylpropyl isobutyrate		1.6 0.05	Class I A3: Intake below threshold	4)	6)	CASrn refers to the racemate Composition of stereoisomers to be specified.
09.728 1458	Ethyl 4-phenylbutyrate		ND 0.01	Class I A3: Intake below threshold	4)	7)	7)
09.729 1464	Methyl 4-phenylbutyrate		ND 0.01	Class I A3: Intake below threshold	4)	7)	7)
09.802 1475	Ethyl 2-ethyl-3-phenylpropionate		ND 0.9 8)	Class I A3: Intake below threshold	4)	7)	7) 9) CASrn refers to the racemate, composition of stereoisomers to be specified.

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.

8) No production volume was recorded and the MSDI was calculated on the basis of annual production volume anticipated by the manufacturer.

9) For this flavouring substance, JECFA requested use levels or production volume to be provided and the existing JECFA assessment will be revoked if such data are not forthcoming by December 2007 (JECFA, 2006b).

ND: not determined

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14)

Table 3.2: Summary of Safety Evaluation Applying the Procedure (FGE.14) (based on intakes calculated by the MSDI approach)

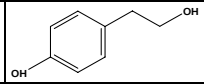
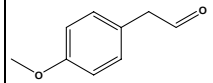
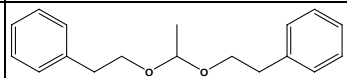
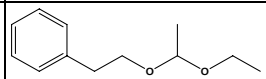
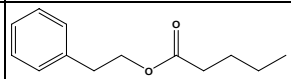
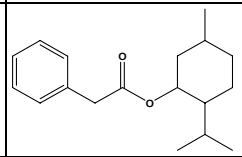
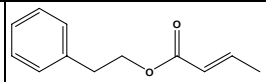
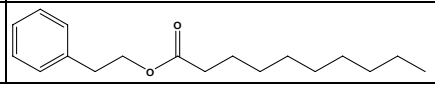
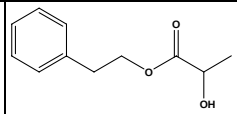
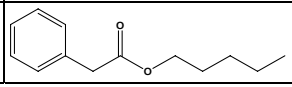
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.166	2-(4-Hydroxyphenyl)ethan-1-ol		0.12	Class I A3: Intake below threshold	4)	6)	
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)	
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)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (FGE.14) (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
09.686	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)	

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.

Table 3.3: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.15)

Table 3.3: Summary of Safety Evaluation Applying the Procedure (FGE.15) (based on intakes calculated by the MSDI approach)

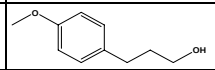
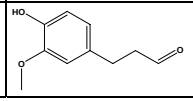
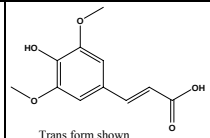
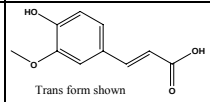
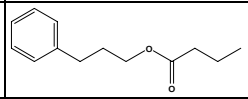
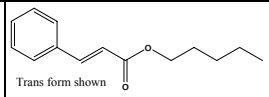
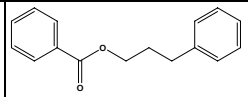
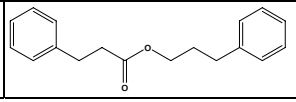
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.173	3-(4-Methoxyphenyl)propan-1-ol		0.061	Class I A3: Intake below threshold	4)	6)	
05.156	3-(4-Hydroxy-3-methoxyphenyl)propanal		0.12	Class I A3: Intake below threshold	4)	6)	

Table 3.3: Summary of Safety Evaluation Applying the Procedure (FGE.15) (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
08.088	4-Hydroxy-3,5-dimethoxycinnamic acid	 Trans form shown	0.012	Class I A3: Intake below threshold	4)	7)	
08.089	4-Hydroxy-3-methoxycinnamic acid	 Trans form shown	0.097	Class I A3: Intake below threshold	4)	7)	
09.690	3-Phenylpropyl butyrate		0.012	Class I A3: Intake below threshold	4)	6)	
09.735	Pentyl cinnamate	 Trans form shown	0.012	Class I A3: Intake below threshold	4)	7)	
09.836	3-Phenylpropyl benzoate		0.37	Class I A3: Intake below threshold	4)	6)	
09.837	3-Phenylpropyl 3-phenylpropionate		0.012	Class I 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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