European Food Safety Authority

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SCIENTIFIC OPINION

Flavouring Group Evaluation 53, Revision 1 (FGE.53Rev1):

Consideration of phenethyl alcohol, aldehyde, acid and related acetals and esters evaluated by JECFA (59th meeting) and structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14Rev1 (2009) and one phenoxyethyl ester evaluated in FGE.23Rev1 (2008)

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

(Question No EFSA-Q-2009-00482)

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PANEL MEMBERS

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SUMMARY

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

The JECFA has evaluated a group of 43 flavouring substances consisting of phenethyl alcohol, aldehyde, acid and related acetals and esters. Two of the JECFA evaluated substances [FL-no:

09.704 and 09.712] may be metabolised to alpha,beta-unsaturated aldehydes. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b), these two substances have been given special considerations.

The remaining 41 flavouring substances have originally been considered by the European Food Safety Authority (EFSA) in the Flavouring Group Evaluation (FGE) 53 (EFSA, 2008z).

The genotoxicity of one of the alpha,beta-unsaturated substances, geranyl phenylacetate [FL-no: 09.704] has been considered in FGE.202 (EFSA, 2009ac). The structural alert for genotoxicity is present in the metabolite citral. The Panel concluded that the data available on citral did rule out the concern for genotoxicity and thus concluded that geranyl phenylacetate can be evaluated through the Procedure in this FGE.

For the second substance, santalyl phenylacetate [FL-no: 09.712], considered in subgroup 2.1 of FGE.19 (EFSA, 2008b), concern with respect to genotoxicity could not be ruled out and additional data were requested. Accordingly, this substance will not be considered in the present FGE.

The present FGE.53Rev1 therefore only deals with 42 flavouring substances.

The Panel concluded that all the 42 substances in the JECFA flavouring group of phenethyl alcohol, aldehyde, acid and related acetals and esters are structurally related to the group of 13 phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in the Flavouring Group Evaluation 14, Revision 1 (FGE.14Rev1) and one phenoxyethyl ester evaluated in the Flavouring Group Evaluation 23, Revision1 (FGE.23Rev1).

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the 42 phenylethyl derivatives. However, 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. Accordingly, the safety in use in Europa could not be assessed using the Procedure, so EU production figures are needed in order to finalise the evaluation of these four substances.

For all 42 substances use levels are needed to calculate the modified Theoretical 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 42 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications are available for 39 of the 42 materials of commerce. For two substances [FL-no: 06.007 and 06.027] 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 of mixture is requested. Thus, for six substances [FL-no: 06.007, 06.027, 09.702, 09.783, 09.805 and 16.041] the Panel has reservations (no European production volumes available, preventing them to be evaluated using the Procedure, and/or stereoisomerism/composition of mixture).

For the remaining 36 substances [FL-no: 02.019, 05.030, 05.042, 05.044, 06.006, 06.016, 06.024, 06.036, 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, 09.538, 09.703, 09.704, 09.707, 09.758, 09.772, 09.784, 09.785, 09.786, 09.787, 09.788, 09.789, 09.791, 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.14Rev1, FGE.23Rev1.

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BACKGROUND

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

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

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

TERMS OF REFERENCE

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

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ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the "EFSA Procedure". This Procedure is based on the opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the "JECFA Procedure". The Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of

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

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

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

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

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

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

amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 microgram per day?")" (JECFA, 1999b).

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

Genotoxicity

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

Specifications

Regarding specifications, the 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.

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

At its 59th meeting the JECFA evaluated a group of 43 flavouring substances consisting of phenethyl alcohol, aldehyde, acid and related acetals and esters. Two of the substances evaluated by the JECFA [FL-no: 09.704 and 09.712] may be metabolised to alpha,beta-unsaturated aldehydes. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b), they have been given special considerations in the Flavouring Group Evaluation 19 (FGE.19). The remaining 41 flavouring substances have originally been considered by EFSA in the FGE.53 (EFSA, 2008z).

FGE.19 contains 360 flavouring substances from the EU Register being alpha, beta-unsaturated aldehydes or ketones and precursors which could give rise to such carbonyl substances via hydrolysis and / or oxidation (EFSA, 2008b). The alpha, beta-unsaturated carbonyls were subdivided into 28 subgroups on the basis of structural similarity (EFSA, 2008b). In an attempt to decide which of the substances could go through the Procedure, a (quantitative) structure-activity relationship ((Q)SAR) prediction of the genotoxicity of these substances was undertaken. The Panel took note of the (Q)SAR predictions by using two ISS Local Models (Benigni & Netzeva, 2007a; Benigni & Netzeva, 2007b)and four DTU-NFI MultiCASE Models (Gry et al., 2007; Nikolov et al., 2007) and the fact that there are available data on genotoxicity, *in vitro* and *in vivo*, as well as data on carcinogenicity for several substances. The Panel decided that 11 subgroups (1.1.2, 1.1.3, 1.1.4, 2.4, 2.6, 2.7, 3.1, 3.3, 4.1, 4.2 and 4.4) (EFSA, 2008b) should be further examined to determine whether evaluation through the Procedure is feasible. Corresponding to these 11 subgroups 11 Flavouring Group Evaluations (FGEs) were established (FGE.201, 202, 203, 210, 212, 213, 214, 216, 217, 218 and 220).

History of FGE.53:

FGE	Opinion Adopted by EFSA	Link	No. of Candidate Substances
FGE.53	April 2007	http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178710471471.htm	41
FGE.53Rev1	March 2009		42

The present Revision of FGE.53, FGE.53Rev1, includes the assessment of one additional substance [FL-no: 09.704] originally considered in FGE.202 (subgroup 1.1.3 in FGE.19) and for which the Panel concluded that the genotoxicity data available do not preclude its evaluation through the Procedure.

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.

1.1.2. EFSA Considerations

Fourty-one of 43 flavouring substances have originally been considered by EFSA in the FGE.53 (EFSA, 2008z).The remaining two of the JECFA evaluated substances, geranyl phenylacetate [FL-no: 09.704] and santalyl phenylacetate [and 09.712] may be metabolised to alpha,beta-unsaturated aldehydes. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b), these two substances have been given special considerations.

The genotoxicity of one of the alpha,beta-unsaturated substances, geranyl phenylacetate [FL-no: 09.704], has been considered in FGE.202 (EFSA, 2009ac). The structural alert for genotoxicity, relevant to this substance is present in the metabolite citral and the Panel concluded that the data available on citral did rule out the concern for genotoxicity and thus concluded that geranyl phenylacetate [FL-no: 09.704] can be evaluated through the Procedure.

For the second substance, santalyl phenylacetate [FL-no: 09.712], considered with respect to genotoxicity in FGE.202 (EFSA, 2009ac), subgroup 2.1 of FGE.19 (EFSA, 2008b), a final conclusion as to its genotoxic properties could not be reached and additional data were requested. Accordingly, this substance will not be considered in this FGE.

The present FGE.53Rev1 therefore only deals with 42 flavouring substances (see Table 1).

The Panel concluded that the 42 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, Revision 1 (FGE.14Rev1) and one phenoxyethyl ester evaluated in the Flavouring Group Evaluation 23, Revision1 (FGE.23Rev1).

1.2. Isomers

1.2.1. JECFA Status

Twelve 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, 09.704, 09.772, 09.785, 09.791, 09.805 and 16.041].

1.2.2. EFSA Considerations

Information is lacking about the stereoisomerism for two substance [FL-no: 06.007 and 06.027].

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 42 substances (JECFA, 2001c). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate for 39 substances. Information on stereoisomerism is lacking for two [FL-no: 06.007 and 06.027], see Section 1.2, and further compositional information for three substances [FL-no: 06.007, 06.027 and 09.805] is requested.

2. Intake Estimations

2.1. JECFA Status

For 38 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[1] 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

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

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 FGE.14Rev1 (EFSA, 2009f)

In vitro / in vivo

Valid *in vitro* mutagenicity and/or genotoxicity data are available for the 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[2] (syn. 2-phenylethan-1-ol) [FL-no: 02.019] and ethyl phenylacetate [FL-no: 09.784][3] 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).

[2] *EFSA evaluated (in FGE.14) 2-(4-hydroxyphenyl)ethan-1-ol [FL-no: 02.166].*

[3] *EFSA evaluated (in FGE.14) pentyl phenylacetate [FL-no: 09.761], menthyl phenylacetate [FL-no: 09.620].*

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 of the candidate substances in FGE.14Rev1.

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

3.3. Genotoxicity and Conclusion on Genotoxicity and Carcinogenicity – Text from FGE.202 (EFSA, 2009ac)

"There are ten *in vitro* studies and three *in vivo* study available on citral [FL-no: 05.020] and on 3-methylcrotonaldehyde (3-methyl-2-butenal) [FL-no: 05.124].

3-Methylcrotonaldehyde was found to be mutagenic in a valid modified Ames test, i.e. the liquid suspension assay, both in the absence and, to a lower extent, in the presence of metabolic activation (S9-mix), in TA100 *S. typhimurium* strain (BASF, 1991b). Of doubtful relevance was a slight increase (factor 2.1) in the number of revertants observed with TA98 strain, only in the absence of S9 at the highest concentration (2500 microgram/plate). It was found negative in a valid bone marrow micronucleus assay in mice, treated orally at 175, 350 and 750 mg/kg body weight, with signs of toxicity at the highest dose, as shown by the ratio of polychromatic to normochromatic erythrocytes (BASF, 1992c). Moreover, it was found negative in a valid *in vivo* unscheduled DNA synthesis (UDS) assay, carried out on hepatocytes from rats treated orally at dose levels of 350 and 700 mg/kg body weight (BASF, 2001). In conclusion, based on the negative results in two valid *in vivo* assays (rat liver UDS and mouse bone marrow micronucleus), the positive result observed in the modified Ames test is considered of limited relevance for the overall evaluation. Therefore, for this substance, the Panel considers that genotoxicity is of no concern.

Citral was not mutagenic in several valid Ames tests (Ishidate et al., 1984; Zeiger et al., 1987; Gomes-Carneiro et al., 1998; NTP, 2003e), and it did not induce chromosome aberrations in a valid *in vitro* study with chinese hamster ovary (CHO) cells (NTP, 2003e). Moreover, it was negative in a valid *in vivo* mouse bone marrow micronucleus assay (NTP, 2003e). The positive results in an *in vitro* test for sister chromatid exchanges (SCE) (NTP, 2003e) and in inappropriate test systems like the *Rec* assay in *B. subtilis* (Yoo, 1986) and the induction of the tumour suppressor protein p53

(Duerksen-Hughes et al., 1999) are considered of limited relevance for the overall evaluation. The Panel concluded that for citral genotoxicity is not of concern.

Overall, the Panel concluded that the genotoxicity data available do not give rise to concern for the 37 substances in FGE.202 using the Procedure.

Study validation and results are presented in Table 2.4 and 2.5.

Conclusion on Genotoxicity and Carcinogenicity

Based on the available data, the Panel concluded that there would be no safety concern with respect to genotoxicity or carcinogenicity for the 37 alpha,beta-unsaturated substances presented in this FGE."

For a summary of genotoxicity data see Table 2.4: Genotoxicity data (*in vitro*) EFSA / FGE.202 and Table 2.5 Genotoxicity data (*in vivo*) EFSA / FGE.202.

3.4. EFSA Considerations

In the FGE.53 there were valid *in vitro* genotoxicity data available for one [FL-no: 02.166] of the ten substances evaluated in FGE.14 and valid *in vitro* and a limited number of *in vivo* mutagenicity data available for two of the substances evaluated by the JECFA and on a further structurally related substance (isoeugenyl phenylacetate).

For 2-(4-hydroxyphenyl)ethan-1-ol [FL-no: 02.166] evaluated by the EFSA in FGE.14Rev1, the only available study gave no indication of a genotoxic potential *in vitro*.

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

There are no genotoxicity studies available for the phenoxyethyl ester [FL-no: 09.687] evaluated in FGE.23Rev1.

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.

Based on the available data on citral evaluated in FGE.202 the Panel concluded that there would be no safety concern with respect to genotoxicity and carcinogenicity of geranyl phenylacetate [FL-no: 09.704] and therefore the 42 flavouring substances consisting of phenethyl alcohol, aldehyde, acid, and related acetals and esters could be evaluated through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 42 Phenylethyl Alcohol and Related Substances Evaluated by the JECFA (JECFA, 2003a):

According to the JECFA 38 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 41 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 42 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 42 phenetyl alcohol, aldehyde, acid and related acetals and esters are summarised in Table 3.1: Summary of Safety Evaluation of 42 Phenylethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters (JECFA, 2003a).

4.2. Application of the Procedure to Ten Phenethyl Derivatives by EFSA (EFSA, 2009f):

Thirteen candidate substances were evaluated in FGE.14Rev1. Twelve substances are classified into structural class I and one substance into structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The 13 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 13 substances as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The substance in FGE.23Rev1 (EFSA, 2008bg) was concluded at step A3 – i.e. the substance is expected to be metabolised to innocuous products (step 2) and the estimated daily intake is below the threshold for the structural class III (step A3).

The stepwise evaluations of the 13 substances evaluated in FGE.14Rev1 and the phenoxythyl ester evaluated in FGE.23Rev1 are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14Rev1 and One Phenoxyethyl Ester Evaluated in FGE.23Rev1).

4.3. EFSA Considerations

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for all the 42 substances in the group of phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances.

However, for four substances [FL-no: 06.027, 09.702, 09.783 and 16.041] no European production figures were available and consequently no European exposure estimate could be calculated. Accordingly, the safety in use in Europe could not be assessed using the Procedure for these four substances.

5. Conclusion

The JECFA has evaluated a group of 43 flavouring substances consisting of phenethyl alcohol, aldehyde, acid and related acetals and esters. Two of the JECFA evaluated substances [FL-no: 09.704 and 09.712] may be metabolised to alpha,beta-unsaturated aldehydes. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b), these two substances have been given special considerations.

The remaining 41 flavouring substances have originally been considered by EFSA in the FGE.53 (EFSA, 2008z).

The genotoxicity of one of the alpha,beta-unsaturated substances, geranyl phenylacetate [FL-no: 09.704] has been considered in FGE.202. The structural alert for genotoxicity is present in the metabolite citral. The Panel concluded that the data available on citral did rule out the concern for genotoxicity and thus concluded that geranyl phenylacetate can be evaluated through the Procedure.

For the second substance, santalyl phenylacetate [FL-no: 09.712], considered in subgroup 2.1 of FGE 19 (EFSA, 2008b), concern with respect to genotoxicity could not be ruled out and additional data were requested. Accordingly, this substance will not be considered in the present FGE.

The present FGE.53Rev1 therefore only deals with 42 flavouring substances.

The Panel concluded that all the 42 substances in the JECFA flavouring group of phenethyl alcohol, aldehyde, acid and related acetals and esters are structurally related to the group of 13 phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14Rev1 and one phenoxyethyl ester evaluated in FGE.23Rev1.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the 42 phenylethyl derivatives. However, 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. Accordingly, the safety in use in Europa could not be assessed using the Procedure, so EU production figures are needed in order to finalise the evaluation of these four substances.

For all 42 substances use levels are needed to calculate the 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 42 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications are available for 39 of the 42 materials of commerce. For two substances [FL-no: 06.007 and 06.027] 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 of mixture is requested. Thus, for six substances [FL-no: 06.007, 06.027, 09.702, 09.783, 09.805 and 16.041] the Panel has reservations (no European production volumes available, preventing them to be evaluated using the Procedure, and/or stereoisomerism/composition of mixture).

For the remaining 36 substances [FL-no: 02.019, 05.030, 05.042, 05.044, 06.006, 06.016, 06.024, 06.036, 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, 09.538, 09.703, 09.704, 09.707, 09.758, 09.772, 09.784, 09.785, 09.786, 09.787, 09.788, 09.789, 09.791, 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 (JECFA, 2002D)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

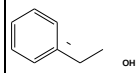
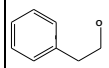
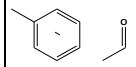
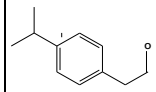
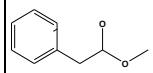
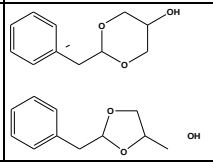
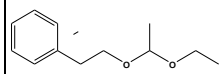
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.019 987	2-Phenylethan-1-ol		2858 68 60-12-8	Liquid $C_8H_{10}O$ 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	
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		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	Racemate.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

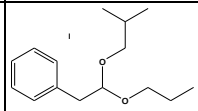
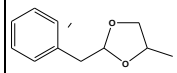
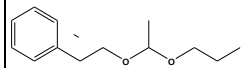
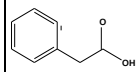
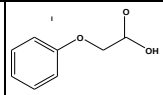
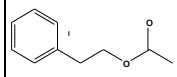
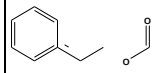
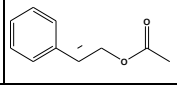
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
06.024 1006	1,1-Di-isobutoxy-2-phenylethane		3384 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	According to the JECFA: Min. assay value is "93 %" and secondary components "butane-2,3-diol".
06.036 1001	1-Butoxy-1-(2-phenylethoxy)ethane		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	Racemate.
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	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

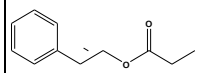
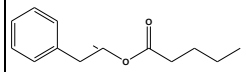
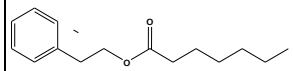
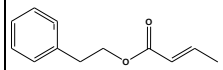
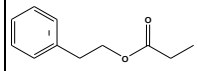
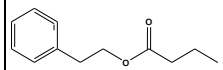
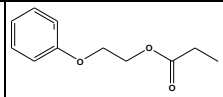
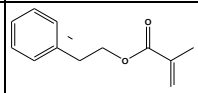
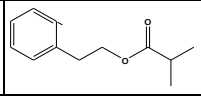
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.168 991	Phenethyl butyrate		2861 506 103-52-6	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	
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		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 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

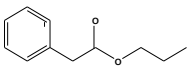
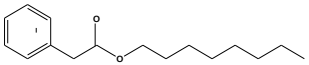
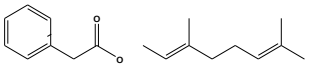
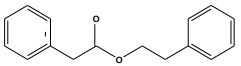
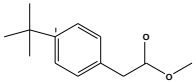
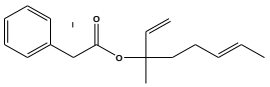
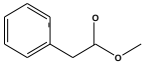
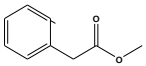
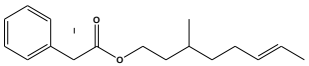
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.702 1010	Propyl phenylacetate		2955 229 4606-15-9	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	
09.704 1020	Geranyl phenylacetate		2516 231 102-22-7	Liquid $C_{18}H_{24}O_2$ 272.39		307-308 IR 97 %	1.501-1.512 0.971-0.978	CASrn in Register refers to (2E)-isomer. Register name to be changed to (2E)-Geranyl phenylacetate.
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		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	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	
09.785 1021	Citronellyl phenylacetate		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	Racemate.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

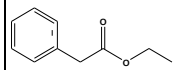
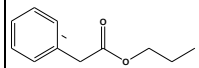
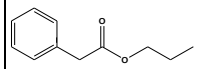
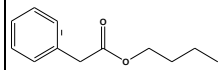
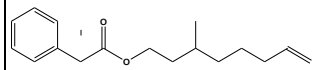
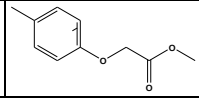
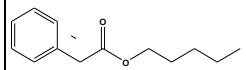
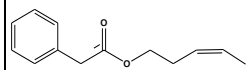
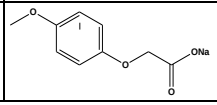
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.786 1011	Isopropyl phenylacetate		2956 2158 4861-85-2	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		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. Register name to be changed to (3S)-Rhodinyl phenylacetate.
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	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 42 Phenethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances (JECFA, 2002d)

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
09.805 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		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.	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 42 Phenetyl Alcohol, Aldehyde, Acid , and Related Acetals and Esters (JECFA, 2003a)

Table 2.1: Summary of Genotoxicity Data for 42 Phenethyl Alcohols, Aldehydes and Acids and Related Acetals and Esters (JECFA, 2003a)

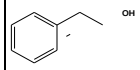
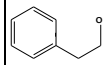
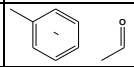
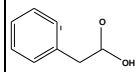
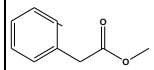
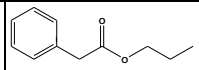
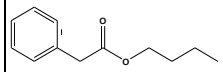
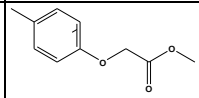
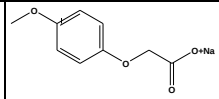
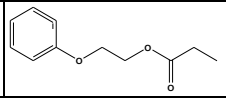
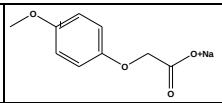
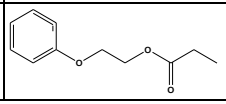
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
02.019	2-Phenylethan-1-ol		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 mmol/plate	Negative[a]	(Florin et al., 1980)
			Sister chromatid exchange	Human 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)
			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)

Table 2.1: Summary of Genotoxicity Data for 42 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
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)
In vivo							
16.041	Sodium 2-(4-methoxyphenoxy)propionate		Micronucleus formation	Mouse bone marrow cells	2000 mg/kg/bw	Negative[c]	(Asquith & Pickering, 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.14Rev1

Substances listed in brackets are JECFA evaluated supporting substances in FGE.14Rev1.

Table 2.2: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.14Rev1

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
(2-Phenylethan-1-ol [02.019] (Phenethyl alcohol))	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.
	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.

Table 2.2: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.14Rev1

Chemical Name	Test System	Test Object	Concentration	Result	Reference	Comments
(3-Methylbutyl phenylacetate [09.789] (Isoamyl phenylacetate))	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 Data (*in vivo*) EFSA / FGE.14Rev1

Substances listed in brackets are JECFA evaluated supporting substances in FGE.14Rev1.

Table 2.3: Summary of Genotoxicity Data (*in vivo)* EFSA / FGE.14Rev1

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 Data (*in vitro*) EFSA / FGE.202

Table 2.4: Genotoxicity Data (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments e)
Citral [05.020]	Reverse mutation	*S. typhimurium* TA98, TA100, TA97a, TA102	5–700 µg/plate	Negative[a]	(Gomes-Carneiro et al., 1998)	Valid. Published non-GLP study containing sufficient details. Result is considered as valid.
	Reverse mutation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 100 µg/plate	Negative[b]	(Ishidate et al., 1984)	Valid. According to current guidelines.The study is considered valid.
	Reverse mutation	*S. typhimurium* TA100	NR	Negative[a]	(Lutz et al., 1982)	Validity cannot be evaluated. One strain only; concentrations tested not specified; no re-run of the test; no other data on experimental results or design apart from a description of the test method.
	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	1–160 µg/plate	Negative[a]	(Zeiger et al., 1987) (NTP, 2003e)	Valid. Standard NTP study carried out according to US.EPA guidelines; result is considered valid.
	Mutation	E. coli WP2uvrA (trp -)	13–100 µg/plate	Negative	(Yoo, 1986)	Validity cannot be evaluated (study in Japanese).
	Sister chromatid exchange	Chinese hamster ovary cells	0.289–40.2 µg/ml	Positive[a]	(NTP, 2003e)	Valid. Standard NTP study carried out according to US EPA guidelines. Result is considered valid.
	Chromosomal aberration	Chinese hamster ovary cells	12.5–60.6 µg/ml	Negative[a]	(NTP, 2003e)	Valid. Standard NTP study carried out according to US.EPA guidelines. Result is considered valid.
	Chromosomal aberration	Chinese hamster fibroblast cells	Up to 30 µg/ml	Negative[c]	(Ishidate et al., 1984)	Limited validity (performed only in the presence of metabolic activation).
	Rec assay	*B. subtilis* M45 and H17	17 µg/disk	Negative	(Oda et al., 1979)	The test system used is considered inappropriate; insufficient validity.
	Rec assay	*B. subtilis* M45 and H17	0.16, 0.32, 0.63 µl/disk (142, 284, 560 µg/disk)[d] 1.25, 2.5 µl/disk (1110, 2220 µg/disk)[d]	Negative Positive	(Kuroda et al., 1984a)	Validity cannot be evaluated. Article in Japanese; with limited information in tables and abstract. Assay of limited relevance.
	Rec assay	*B. subtilis* M45 and H17	<2.5 µl/disk (<2220 µg/disk)	Positive	(Yoo, 1986)	Validity cannot be evaluated (study in Japanese). Study of limited relevance.
	Induction of tumour suppressor protein p53 (DNA damage)	Mouse fibroblast cells (NTCT 929)	10–30 µg/ml	Positive	(Duerksen-Hughes et al., 1999)	The Induction of tumor suppressor protein p53 may be considered as indicator for genotoxicity. Result is considered valid, however, it has only limited relevance.
3-methyl-2-butenal [05.124]	Ames test (preincubation)	*S. typhimurium* TA98, TA100		Positive[a]	(BASF, 1991b)	Valid. Modified Ames test: Unpublished non-GLP study, carried out in accordance with the OECD guideline no 471. The study contains sufficient details and is considered valid.

NR not reported.

[a] *With and without metabolic activation.*

[b] *With metabolic activation.*

[c] *Without metabolic activation.*

[d] *Calculated using a density of 0.888 (Merck, 1997).*

e) Validity of genotoxicity studies:

1. *Valid.*
2. *Limited validity (e.g. if certain aspects are not in accordance with OECD guidelines or current standards and / or limited documentation).*
3. *Insufficient validity (e.g. if main aspects are not in accordance with any recognised guidelines (e.g. OECD) or current standards and/or inappropriate test system).*
4. *Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).*

Table 2.5: Genotoxicity Data (*in vivo*) EFSA / FGE.202

Table 2.5: GENOTOXICITY DATA (*in vivo*)

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments a)
Citral [05.020]	Micronucleus formation	Mouse bone marrow erythrocytes	Three intraperitoneal injections given at 24-h intervals; male mice only	250, 500, or 750 mg/kg bw	Negative	(NTP, 2003e)	NTP study carried out according to US-EPA guideline. Result is considered as valid.
	Micronucleus formation	Mouse peripheral blood erythrocytes	Microencapsulated citral was administered in the diet for 14 weeks	745, 1840, 3915, or 8110 mg/kg bw per day (males) 790, 1820, 3870, or 7550 mg/kg bw per day (females)	Negative Negative	(NTP, 2003e)	NTP study carried out according to a non-standard guideline; result is considered of limited validity.
3-methyl-2-butenal [05.124]	UDS	Rat hepatocytes	Oral administration	350 and 700 mg/kg body weight	Negative	(BASF, 2001)	Unpublished GLP study, carried out in accordance with OECD guideline no 486. The study is considered valid.
	Micronucleus test	Mouse bone marrow erythrocytes	Oral administration	175, 350 and 750 mg/kg body weight	Negative	(BASF, 1992c)	Unpublished GLP study, carried out in accordance with OECD guideline (1991). The study is considered valid.

Validity of genotoxicity studies:

1. *Valid.*
2. *Limited validity (e.g. if certain aspects are not in accordance with OECD guidelines or current standards and / or limited documentation).*
3. *Insufficient validity (e.g. if main aspects are not in accordance with any recognised guidelines (e.g. OECD) or current standards and/or inappropriate test system).*
4. *Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).*

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 42 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)

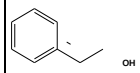
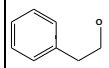
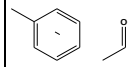
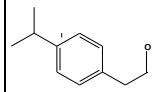
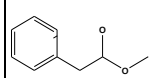
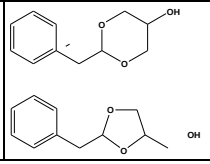
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.019 987	2-Phenylethan-1-ol		1200 330	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
05.030 1002	Phenylacetaldehyde		37 60	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
05.042 1023	p-Tolylacetaldehyde		5.5 3	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
05.044 1024	p-Isopropyl phenylacetaldehyde		0.061 0.01	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
06.006 1003	1,1-Dimethoxy-2-phenylethane		17 40	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
06.007 1004	Phenylacetaldehyde glyceryl acetal		0.12 1	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition and composition of mixture to be specified.

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

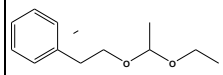
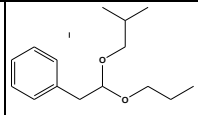
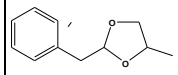
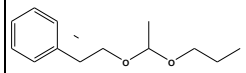
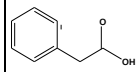
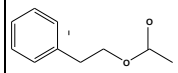
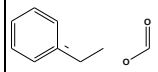
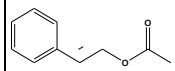
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
06.016 1000	1-Phenylethoxy-1-propoxy ethane		0.12 6	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
06.024 1006	1,1-Di-isobutoxy-2-phenylethane		27 0.4	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
06.027 1005	4,5-Dimethyl-2-benzyl-1,3-dioxolan		ND 1	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure. Stereoisomeric composition and composition of mixture to be specified.
06.036 1001	1-Butoxy-1-(2-phenylethoxy)ethane		0.012 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
08.038 1007	Phenylacetic acid		240 60	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.031 989	Phenethyl acetate		89 60	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.083 988	Phenethyl formate		2.1 30	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.137 990	Phenethyl propionate		0.97 3	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

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

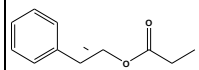
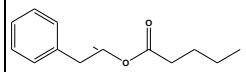
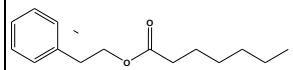
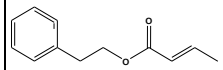
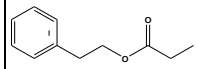
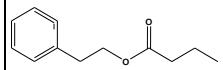
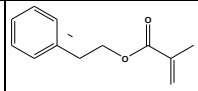
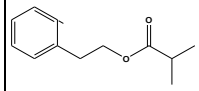
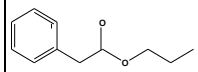
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (μg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.168 991	Phenethyl butyrate		28 30	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.261 995	2-Phenethyl hexanoate		12 2	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.262 996	Phenethyl octanoate		23 0.1	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.407 998	2-Phenethyl 3-methylcrotonate		1.3 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.427 992	Phenethyl isobutyrate		19 60	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.466 994	Phenethyl isovalerate		81 30	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.496 997	Phenethyl 2-methylcrotonate		0.24 1	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.538 993	Phenethyl 2-methylbutyrate		0.37 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.702 1010	Propyl phenylacetate		ND 0.3	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.

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

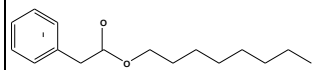
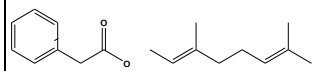
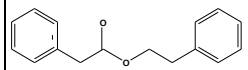
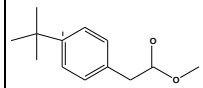
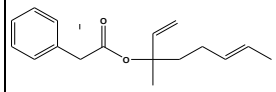
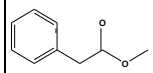
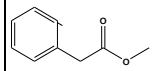
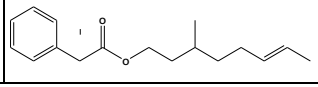
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (μg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.703 1017	Octyl phenylacetate		0.0037 0.006	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.704 1020	Geranyl phenylacetate		1.7 2	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	Register name to be changed to (2E)-Geranyl phenylacetate. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.707 999	Phenethyl phenylacetate		33 80	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.758 1025	Methyl p-tert-butylphenylacetate		17 20	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.772 1019	Linalyl phenylacetate		0.073 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.783 1008	Methyl phenylacetate		ND 20	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.
09.784 1009	Ethyl phenylacetate		110 20	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.785 1021	Citronellyl phenylacetate		1.2 2	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

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

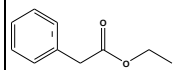
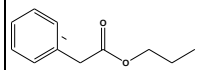
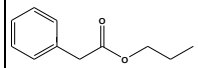
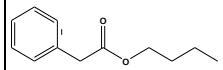
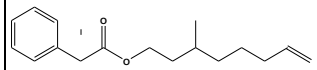
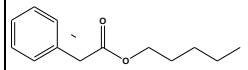
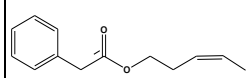
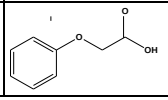
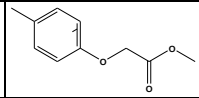
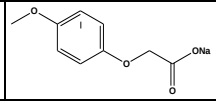
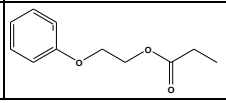
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (μg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.786 1011	Isopropyl phenylacetate		0.061 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.787 1012	Butyl phenylacetate		2.4 3	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.788 1013	Isobutyl phenylacetate		18 20	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.789 1014	3-Methylbutyl phenylacetate		28 30	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.791 1018	Rhodinyl phenylacetate		0.0012 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	Register name to be changed to (3S)-Rhodinyl phenylacetate. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.804 1015	Hexyl phenylacetate		6.9 ND	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
09.805 1016	Hex-3(cis)-enyl phenylacetate		0.73 0.05	Class I A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	Composition of mixture to be specified.
08.049 1026	Phenoxyacetic acid		30 0.1	Class III A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

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
09.797 1027	Ethyl (p-tolyloxy)acetate		0.12 ND	Class III A3: Intake below threshold	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
16.041 1029	Sodium 2-(4-methoxyphenoxy)propionate		ND 6	Class III A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.
09.487 1028	2-Phenoxyethyl isobutyrate		1.7 110	Class III A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

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.

ND: Not determined.

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.14Rev1 and One Phenoxyethyl Ester Evaluated in FGE.23Rev1)

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

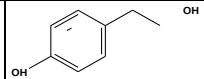
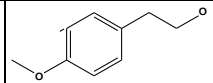
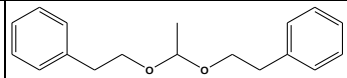
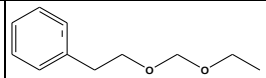
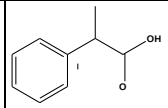
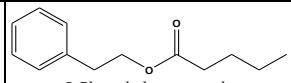
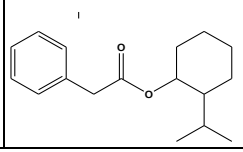
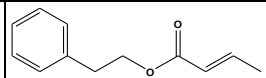
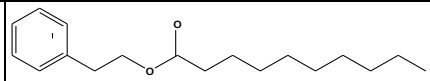
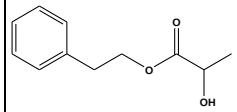
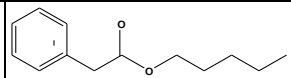
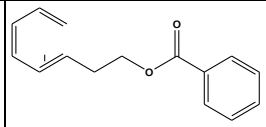
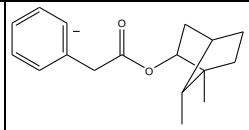
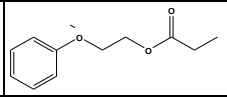
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.166	2-(4-Hydroxyphenyl)ethan-1-ol		0.12	Class I A3: Intake below threshold	4)	6)	
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)	6)	
06.080	1-Ethoxy-1-(2-phenylethoxy)ethane		0.012	Class I A3: Intake below threshold	4)	6)	
08.108	2-Phenylpropionic acid		0.0012	Class I A3: Intake below threshold	4)	7)	
09.201	Phenethyl valerate	 2-Phenethyl structure shown	0.012	Class I A3: Intake below threshold	4)	6)	
09.620	Menthyl phenylacetate		1.5	Class I A3: Intake below threshold	4)	6)	

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
09.684	Phenethyl crotonate	 2-Phenethyl structure shown	0.73	Class I A3: Intake below threshold	4)	6)	
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)	6)	
09.761	Pentyl phenylacetate		1.9	Class I A3: Intake below threshold	4)	6)	
09.774	Phenethyl benzoate		33	Class I A3: Intake below threshold	4)	6)	
09.756	Isobornyl phenylacetate		0.012	Class II A3: Intake below threshold	4)	7)	
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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ABBREVIATIONS

CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DNA	Deoxyribonucleic acid
DTU-NFI	Danish Technical University – National Food Institute
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good Laboratory Practise
ID	Identity
IR	Infrared spectroscopy
ISS	Istituto Superiore di Sanita
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal Dose, 50%; Median lethal dose
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NMR	Nuclear magnetic resonance
No	Number
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PCE/NCE	Polychromatic eryhtrocyte/normochromatic erythrocyte ratio
(Q)SAR	(Quantitative) structure-activity relationship
SCE	Sister chromatid exchange
SCF	Scientific Committee on Food
SLRL	Sex-linked recessive lethal mutations
TAMDI	Theoretical Added Maximum Daily Intake

UDS	Unscheduled DNA synthesis
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation.