European Food Safety Authority

The EFSA Journal (2008) 711, 1-50

Flavouring Group Evaluation 58 (FGE.58)

Consideration of phenol derivatives evaluated by JECFA (55th meeting) structurally related to ring substituted phenolic substances evaluated by EFSA in FGE.22 (2006)

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

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

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

(Adopted on 3 July 2007)

PANEL MEMBERS

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SUMMARY

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

The present consideration concerns 48 phenol and phenol derivatives evaluated by JECFA (55th meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluation of 23 ring substituted phenolic substances evaluated in the Flavouring Group Evaluation 22 (FGE.22).

The Panel concluded that the 44 substances in the JECFA flavouring group of phenol derivatives are structurally related to the group of ring substituted phenolic substances evaluated by EFSA in FGE.22.

Further four substances were evaluated by the JECFA in this group, one is not in the Register (2-phenylphenol [JECFA-no: 735]), and phenol [FL-no: 04.041] and two phenyl esters, phenyl acetate and phenyl salicylate [FL-no: 09.688 and 09.689] will be considered together in a separate FGE.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 44 substances considered in this FGE.

For eight substances [FL-no: 04.037, 04.052, 04.053, 04.056, 07.046, 09.036, 09.102 and 09.288] the JECFA evaluation is only based on Maximised Survey-derived Daily Intake (MSDI) values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances.

For all 44 substances evaluated through the Procedure 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 44 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications including complete purity criteria and identity are available for 41 of the 44 JECFA evaluated substances. For one substance [FL-no: 07.046] information of the stereoisomeric composition is lacking and for two other substances [FL-no: 07.135 and 09.102] further information on the composition is requested.

Thus, for nine substances [FL-no: 04.037, 04.052, 04.053, 04.056, 07.046, 07.135, 09.036, 09.102 and 09.288] the Panel has reservations (only USA production volumes available and/or missing data on isomerism/composition). For the remaining 35 of the 44 JECFA evaluated phenol derivatives [FL-no: 04.005, 04.006, 04.007, 04.008, 04.009, 04.019, 04.022, 04.026, 04.027, 04.028, 04.031, 04.036, 04.042, 04.044, 04.045, 04.046, 04.047, 04.048, 04.049, 04.050, 04.051, 04.057, 04.064, 04.085, 07.005, 07.055, 07.124, 09.174, 09.228, 09.301, 09.429, 09.480, 09.518, 09.709 and 09.711] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

KEYWORDS

Phenol derivatives, JECFA, 55th meeting, phenyl, FGE.22

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2006/252/EC (EC, 2006). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

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

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

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

TERMS OF REFERENCE

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

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000), hereafter named the “EFSA Procedure”. This Procedure is based on the opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b) hereafter named the “JECFA Procedure”. The AFC Panel (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 JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

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

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

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

Threshold Criterion 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 criterion 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 Panel evaluation could lead to a different opinion than that of the JECFA, e.g. Panel requests additional information on isomerism.

Structural Relationship

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

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has evaluated a group of 48 flavouring substances consisting of phenol and phenol derivatives. One of the JECFA evaluated substances, 2-phenylphenol [JECFA-no: 735], is not in the Register. Further three substances will not be dealt with in this FGE: phenol itself [FL-no: 04.041] and two phenyl esters, phenyl acetate and phenyl salicylate [FL-no: 09.688 and 09.689]. These three substances will be considered together in a separate FGE. This consideration will therefore only deal with 44 JECFA evaluated substances.

1.1.2. EFSA Considerations

The Panel concluded that all the 44 substances in the JECFA flavouring group of phenol derivatives are structurally related to the group of 23 ring-substituted phenolic substances evaluated by EFSA in the Flavouring Group Evaluation 22 (FGE.22).

1.2. Isomers

1.2.1. JECFA Status

None of the 44 Register substances in the group of the JECFA evaluated phenol derivatives have a chiral centre. One substance vanillylidene acetone [FL-no: 07.046] has a double bond corresponding to two possible geometric isomers.

1.2.2. EFSA Considerations

Information is lacking about the stereoisomerism for [FL-no: 07.046].

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 44 substances (JECFA, 2000d). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate except that information on isomerism is lacking for [FL-no: 07.046], see Section 1.2 and further information on the composition of [FL-no: 07.135 and 09.102] is requested.

2. Intake Estimations

2.1. JECFA Status

For 36 substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining eight substances production figures are only available for the USA

2.2. EFSA Considerations

As production figures are only available for the USA for eight substances, MSDI values for the EU cannot be calculated for these [FL-no: 04.037, 04.052, 04.053, 04.056, 07.046, 09.036, 09.102 and 09.288].

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text Taken from JECFA (JECFA, 2001b)

In vitro

Negative results were reported in the standard assay for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 incubated with *ortho*-cresol at up to 5000 µg/plate (Douglas et al., 1980; Florin et al., 1980; Nestmann et al., 1980; Pool & Lin, 1982; Haworth et al., 1983; Massey et al., 1994); *meta*-cresol and *para*-cresol at up to 5000 µg/plate (Douglas et al., 1980); Florin et al., 1980; (Nestmann et al., 1980; Pool & Lin, 1982; Haworth et al., 1983)); *para*-ethylphenol, 2,5-xylenol, 2,6-xylenol, and 3,4-xylenol at 367 µg/plate (Florin et al., 1980) 4-(1,1-dimethyl)ethyl phenol at up to 2000 µg/plate (Dean et al., 1985); thymol at up to 1000 µg/plate (Florin et al., 1980; Azizan & Blevins, 1995); resorcinol at up to 7700 µg/plate (Gocke et al., 1981; Haworth et al., 1983); guaiacol at up to 111 726 µg/plate (Douglas et al., 1980; Nestmann et al., 1980; Pool & Lin, 1982; Haworth et al., 1983; Aeschbacher et al., 1989)-dimethoxyphenol at up to 16 000 µg/plate (McMahon et al., 1979; Douglas et al., 1980; Florin et al., 1980; Pool & Lin, 1982) and 2-hydroxyacetophenone at 408 µg/plate (Florin et al., 1980), with and without metabolic activation. However, in an assay with a modified minimal ZLM medium for *Escherichia coli*, the results varied by bacterial strain (Gocke et al., 1981). Resorcinol was mutagenic at doses of 550-7700 µg/plate only in TA1535 without metabolic activation and in TA100 with metabolic activation. The same authors reported negative results in all five *S. typhimurium* strains with and without metabolic activation in the standard Vogel-Bonner medium, which contains a concentration of citrate and other ions that is two to four times higher (Gocke et al., 1981). Negative results with resorcinol at doses up to 3333 µg/plate were reported in another study when Vogel-Bonner medium

was used (Haworth et al., 1983). No mutagenicity was found in *E. coli* exposed to 2,6-dimethoxyphenol at concentrations up to 1000 µg/ml (McMahon et al., 1979).

Forward mutation was not induced in mouse lymphoma L5178YTk+/- cells by resorcinol at 125-2000 µg/ml without metabolic activation (McGregor et al., 1988a). Positive results in this assay were reported with 2-phenylphenol at doses of 0.32-60 µg/ml without metabolic activation and 0.32-5 µg/ml with activation, but these doses were cytotoxic (NTP, 1986e).

Sister chromatid exchange was not induced in human lymphocytes by *ortho*-cresol at concentrations up to 54 µg/ml, *meta*-cresol at up to 108.µg/ml, *para*-cresol at up to 54 µg/ml, *para*-ethyl phenol at up to 27 µg/ml, 2,6-xylenol at up to 31 µg/ml, resorcinol at up to 28 µg/ml, 2,6-dimethoxyphenol at up to 77 µg/ml (Jansson et al., 1986; Jansson et al., 1988) or *para*-vinylphenol at up to 12 µg/ml (Jansson et al., 1986). No evidence of sister chromatid exchange was found in human fibroblasts exposed to *ortho*-cresol at concentrations up to 433 µg/ml or to *meta*- or *para*-cresol at 865 µg/ml (Cheng & Kligerman, 1984), or in Chinese hamster ovary cells exposed to resorcinol at 0.6-2 µg/ml (Wild et al., 1981). Weakly positive results were reported with ortho-cresol at a concentration of 865 µg/ml (Cheng & Kligerman, 1984).

In vivo

The results of assays for genotoxicity *in vivo* were predominantly negative. The frequency of micronucleated polychromatic erythrocytes was not increased in mice after intraperitoneal injections of resorcinol of doses of 55-220 mg/kg bw (Gocke et al., 1981) [two doses of 220 mg/kg bw administered 24 h apart]. (Wild et al., 1981)).

The ability of ortho-cresol [FL-no: 04.027], meta-cresol [FL-no: 04.026], and para-cresol [FL-no: 04.028] to induce sister chromatid exchange was also studied *in vivo* (Cheng & Kligerman, 1984). Mouse bone-marrow cells, alveolar macrophages, and regenerating liver cells were examined after intraperitoneal administration of *ortho*- or *meta*-cresol at 200 mg/kg bw or *para*-cresol at 75 mg/kg bw. The results were negative.

Conclusion on genotoxicity

Overall, the 44 phenol derivatives in this group of flavouring substances are unlikely to be genotoxic *in vivo*.

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

3.2. Genotoxicity Studies - Text Taken from EFSA (EFSA, 2006h)

In vitro / in vivo

Data from *in vitro* tests are available for 12 candidate [FL-no: 04.020, 04.021, 04.065, 04.066, 04.070, 04.076, 04.077, 04.080, 04.095, 07.142, 07.164 and 07.243] and 18 supporting substances. Data from *in vivo* tests are available for one candidate [FL-no: 04.077] and six supporting substances. Most studies are of limited or insufficient quality or are inadequately reported, thus for some of the studies the validity of the results could not be evaluated.

Positive results were observed with three candidate substances [FL-no: 04.077, 04.080 and 07.142].

4-Methoxyphenol [FL-no: 04.077] did not induce gene mutations in bacteria (Haworth et al., 1983). In a gene mutation assay in mammalian cells (MLTK assay) a positive result was observed for 4-

methoxyphenol without metabolic activation and a negative result with metabolic activation using an S9 homogenate (Rogers-Back, 1986). In the test without metabolic activation an increase in the percentage of small colonies was noted indicating a potential for chromosomal aberrations. 4-Methoxyphenol induced chromosomal aberrations in CHO cells in the presence and absence of metabolic activation (Putman, 1986). 4-Methoxyphenol did not induce sister chromatid exchanges in human lymphocytes (Jansson et al., 1988), however, the study was of limited quality. Since 4-methoxyphenol did not induce chromosomal aberration *in vivo* in rat bone marrow cells after oral application (Esber, 1986) the results observed *in vitro* with 4-methoxyphenol were considered to be of no concern.

3,4-Methylenedioxyphenol [FL-no: 04.080] was reported to be negative in a bacterial mutagenicity assay in the presence and absence of metabolic activation while a positive result was reported in a gene mutation assay in mammalian cells (MLTK assay) both in the presence and absence of metabolic activation (Longfellow, 1985/1986). However, this information was only available as a very short abstract and the study reports were not available for evaluation. *In vivo* studies were not available for this candidate substance.

Acetovanillone [FL-no: 07.142] was positive in a yeast assay without metabolic activation (Nestmann & Lee, 1983). This result is not considered to preclude the substance to be evaluated through the Procedure. The substance was negative in bacterial mutagenicity assays in the presence and absence of metabolic activation (Nestmann et al., 1980; Xu et al., 1984). However, reporting of the bacterial assays and the quality of data were insufficient and the validity of the results could not be evaluated.

With the candidate substances 2-ethylphenol [FL-no: 04.070] and 2,4-dimethylphenol [FL-no: 04.066] negative results were observed in bacterial gene mutation assays (Zeiger et al., 1992; Mortelmans et al., 1986; Pool & Lin, 1982). All other results observed in several assays with these two and seven further candidate substances for which data were available were negative. However, these data were of limited or insufficient quality and the validity of the studies could not be evaluated.

With supporting substances positive and negative results were obtained in *in vitro* tests.

2-Methylphenol [FL-no: 04.027], 3-methylphenol [FL-no: 04.026], 4-methylphenol [FL-no: 04.028], 2-methoxyphenol [FL-no: 04.005], and 2,6-dimethoxyphenol [FL-no: 04.036] did not induce gene mutations in bacterial assays of acceptable quality (Haworth et al., 1983; Pool & Lin, 1982). The validity of a positive result observed with 2-methylphenol FL-no: 04.027] in bacteria (Claxton, 1985) cannot be evaluated.

2,6-Dimethylphenol [FL-no: 04.042] induced chromosomal aberrations in mammalian cells in the presence of S9 while the result was negative in the absence of metabolic activation (Völkner, 1994). The *in vitro* genotoxic potential of 2,6-dimethylphenol does not give rise to concern with respect to other alkylated phenols in this FGE, as they are alkyl substituted in either *m*- or *p*-positions. Phenols, substituted in *m*- or *p*-posititon are expected to be metabolised differently from 2,6-dimethylphenol.

2-Methoxyphenol [FL-no: 04.005], 2-methoxy-4-methylphenol [FL-no: 04.007], 2-methylphenol [FL-no: 04.027] and a mixture of 2-methylphenol [FL-no: 04.027], 3-methylphenol [FL-no: 04.026] and 4-methylphenol [FL-no: 04.028] induced sister chromatid exchanges in human lymphocytes or CHO cells (Jansson et al., 1986) [FL-no: 04.005]; (Jansson et al., 1988) [FL-no: 04.007]; (Galloway

& Brusick, 1981) [FL-no: 04.027]; (Galloway & Brusick, 1980) [mixture]). In most cases the effects were observed in the presence and absence of metabolic activation.

The mixture of 2-methylphenol FL-no: 04.027], 3-methylphenol FL-no: 04.026] and 4-methylphenol FL-no: 04.028] resulted in an equivocal response in a UDS assay (Myhr & Brusick, 1980) while induction of UDS was observed with 4-methylphenol FL-no: 04.028] in another *in vitro* study (Crowley & Margard, 1978).

All other results observed in several *in vitro* assays with these and the remaining supporting substances were negative, however, these data were of limited or insufficient quality and the validity of the studies could not be evaluated.

With the supporting substances 2-methylphenol [FL-no: 04.027], 3-methylphenol [FL-no: 04.026] and 4-methylphenol [FL-no: 04.028] negative results were obtained in *in vivo* SCE assays (Cheng & Kligerman, 1984). However, these data were of limited quality. 3-Methylphenol [FL-no: 04.026] did not induce chromosomal aberrations in mice (Ivett et al., 1989). However, the validity of the result cannot be evaluated as the study is inadequately reported. 2-Methylphenol [FL-no: 04.027] and carvacrol [FL-no: 04.031] did not induce mutations in *Drosophila* (Sernau, 1989; Kono et al., 1995).

Conclusion on genotoxicity

Overall, the available genotoxicity data on the supporting substances would not preclude evaluation of the candidate substances through the Procedure. One of the candidate substances, 3,4-methylenedioxyphenol [FL-no: 04.080] was reported to have genotoxic potential *in vitro*. *In vivo* studies were not available for this candidate substance. Therefore, the Panel decided that the Procedure could not be applied to this candidate substance until adequate genotoxicity data become available.

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

3.3. EFSA Considerations

2,6-Dimethylphenol was not mutagenic in four strains of Salmonella typhimurium, when tested for gene mutations by base-pair changes or frame shifts. Neither did it induce gene mutations at the HPRT locus in V79 Chinese Hamster cells (Castle & Larsen, 1997).

2,6-Dimethylphenol induced structural chromosomal aberrations *in vitro* as determined by the chromosomal aberration test in the V79 Chinese hamster cell line. However, when tested *in vivo*, 2,6-Dimethylphenol did not induce chromosomal aberrations in bone marrow cells of male or female Sprague-Dawley rats (Castle & Larsen, 1997). See Table 2.4 for a summary of these studies.

The Panel concluded that the data available do not preclude evaluation of the 44 JECFA evaluated phenol derivatives through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 44 Phenol Derivatives by JECFA (JECFA, 2001a):

According to the JECFA all 44 substances belong to structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded 43 phenol derivatives at step A3 in the JECFA Procedure – i.e. that the substances are expected to be metabolised to innocuous products (step 2) and that the intakes for the substances are below the threshold for structural class I (step A3). One substance [FL-no. 07.055], 4-(p-hydroxyphenyl)-2-butanone, does not occur endogenously in humans, therefore the evaluation proceeded to step A5, where it was considered as of no safety concern at the estimated level of intake based on a 13-week study in which a NOAEL of 280 mg/kg bw/day provides a margin of safety of more than 1000.

In conclusion the JECFA evaluated all 44 substances to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 44 phenol derivatives are summarised in Table 3.1: Summary of Safety Evaluation of phenol derivatives (JECFA, 2001a).

4.2. Application of the Procedure to 23 Ring Substituted Phenolic Substances Evaluated by EFSA (EFSA, 2006h):

Twentythree candidate substances were evaluated in FGE.22. Nineteen substances are classified into structural class I and three into structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

One of the candidate substances, 3,4-methylenedioxyphenol [FL-no: 04.080], showed genotoxic potential *in vitro*. Therefore, the Panel concluded that the Procedure could not be applied to this candidate substance until adequate genotoxicity data become available.

The remaining 22 substances were concluded at step A3 – i.e. that the substances are expected to be metabolised to innocuous products (step 2) and that the estimated daily intakes are below the thresholds for the structural classes I and II (step A3).

In conclusion the Panel considered that the 22 substances evaluated through the Procedure were of no safety concern at the estimated levels of intake based on the MSDI approach.

The stepwise evaluations of the 22 substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.22) (see Table 3.2).

4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 44 substances in the group of phenol derivatives.

5. Conclusion

The Panel concluded that the 44 substances in the JECFA flavouring group of phenol derivatives are structurally related to the group of ring substituted phenolic substances evaluated by EFSA in the Flavouring Group Evaluation 22 (FGE.22).

Further four substances were evaluated by the JECFA in this group, one is not in the Register (2-phenylphenol [JECFA-no: 735]), and phenol [FL-no: 04.041] and two phenyl esters, phenyl acetate and phenyl salicylate [FL-no: 09.688 and 09.689] will be considered together in a separate FGE.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 44 substances considered in this FGE.

For eight substances [FL-no: 04.037, 04.052, 04.053, 04.056, 07.046, 09.036, 09.102 and 09.288] the JECFA evaluation is only based on MSDI values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances.

For all 44 substances evaluated through the Procedure use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 44 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications including complete purity criteria and identity are available for 41 of the 44 JECFA evaluated substances. For one substance [FL-no: 07.046] information of the stereoisomeric composition is lacking and for two other substances [FL-no: 07.135 and 09.102] further information on the composition is requested.

Thus, for nine substances [FL-no: 04.037, 04.052, 04.053, 04.056, 07.046, 07.135, 09.036, 09.102 and 09.288] the Panel has reservations (only USA production volumes available and/or missing data on isomerism/composition). For the remaining 35 of the 44 JECFA evaluated phenol derivatives [FL-no: 04.005, 04.006, 04.007, 04.008, 04.009, 04.019, 04.022, 04.026, 04.027, 04.028, 04.031, 04.036, 04.042, 04.044, 04.045, 04.046, 04.047, 04.048, 04.049, 04.050, 04.051, 04.057, 04.064, 04.085, 07.005, 07.055, 07.124, 09.174, 09.228, 09.301, 09.429, 09.480, 09.518, 09.709 and 09.711] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

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

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

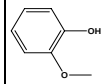
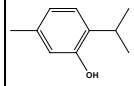
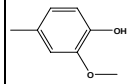
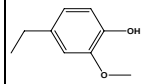
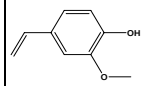
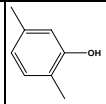
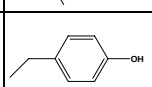
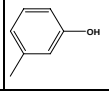
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
04.005 713	2-Methoxyphenol		2532 173 90-05-1	Solid $C_7H_8O_2$ 124.14	Slightly soluble Very soluble	203-206 28 IR 99 %	1.540-1.545 1.129-1.140	According to JECFA: Melting point is "28° (liquid which may crystallize)".
04.006 709	Thymol		3066 174 89-83-8	Solid $C_{10}H_{14}O$ 150.22	Slightly soluble Moderately soluble	232-233 48 IR 98 %	n.a. n.a.	According to JECFA: Melting point is "48° (minimum)".
04.007 715	2-Methoxy-4-methylphenol		2671 175 93-51-6	Liquid $C_8H_{10}O_2$ 138.17	Slightly soluble Miscible	220-222 IR 98 %	1.534-1.538 1.089-1.096	
04.008 716	4-Ethylguaiacol		2436 176 2785-89-9	Liquid $C_9H_{12}O_2$ 152.19	Slightly soluble Miscible	229-235 IR 98 %	1.524-1.534 1.056-1.066	
04.009 725	2-Methoxy-4-vinylphenol		2675 177 7786-61-0	Liquid $C_9H_{10}O_2$ 150.18	Insoluble Miscible	224 IR 96 %	1.534-1.538 1.090-1.096	
04.019 706	2,5-Dimethylphenol		3595 537 95-87-4	Solid $C_8H_{10}O$ 122.17	Slightly soluble Moderately soluble	211-212 70 IR 99 %	n.a. n.a.	According to JECFA: Melting point is "70° (minimum)".
04.022 694	4-Ethylphenol		3156 550 123-07-9	Solid $C_8H_{10}O$ 122.17	Slightly soluble Very soluble	218-219 47-48 IR 99 %	n.a. n.a.	
04.026 692	3-Methylphenol		3530 617 108-39-4	Liquid C_7H_8O 108.14	Slightly soluble Miscible	201 IR 98 %	1.537-1.543 1.028-1.033	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

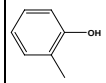
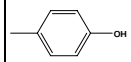
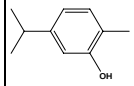
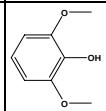
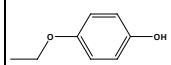
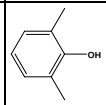
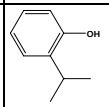
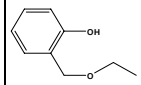
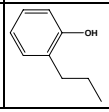
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
04.027 691	2-Methylphenol		3480 618 95-48-7	Solid C_7H_8O 108.14	Soluble Very soluble	191 31-32 IR 98 %	1.544-1.548 1.041-1.046	According to JECFA: Melting point is "31-32° (liquid which may crystallize below 30°)".
04.028 693	4-Methylphenol		2337 619 106-44-5	Solid C_7H_8O 108.14	Slightly soluble Very soluble	201-202 32-36 IR 99 %	n.a. n.a.	
04.031 710	Carvacrol		2245 2055 499-75-2	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	236-238 IR 98 %	1.521-1.528 0.974-0.979	
04.036 721	2,6-Dimethoxyphenol		3137 2233 91-10-1	Solid $C_8H_{10}O_3$ 154.17	Slightly soluble Moderately soluble	261-262 53 IR 98 %	n.a. n.a.	According to JECFA: Melting point is "53° (minimum)".
04.037 720	4-Ethoxyphenol		3695 2258 622-62-8	Solid $C_8H_{10}O_2$ 138.17	Slightly soluble Moderately soluble	246-247 64 IR 95 %	n.a. n.a.	According to JECFA: Melting point is "64° (minimum)".
04.042 707	2,6-Dimethylphenol		3249 11261 576-26-1	Solid $C_8H_{10}O$ 122.17	Very soluble	212 45-49 IR 99 %	n.a. n.a.	SW 8).
04.044 697	2-Isopropylphenol		3461 11234 88-69-7	Liquid $C_9H_{12}O$ 136.19	Slightly soluble Miscible	213-214 IR 98 %	1.525-1.530 0.989-0.999	
04.045 714	2-(Ethoxymethyl)phenol		3485 11905 20920-83-6	Liquid $C_9H_{12}O_2$ 152.19	Slightly soluble Miscible	111-113 (26hPa) MS 99 %	1.517-1.523 1.047-1.052	
04.046 695	2-Propylphenol		3522 11908 644-35-9	Liquid $C_9H_{12}O$ 136.19	Slightly soluble Miscible	224 IR 96 %	1.524-1.528 0.988-0.996	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

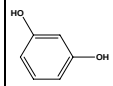
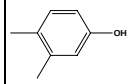
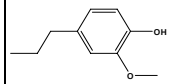
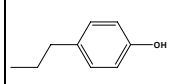
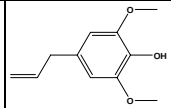
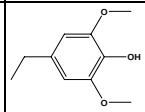
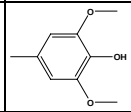
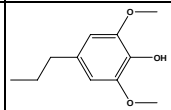
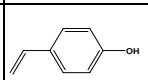
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
04.047 712	Benzene-1,3-diol		3589 11250 108-46-3	Solid $C_6H_6O_2$ 110.11	Soluble Moderately soluble	277-281 109 IR 98 %	n.a. n.a.	
04.048 708	3,4-Dimethylphenol		3596 11262 95-65-8	Solid $C_8H_{10}O$ 122.17	Slightly soluble Moderately soluble	225 62-68 IR 98 %	n.a. n.a.	
04.049 717	2-Methoxy-4-propylphenol		3598 2785-87-7	Liquid $C_{10}H_{14}O_2$ 166.22	Slightly soluble Miscible	250 IR 98 %	1.520-1.525 1.034-1.040	
04.050 696	4-Propylphenol		3649 645-56-7	Liquid $C_9H_{12}O$ 136.19	Insoluble Miscible	232 IR 98 %	1.523-1.527 0.980-0.986	
04.051 726	4-Allyl-2,6-dimethoxyphenol		3655 11214 6627-88-9	Liquid $C_{11}H_{14}O_3$ 194.23	Insoluble Miscible	168 (14 hPa) IR 98 %	1.548-1.550 1.089-1.095	
04.052 723	4-Ethyl-2,6-dimethoxyphenol		3671 11231 14059-92-8	Liquid $C_{10}H_{14}O_3$ 182.22	Insoluble Miscible	106 (0.3 hPa) MS 98 %	1.536-1.537 1.075-1.080	
04.053 722	4-Methyl-2,6-dimethoxyphenol		3704 6638-05-7	Solid $C_9H_{12}O_3$ 168.19	Insoluble Moderately soluble	145-146 (16hPa) 37-42 IR 97 %	n.a. n.a.	
04.056 724	2,6-Dimethoxy-4-propylphenol		3729 6766-82-1	Liquid $C_{11}H_{16}O_3$ 196.25	Insoluble Miscible	115 (0.5 hPa) IR 98 %	1.529-1.530 1.071-1.076	
04.057 711	4-Vinylphenol		3739 11257 2628-17-3	Solid C_8H_8O 120.15	Soluble Moderately soluble	189 68 MS 99 %	n.a. n.a.	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

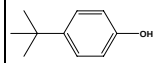
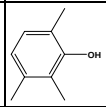
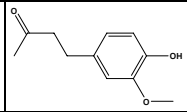
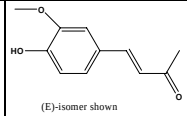
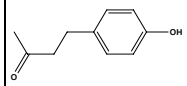
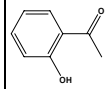
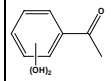
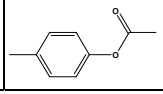
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
04.064 733	4-(1,1-Dimethylethyl)phenol		3918 98-54-4	Solid $C_{10}H_{14}O$ 150.22		236 98-101 IR 98 %	n.a. n.a.	SE 7), SW 8).
04.085 737	2,3,6-Trimethylphenol		3963 2416-94-6	Solid $C_9H_{12}O$ 136.10	Insoluble 50% Soluble in ethyl alcohol	228 63-64 IR 99 %	n.a. n.a.	
07.005 730	Vanillyl acetone		3124 139 122-48-5	Solid $C_{11}H_{14}O_3$ 194.23	Slightly soluble Moderately soluble	187-188 (18hPa) 40-41 IR 95 %	n.a. n.a.	
07.046 732	Vanillylidene acetone 6)	 (E)-isomer shown	3738 691 1080-12-2	Solid $C_{11}H_{12}O_3$ 192.21	Slightly soluble Moderately soluble	 129-130 IR 97 %	n.a. n.a.	CASrn does not specify stereoisomer.
07.055 728	4-(p-Hydroxyphenyl)butan-2-one		2588 755 5471-51-2	Solid $C_{10}H_{12}O_2$ 164.20	Insoluble Moderately soluble	 80 IR 96 %	n.a. n.a.	According to JECFA: Melting point is "80° (minimum)".
07.124 727	2-Hydroxyacetophenone		3548 11784 118-93-4	Liquid $C_8H_8O_2$ 136.15	Slightly soluble Miscible	215-220 IR 95 %	1.556-1.560 1.127-1.133	
07.135 729	2,4-Dihydroxyacetophenone 9)		3662 11884 28631-86-9	Solid $C_8H_8O_3$ 152.15	Insoluble to slightly soluble Moderately soluble	 90 IR 96 %	n.a. n.a.	CASrn does not specify position of hydroxy groups, incompletely defined substance. According to JECFA: Melting point is "90° (minimum)".
09.036 699	p-Tolyl acetate		3073 226 140-39-6	Liquid $C_9H_{10}O_2$ 150.18	Slightly soluble Miscible	208-212 IR 98 %	1.499-1.503 1.044-1.052	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

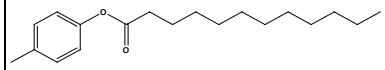
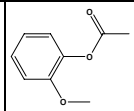
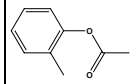
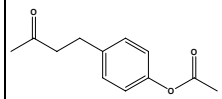
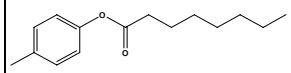
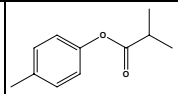
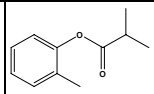
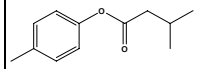
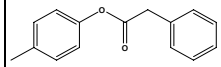
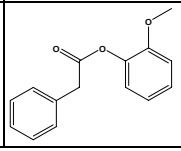
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA Comments
09.102 704	p-Tolyl dodecanoate 9)		3076 378 10024-57-4	Liquid $C_{19}H_{30}O_2$ 290.45	Insoluble	208-210 (13hPa) NMR 90 %	1.494-1.500 0.946-0.952	According to JECFA: Min. assay value is "90" and secondary components "p-Tolyl tetradecanoate, p-Tolyl decanoate, p-Tolyl hexadecanoate".
09.174 718	2-Methoxyphenyl acetate		3687 552 613-70-7	Liquid $C_9H_{10}O_3$ 166.18	Insoluble to slightly soluble Miscible	240-241 IR 98 %	1.507-1.513 1.127-1.134	
09.228 698	o-Tolyl acetate		3072 2078 533-18-6	Liquid $C_9H_{10}O_2$ 150.18	Insoluble Miscible	208 IR 99 %	1.497-1.503 1.046-1.053	
09.288 731	4-(4-Acetoxyphenyl)butan-2-one		3652 3572-06-3	Liquid $C_{12}H_{14}O_3$ 206.24	Insoluble Miscible	155 (3 hPa) IR 93 %	1.506-1.512 1.096-1.100	According to JECFA: Min. assay value is "93 (min. 95% combined o- and p- isomers)" and "contains 2-5% ortho isomer".
09.301 703	p-Tolyl octanoate		3733 59558-23-5	Liquid $C_{15}H_{22}O_2$ 234.34	Insoluble Miscible	265 MS 96 %	1.478-1.488 0.952-0.960	
09.429 701	p-Tolyl isobutyrate		3075 304 103-93-5	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	237 IR 95 %	1.484-1.490 0.990-0.997	
09.480 700	o-Tolyl isobutyrate		3753 681 36438-54-7	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	107 (10 hPa) IR 95 %	1.482-1.488 1.000-1.007	
09.518 702	4-Methylphenyl isovalerate		3387 10545 55066-56-3	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble Miscible	103 (3 hPa) IR 98 %	1.485-1.489 0.977-0.987	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 44 Phenol Derivatives

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
09.709 705	p-Tolyl phenylacetate		3077 236 101-94-0	Solid $C_{15}H_{14}O_2$ 226.27	Insoluble Moderately soluble	310 71 IR 97 %	n.a. n.a.	According to JECFA: Melting point is "71° (minimum)".
09.711 719	Guaiacyl phenylacetate		2535 238 4112-89-4	Solid $C_{15}H_{14}O_3$ 242.27	Insoluble Very soluble	201 (3 hPa) 40-43 IR 97 %	n.a. n.a.	

1) Solubility in water, if not otherwise stated.

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

3) At 1013.25 hPa, if not otherwise stated.

4) At 20°C, if not otherwise stated.

5) At 25°C, if not otherwise stated.

6) Stereoisomeric composition not specified.

7) SE: Missing data on solubility in ethanol.

8) SW: Missing data on solubility.

9) Composition of mixture not specified.

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (*in vitro*) for 44 Phenol Derivatives (JECFA, 2001b)

Table 2.1: Summary of Genotoxicity Data for 44 Phenol Derivatives (JECFA, 2001b)

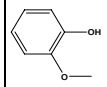
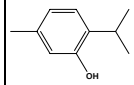
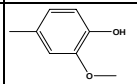
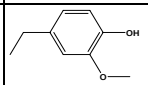
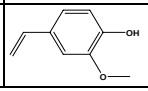
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
04.005 713	2-Methoxyphenol		Reverse mutation	S. typhimurium TA98, TA100, TA102	1-111 726 µg/plate[a,b]	Negative	(Aeschbacher et al., 1989)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	16 000 µg/plate[a,b]	Negative	(Douglas et al., 1980)
			Reverse mutation	S. typhimurium TA1535, TA1537, TA98, TA100	33-10 000 µg/plate[a,b]	Negative	(Haworth et al., 1983)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	16 000 µg/plate[a,b]	Negative	(Nestmann et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5000 µg/plate[a,b]	Negative	(Pool & Lin, 1982)
			Sister chromatid exchange	Human lymphocytes	≤ 31 µg/ml	Positive	(Jansson et al., 1988)
04.006 709	Thymol		Reverse mutation	S. typhimurium TA97, TA98, TA100	1000 µg/ml[a,b]	Negative	(Azizan & Blevins, 1995)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA7537, TA1538	451 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Sister chromatid	Syrian hamster embryo cells	0.3-30 µg/ml	Positive	(Fukuda, 1987)
			Unscheduled DNA synthesis	Syrian hamster embryo cells	0.3-10 µg/ml[a] 1-10 µg/ml[b]	Negative Positive	(Fukuda, 1987)
04.007 715	2-Methoxy-4-methylphenol		Sister chromatid exchange	Human lymphocytes	≤ 138 µg/ml	Positive	(Jansson et al., 1988)
04.008 716	4-Ethylguaiacol		Sister chromatid exchange	Human lymphocytes	0-152 µg/ml	Negative	(Jansson et al., 1988)
04.009 725	2-Methoxy-4-vinylphenol		Sister chromatid exchange	Human lymphocytes	≤ 75 µg/ml	Positive	(Jansson et al., 1988)

Table 2.1: Summary of Genotoxicity Data for 44 Phenol Derivatives (JECFA, 2001b)

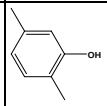
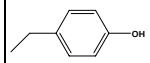
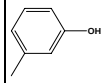
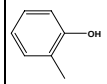
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
04.019 706	2,5-Dimethylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	367 µg/plate[a,b]	Negative	(Florin et al., 1980)
04.022 694	4-Ethylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	367 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Sister chromatid exchange	Human lymphocytes	0-27 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-2.7 µ/ml	Negative	(Jansson et al., 1988)
04.026 692	3-Methylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	2000 µg/plate[a,b]	Negative	(Douglas et al., 1980)
			Reverse mutation	S. typhimurium TA98, A100, TA1535, TA1537, TA1538	324 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Reverse mutation	S. typhimurium TA 1535, TA1537, TA98, TA100	3.3-333 µg/plate[a,b]	Negative[d]	(Haworth et al., 1983)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537 TA1538	2000 µg/plate[a,b]	Negative[d]	(Nestmann et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5000 µg/plate[a,b]	Negative	(Pool & Lin, 1982)
			Sister chromatid exchange	Human fibroblasts	86.5-865 µg/ml	Negative	(Cheng & Kligerman, 1984)
			Sister chromatid exchange	Human lymphocytes	0-108 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-108 µg/ml	Negative	(Jansson et al., 1988)
04.027 691	2-Methylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	2.5 µl/plate[a,b]	Negative	(Douglas et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	324 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Reverse mutation	S. typhimurium TA 1535, TA1537, TA98, TA100	1-100 µg/plate[a,b]	Negative	(Smith et al., 1996)
			Reverse mutation	S. typhimurium TA98, TA100	5 µg/plate[a,b]	Negative	(Massey et al., 1994)
			Reverse mutation	S. typhimurium TA98, TA100, TA7535, TA1537 TA1538	2600 µg/plate[a,b]	Negative[b]	(Nestmann et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5000 µg/plate[a,b]	Negative	(Pool & Lin, 1982)
			Sister chromatid exchange	Human fibroblasts	86.5-433 µg/ml 865 µg/ml	Negative Positive	(Cheng & Kligerman, 1984)
			Sister chromatid exchange	Human lymphocytes	0-54 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-54 µg/ml	Negative	(Jansson et al., 1988)

Table 2.1: Summary of Genotoxicity Data for 44 Phenol Derivatives (JECFA, 2001b)

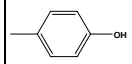
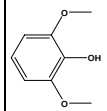
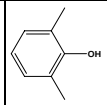
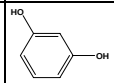
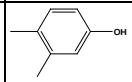
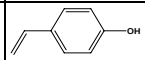
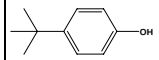
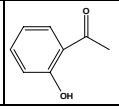
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
04.028 693	4-Methylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	1000 µg/plate[a,b]	Negative	(Douglas et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	324 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Reverse mutation	S. typhimurium TA 1535, TA1537, TA98, TA100	3.3-333 µg/plate[a,b]	Negative	(Haworth et al., 1983)
			Reverse mutation	S. typhimurium TA98, TA 100	5 µg/plate[a,b]	Negative	(Massey et al., 1994)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	1000 µg/plate[a,b]	Negative[d]	(Nestmann et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5000 µg/plate[a,b]	Negative	(Pool & Lin, 1982)
			Sister chromatid exchange	Human fibroblasts	86.5-865 µg/ml	Negative	(Cheng & Kligerman, 1984)
			Sister chromatid exchange	Human lymphocytes	0-54 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-54 µg/ml	Negative	(Jansson et al., 1988)
04.036 721	2,6-Dimethoxyphenol		Reverse mutation	S. typhimurium TA98, TA700, TA1535, TA1537, TA1538	16 000 µg/plate[a,b]	Negative	(Douglas et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	463 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	0.1-1000 µg/ml[a,b]	Negative	(McMahon et al., 1979)
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5000 µg/plate[a,b]	Negative	(Pool & Lin, 1982)
			Reverse mutation	E. coli	1-1000 µg/ml[a,b]	Negative	(McMahon et al., 1979)
			Sister chromatid exchange	Human lymphocytes	0-77 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-77 µg/ml	Negative	(Jansson et al., 1988)
04.042 707	2,6-Dimethylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	367 µg/plate[a,b]	Negative	(Florin et al., 1980)
			Sister chromatid exchange	Human lymphocytes	0-31 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-31 µg/ml	Negative	(Jansson et al., 1988)
04.047 712	Benzene-1,3-diol		Reverse mutation[c]	S. typhimurium TA1535	550-7700 µg/plate[a] 0-7700 µg/plate[b]	Positive Negative	(Gocke et al., 1981)
			Reverse mutation[c]	S. typhimurium TA100	550-7700 µg/plate[b] 0-7700 µg/plate[a]	Positive Negative	(Gocke et al., 1981)
			Reverse mutations	S. typhimurium TA98, TA1537, TA1538	0-7700 µg/plate[a,b]	Negative	(Gocke et al., 1981)

Table 2.1: Summary of Genotoxicity Data for 44 Phenol Derivatives (JECFA, 2001b)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
			Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	0-7700 µg/plate[a,b]	Negative	(Gocke et al., 1981)
			Reverse mutation	S. typhimurium TA 1535, TA1537, TA98, TA100	33-3333 µg/plate[a,b]	Negative	(Haworth et al., 1983)
			Forward mutation	Mouse lymphoma cells	125-2000 µg/ml[a]	Positive	(McGregor et al., 1988b)
			Sister chromatid exchange	Human lymphocytes	0-28 µg/ml	Negative	(Jansson et al., 1986)
			Sister chromatid exchange	Human lymphocytes	0-28 µg/ml	Negative	(Jansson et al., 1988)
			Sister chromatid exchange	Chinese hamster embryo cells	0.6-2.2 µg/ml	Negative	(Wild et al., 1981)
04.048 708	3,4-Dimethylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	367 µg/plate[a,b]	Negative	(Florin et al., 1980)
04.057 711	4-Vinylphenol		Sister chromatid exchange	Human lymphocytes	0-12 µg/ml	Negative	(Jansson et al., 1988)
04.064 733	4-(1,1-Dimethylethyl)phenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	0.2-2000 µg/plate[a,b]	Negative	(Dean et al., 1985)
			Reverse mutation	E. coli. WP_2 and WP_2 uvrA	0.2-2000 µg/plate[a,b]	Negative	(Dean et al., 1985)
			Mitotic gene conversion	S. cerevisiae JD1	0.2-2000 µg/plate[a,b]	Negative	(Dean et al., 1985)
			Chromosomal aberration	Rat liver cell lines RL_1, RL_2	Not specified[e]	Negative	(Dean et al., 1985)
07.124 727	2-Hydroxyacetophenone		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	408 µg/plate[a,b]	Negative	(Florin et al., 1980)

[a] *Without metabolic activation.*

[b] *With metabolic activation.*

[c] *ZLM medium used in place of Vogel-Bonner medium.*

[d] *Presumably non-mutagenic, but solubility did not allow testing in amounts that result in lethality.*

[e] *Concentrations selected corresponded to 0.5, 0.25, and 0.125 of the concentration that caused 50% growth, inhibition (not specified) as determined in an assay for cytotoxicity.*

Table 2.2: Genotoxicity (*in vitro*) EFSA / FGE.22

Substances listed in brackets are JECFA evaluated substances in FGE.22

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(2-Methylphenol [04.027])	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	2.5 µl/plate (26,200µg/plate)	Negative[1, 2]	(Douglas et al., 1980)	17
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	324 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17 Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537	5 concentrations from 1 to 100 µg/plate	Negative[1, 2]	(Haworth et al., 1983)	17 Acceptable quality. Published summary report including detailed results from studies on 250 chemicals tested in various laboratories within the NTP. In accordance with OECD guideline 471 (1983).
	Ames assay	*S. typhimurium* TA98; TA100	5 µg/plate	Negative[1, 2]	(Massey et al., 1994)	17
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 2600 µg/plate (range not reported)	Negative[1, 2, 3]	(Nestmann et al., 1980)	17 Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	4 concentrations from 5 to 5000 µg/plate	Negative[1, 2]	(Pool & Lin, 1982)	17 Acceptable quality.
	Ames assay (preincubation assay)	*S. typhimurium* TA98; TA100; TA1535; TA1537	1000 µg/plate	Negative[1, 2]	(Canter, 1981)	17
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	500 µg/plate	Negative[1, 2]	(Nuodex Inc., 1980a)	17
	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[4] Positive[5]	(Claxton, 1985)	17 Result cannot be evaluated since it was reported only as a very short summary in table format. The paper was on methodological aspects of the assay and not specifically on this compound.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.5 mM (54 µg/ml)	Negative	(Jansson et al., 1986; Jansson et al., 1988)	17 Limited quality (selection of maximum concentration not justified and experiment not repeated).
	Sister chromatid exchange	Human fibroblasts	86.5 - 865 µg/ml without S9	Equivocal	(Cheng & Kligerman, 1984)	17 Limited quality. Only the highest concentration resulted in a result statistically significantly different from control (1.2-fold increase only). A second experiment was not performed.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Sister chromatid exchange	Chinese Hamster ovary cells	4 concentrations from 12.5 to 75 nl/ml (78.6 µg/ml) without S9, 11 concentrations from 1.56 to 700 nl/ml (733 µg/ml) with S9	Positive[1] Positive[2]	(Galloway & Brusick, 1981)	17 Acceptable quality. Statistically significant dose-related increase (up to two-fold).
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 500 nl/ml (524 µg/ml)[4]	Positive[1, 2]	(Galloway & Brusick, 1980)	17 Acceptable quality but limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33 1/3 % each).
	Unscheduled DNA synthesis	Rat primary hepatocytes	7 concentrations from 0.5 to 50 nl/ml (52.4 µg/ml)[4]	Equivocal	(Myhr & Brusick, 1980)	17 Limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33 1/3 % each). Response was not dose-related. A slight response was observed at concentrations up to 5.0 nl/ml, while UDS was not observed at concentrations from 10 to 50 nl/ml.
	DNA Repair assay	*E. coli* W3110	5000 µg/ml	Negative[1, 2]	(Pepper Hamilton and Scheetz, 1980)	17 Test substance included 60 % *o*-cresol.
	DNA repair assay	*E. coli*	5000 µg/ml	Negative[1, 2]	(Nuodex Inc., 1980b)	17.
(3-Methylphenol [04.026])	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	2000 µg/plate	Negative[1, 2]	(Douglas et al., 1980)	17.
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	324 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537	5 concentrations from 3.3 to 333 µg/plate	Negative[1, 2]	(Haworth et al., 1983)	17. Acceptable quality. Published summary report including detailed results from studies on 250 chemicals tested in various laboratories within the NTP. In accordance with OECD guideline 471 (1983).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 2000 µg/plate (range not reported)	Negative[1, 2, 3]	(Nestmann et al., 1980)	17. Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	5 concentrations from 0.5 to 5000 µg/plate	Negative[1, 2]	(Pool & Lin, 1982)	17. Acceptable quality.
	Ames assay (preincubation assay)	*S. typhimurium* TA98; TA100; TA1535; TA1537	3333 µg/plate	Negative[1, 2]	(Canter, 1981)	17.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 1 mmol/L (108 µg/ml)	Negative	(Jansson et al., 1986); (Jansson et al., 1988)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).
	Sister chromatid exchange	Human fibroblasts	865 µg/ml	Negative	(Cheng & Kligerman, 1984)	17
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 500 nl/ml (524 µg/ml)[4]	Positive[1, 2]	(Galloway & Brusick, 1980)	17. Acceptable quality but limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33 1/3 % each).
	Unscheduled DNA synthesis	Rat primary hepatocytes	10 µg/ml	Negative	(Cifone, 1988a)	17.
	Unscheduled DNA synthesis	Rat primary hepatocytes	7 concentrations from 0.5 to 50 nl/ml (51.7 µg/ml)[4]	Equivocal	(Myhr & Brusick, 1980)	17. Limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33 1/3 % each). Response was not dose-related. A slight response was observed at concentrations up to 5.0 nl/ml, while UDS was not observed at concentrations from 10 to 50 nl/ml.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(4-Methylphenol [04.028])	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	1000 µg/plate	Negative[1, 2]	(Douglas et al., 1980)	17.
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	324 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537	5 concentrations from 3.3 to 333 µg/plate	Negative[1, 2]	(Haworth et al., 1983)	17. Acceptable quality. Published summary report including detailed results from studies on 250 chemicals tested in various laboratories within the NTP. In accordance with OECD guideline 471 (1983).
	Ames assay	*S. typhimurium* TA98; TA100	5 µg/plate	Negative[1, 2]	(Massey et al., 1994)	17.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 1000 µg/plate (range not reported)	Negative[1, 2, 3]	(Nestmann et al., 1980)	17. Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	5 concentrations from 0.5 to 5000 µg/plate	Negative[1, 2]	(Pool & Lin, 1982)	17. Acceptable quality.
	Ames assay (preincubation assay)	*S. typhimurium* TA98; TA100; TA1535; TA1537	1000 µg/plate	Negative[1, 2]	(Canter, 1981)	17.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	1 µl/plate (1030 µg/plate)	Negative[1, 2]	(Crowley & Margard, 1978)	17.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.5 mmol/L (54 µg/ml)	Negative	(Jansson et al., 1986)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).
	Sister chromatid exchange	Human fibroblasts	865 µg/ml	Negative	(Cheng & Kligerman, 1984)	17.
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 500 nl/ml (524 µg/ml)[4]	Positive[1, 2]	(Galloway & Brusick, 1980)	17. Acceptable quality but limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33 1/3 % each).
	Unscheduled DNA synthesis	Human lymphocytes	25 µM (2.7 µg/ml)	Negative	(Daugherty & Franks, 1986)	17. Not relevant since only an inhibition of UV-induced UDS was measured.. Additionally, a result is reported only for one concentration (resulting in inhibition by 30 %) and a negative control was not included.
	Unscheduled DNA synthesis	Rat primary hepatocytes	7 concentrations from 0.5 to 50 nl/ml (51.5 µg/ml)	Equivocal	(Myhr & Brusick, 1980)	17. Limited relevance because the test material was a mixture of *p*-cresol, *m*-cresol and *o*-cresol (33

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
						1/3 % each). Response was not dose-related. A slight response was observed at concentrations up to 5.0 nl/ml, while UDS was not observed at concentrations from 10 to 50 nl/ml.
	Unscheduled DNA synthesis	WI-38 human embryonic lung fibroblast cells	Not unambiguously reported	Positive	(Crowley & Margard, 1978)	17. Unpublished study report of limited quality because concentrations were not unambiguously reported and only 3 concentrations have been tested. However, the result was reproducible. Liquid scintillation counting.
2-Ethylphenol [04.070]	Ames assay (preincubation method)	*S. typhimurium* TA97; TA98; TA100; TA1535	5 doses from 0.01 to 10 mg/plate	Negative[1, 2]	(Zeiger et al., 1992)	Acceptable quality.
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	3 µmol/plate (367 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.25 mmol/L (30.5 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
3-Ethylphenol [04.021]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	3 µmol/plate (366 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.25 mmol/L (30.5 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
(4-Ethylphenol [04.022])	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	367 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Epler et al., 1979)	17. Insufficient quality. Not in accordance with OECD guideline 471. Only two strains tested. Results not reported in detail.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.25 mmol/L (27 µg/ml)	Negative	(Jansson et al., 1986)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).
(4-(1,1-Dimethyl)ethyl phenol [04.064])	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	2000 µg/plate	Negative[1, 2]	(Dean et al., 1985)	17. Insufficiently reported. Validity cannot be evaluated as the results were not reported in detail.
	Mutation assay	*E. coli* WP2 and WP2 *uvrA*	2000 µg/plate	Negative[1, 2]	(Dean et al., 1985)	17. Insufficiently reported. Validity cannot be evaluated as main details of the method (e.g. concentration range tested) were not reported. Additionally, the result was not reported in detail.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Mutation assay	*S. cerevisiae* JD1	2000 µg/plate	Negative[1, 2]	(Dean et al., 1985)	17. Insufficiently reported. Validity cannot be evaluated as main details of the method (e.g. concentration range tested) were not reported. Additionally, the result was not reported in detail.
	Chromosomal aberration assay	Rat liver cell RL_1, RL_2	Not specifically indicated[7]	Negative	(Dean et al., 1985)	17. Insufficiently reported. Validity cannot be evaluated as main details of the method (e.g. concentrations tested) were not reported. Additionally, the result was not reported in detail.
	Chromosome aberration assay	Chinese hamster lung cells	Not reported	Negative[8]	(Kusakabe et al., 2002)	17.
	Mouse lymphoma assay	L5178Y *tk* +/- mouse lymphoma cells	80 µg/ml	Negative	(Honma et al., 1999b)	17.
2,3-Dimethylphenol [04.065]	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Epler et al., 1979)	Insufficient quality. Not in accordance with OECD guideline 471. Only two strains tested. Results not reported in detail.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.5 mmol/L (61 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
2,4-Dimethylphenol [04.066]	Ames assay (preincubation method)	*S. typhimurium* TA97; TA98; TA100; TA1535; TA1537	0, 0.33, 1, 3.3, 10, 33 µg/plate	Negative[1, 2]	(Mortelmans et al., 1986)	Acceptable quality.
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	3 µmol/plate[9] (366 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	5 concentrations from 0.5 to 5000 µg/plate[10]	Negative[1, 2]	(Pool & Lin, 1982)	Acceptable quality.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.1 mmol/L (12 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
(2,5-Dimethylphenol [04.019])	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	367 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Epler et al., 1979)	17. Insufficient quality. Not in accordance with OECD guideline 471. Only two strains tested. Results not reported in detail.
(2,6-Dimethylphenol [04.042])	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	367 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium*	5 mg/plate	Negative[1, 2]	(Schechtman et al., 1980)	17.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	(preincubation method)	TA98; TA100; TA1535; TA1537; TA1538	(5000 µg/plate)			
	Chromosome aberration assay	Chinese hamster V79 cells	3 concentrations from 10 to 100 µg/ml (without S9) and 5 concentrations from 30 to 600 µg/ml (with S9)	Negative[1] Positive[2]	(Völkner, 1994)	17. Acceptable quality. This GLP-study was in accordance with OECD guideline 473 (1983). A final report was not available and the draft was not signed. However, the results and conclusions available as draft report are considered valid.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.25 mmol/L (31 µg/ml)	Negative	(Jansson et al., 1986)	17 . Limited quality (selection of maximum concentration not justified and experiment not repeated).
(3,4-Dimethylphenol [04.048])	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	367 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Epler et al., 1979)	17 Insufficient quality. Not in accordance with OECD guideline 471. Only two strains tested. Results not reported in detail.
3,5-Dimethylphenol [04.020]	Ames assay (plate incorporation, preincubation, spot test, and treat-and-plate methods)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538; *E. coli* WP2; WP2*uvrA*	6 concentrations from 125 to 4000 µg/plate	Negative[1, 2]	(Dean et al., 1985)	Insufficiently reported. Validity cannot be evaluated as the results were not reported in detail.
	Mitotic gene conversion assay	*S. cerevisiae* JD1	Not reported	Negative[1, 2]	(Dean et al., 1985)	Insufficiently reported. Validity cannot be evaluated as main details of the method (e.g. concentration range tested) were not reported. Additionally, the result was not reported in detail.
	Chromosome aberration assay	Rat liver cells RL_4	3 concentrations from 0.125 to 0.5 of GI_{50} (50% growth inhibition). Values in µg/ml or µmol/ml not reported.	Negative[1, 2]	(Dean et al., 1985)	Insufficiently reported. Validity cannot be evaluated as main details of the method (e.g. concentrations tested) were not reported. Additionally, the result was not reported in detail.
2,4,6-Trimethylphenol [04.095]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	3 µmol/plate[10] (409 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Epler et al., 1979)	Insufficient quality. Not in accordance with OECD guideline 471. Only two strains tested. Results not reported in detail.
(Thymol [04.006])	Ames assay	*S. typhimurium* TA97; TA98; TA100	1000 µg/ml	Negative[1, 2]	(Azizan & Blevins, 1995)	17.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	451 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay (preincubation method)	*S. typhimurium* TA97; TA98; TA100	Not reported	Negative[1, 2]	(Azizan & Blevins, 1995)	17.
	Sister chromatid exchange	SHE cells	5 concentrations from 0.3 to 30 µg/ml	Equivocal	(Fukuda, 1987)	17. Validity cannot be evaluated since the study was published in Japanese (e.g. presence or absence of S9 is not clear). However, the results reported in a table were not dose-related.
	Unscheduled DNA synthesis	SHE cells	4 concentrations from 0.3 to 10 µg/ml	Equivocal	(Fukuda, 1987)	17. Validity cannot be fully evaluated since the study was published in Japanese (e.g. presence or absence of S9 is not clear). However, the results reported in a table were not dose-related.
(Carvacrol [04.031])	Ames assay	*S. typhimurium* TA98; TA100	2 concentrations (8 and 16 ppm)	Negative[1, 2]	(Kono et al., 1995)	17. Not in accordance with OECD guideline 471 (only two strains used and only two concentrations tested). In Japanese with a short summary in English.
	Ames assay (plate incorporation assay)	*S. typhimurium* TA98; TA100	3 concentrations from 0.6 to 2.5 µmol/plate	Negative[1, 2]	(Stammati et al., 1999)	17. This study was not in accordance with OECD guideline 471 (only two strains used and only 3 concentrations tested).
	Bacterial DNA repair test	*E. coli* WP2 *trpE65*; CM8781 *trpE65; uvrA155, recA56, lexA*	4 concentrations from 2.5 to 6 µmol/paper disk	Positive	(Stammati et al., 1999)	17. Effects were measured as inhibition zones. This assay is considered to be of minor relevance. Positive results from such assays may be interpreted as an indication of a genotoxic potential which needs to be clarified by other assays.
	SOS Chromotest	*E. coli* PQ37	4 concentrations (not unambiguously reported)	Negative	(Stammati et al., 1999)	17. Concentrations not unambiguously reported, only without S9 tested. This assay is considered to be of minor relevance. Positive results from such assays may be interpreted as an indication of a genotoxic potential which needs to be clarified by other assays.
(4-Vinylphenol [04.057])	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.1 mmol/L (12 µg/ml)	Negative	(Jansson et al., 1988)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(2-Methoxyphenol [04.005])	Ames assay	*S. typhimurium* TA98; TA100; TA102	111,726 µg/plate	Negative[1, 2]	(Aeschbacher et al., 1989)	17.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	16,000 µg/plate	Negative[1, 2]	(Douglas et al., 1980)	17.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537	5 concentrations from 333 to 11,740 µg/plate in one experiment and 5 concentrations from 33 to 3333 µg/plate in two further experiments performed in another laboratory	Negative[1, 2]	(Haworth et al., 1983)	17. Acceptable quality. Published summary report including detailed results from studies on 250 chemicals tested in various laboratories within the NTP. Three experiments performed in two laboratories. In accordance with OECD guideline 471 (1983).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 16,000 µg/plate (range not reported)	Negative[1, 2]	(Nestmann et al., 1980)	17. Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	5 conentrations from 0.5 to 5000 µg/plate	Negative[1, 2]	(Pool & Lin, 1982)	17. Acceptable quality.
	Sister chromatid exchange	Human lymphocytes	5 concentration up to 0.5 mmol/L (62 µg/ml)	Positive	(Jansson et al., 1988)	17. Acceptable quality. Only the highest concentration resulted in a statistically significant increase. The effect was very waek but reproducible.
3-Methoxyphenol [04.076]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	30 µmol/plate (3724 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 1 mmol/L (124 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
4-Methoxyphenol [04.077]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	5 concentrations from 3.3 to 167 µg/plate in the first experiment and 5 concentrations from 100 to 5000 µg/plate in the second experiment performed in another laboratory	Negative[2,]	(Haworth et al., 1983)	Acceptable quality. Published summary report including detailed results from studies on 250 chemicals tested in various laboratories within the NTP. Experiments performed in two laboratories. In accordance with OECD guideline 471 (1983).
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	30 µmol/plate (3724 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay (plate incorporation method)	*S. typhimurium* TA100; TA1530	Up to 4 µmol/plate	Negative[1, 2, 12]	(Bartsch et al., 1980)	As only two strains were used the quality of the study must be considered insufficient for the purpose of this Flavouring Group Evaluation Validity cannot be evaluated as details of the

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
						result were not reported.
	Mouse lymphoma assay	Mouse L5178Y TK +/- lymphocytes	27 to 2000 µg/ml (without S9) 1.3 to 100 µg/ml (with S9)	Positive[1] Negative[2]	(Rogers-Back, 1986)	The validity of this unpublished report cannot fully be evaluated since all pages in table format are lacking.
	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.05 mmol/L (6.2 µg/ml)	Negative[6]	(Jansson et al., 1986)	Limited quality (selection of maximum concentration not justified and experiment not repeated).
	Chromosome aberration assay	Chinese hamster ovary cells	954, 1269, and 1692 µg/ml (each in the presence and absence of S9)	Positive[1, 2]	(Putman, 1986)	The validity of this unpublished report cannot fully be evaluated since all pages in table format are lacking.
	Unscheduled DNA synthesis	Human lymphocytes	25 µM (3.1 µg/ml)	Equivocal	(Daugherty & Franks, 1986)	Not relevant since only an inhibition of UV-induced UDS was measured. Additionally, a result is reported only for one concentration (resulting in inhibition by 30 %) and a negative control was not included.
(2-Methoxy-4-methylphenol [04.007])	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 1 mmol/L (138 µg/ml)	Positive	(Jansson et al., 1988)	17. Acceptable quality. The effect was weak (twofold increase) but dose-related and statistically significant.
(4-Ethylguaiacol [04.008])	Sister chromatid exchange	Human lymphocytes	5 concentration up to 1 mmol/L (152 µg/ml)	Negative	(Jansson et al., 1988)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).
(2,6-Dimethoxyphenol [04.036])	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	16,000 µg/plate	Negative	(Douglas et al., 1980)	17.
	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	463 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537	1000 µg/ml	Negative[1, 2]	(McMahon et al., 1979)	17.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	5 concentrations from 0.5 to 5000 µg/plate	Negative[1, 2]	(Pool & Lin, 1982)	17. Acceptable quality.
	Mutation assay	*E. coli*	1000 µg/ml	Negative[1, 2]	(McMahon et al., 1979)	17.
	Sister chromatid exchange	Human lymphocytes	4 concentrations up to 0.5 mmol/L (77 µg/ml)	Negative	(Jansson et al., 1986)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated).
4-Hydroxy-3,5-dimethoxyacetophenone [07.164]	Ames assay (plate incorporation assay)	*S. typhimurium* TA97; TA98; TA100; TA102	6 concentrations from 10 to 4000 µg/plate	Negative[1, 2]	(Pfuhler et al., 1995)	Limited quality. Strain TA 1535 was not used although recommended by OECD 471 (1983 and 1997) which may be acceptable but the test

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
						was not repeated.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 1 mg/plate (range not reported)	Negative[1, 2]	(Nestmann et al., 1980)	Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Mutagenicity assay	*S. cerevisiae* D7; XV185-14C	Not reported	Negative[1]	(Nestmann & Lee, 1983)	Insufficient quality. Details of concentrations and results not reported.
	Sister chromatid exchange	Human peripheral lymphocytes	4 concentrations from 3.3 to 100 µg/ml	Negative[1, 2]	(Pfuhler et al., 1995)	Limited quality as the test was not repeated in an independent experiment. Otherwise in accordance with OECD 479 (1986).
(2-Methoxy-4-vinylphenol [04.009])	Sister chromatid exchange	Human lymphocytes	5 concentrations up to 0.5 mmol/L (75 µg/ml)	Equivocal	(Jansson et al., 1988)	17. Limited quality (selection of maximum concentration not justified and experiment not repeated). Weak effect (only the highest concentration resulted in a twofold increase of SCE frequency which was statistically significant but was not repeated in a second experiment).
3,4- Methylenedioxyphenol [04.080]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA102	4 concentrations from 1 to 10 µM/plate (1381 µg/plate)	(Not applicable)[13]	(Kaur & Saini, 2000)	Limited relevance. Antimutagenic activity was investigated only. The substance was tested only in combination with mutagens.
	Ames Assay (plate incorporation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	33 - 3333 µg/plate	Negative[1, 2, 14]	(Longfellow, 1985/1986)	Validity cannot be evaluated. The information was generated from the Chemical Carcinogenesis Research Information System database. Details of methods and results were not available.
	Mouse lymphoma assay	Mouse L5178Y TK +/- lymphocytes	25 - 215 µg/ml	Positive[1, 2]	(Longfellow, 1985/1986)	Validity cannot be evaluated. The information was generated from the CCRIS database. Details of methods and results were not available.
(2-Hydroxyacetophenone [07.124])	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	408 µg/plate	Negative[1, 2]	(Florin et al., 1980)	17. Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
4- Hydroxy acetophenone [07.243]	Ames assay (preincubation method)	*S. typhimurium* TA98; TA100; TA1535; TA1537	30 µmol/plate (4085 µg/plate)	Negative[1, 2]	(Florin et al., 1980)	Insufficient quality. Not in accordance with OECD guideline 471. Inadequate study design (Spot test).
Acetovanillone [07.142]	Ames assay (preincubation and plate incorporation methods)	*S. typhimurium* TA98; TA100	Not reported	Negative[1, 2]	(Xu et al., 1984)	Insufficient quality. Not in accordance with OECD guideline 471. Only two strains used. Concentration range not reported. Details of results not reported.
	Ames assay	*S. typhimurium* TA98; TA100; TA1535; TA1537; TA1538	Up to 1 mg/plate (range not reported)	Negative[1, 2]	(Nestmann et al., 1980)	Insufficient quality as main details of method and results were not reported. Additionally, the test was not repeated.
	Mutagenicity assay	*S. cerevisiae* D7; *S. cerevisiae* XV185-14C	6 concentrations from 100 to 1000 µg/ml	Negative[15] Positive[15]	(Nestmann & Lee, 1983)	Tested only without S9, however the positive results reported seem to be reliable.
(Vanillyl acetone [07.005])	Ames assay	*S. typhimurium*	1000 µg/plate	Negative[2, 16]	(Mikulasova & Bohovicova,	17.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
	(plate incorporation method)	TA98; TA100			2000)	
	DNA Repair test	*E. coli* WP2, WP2*uvrA*, CM611; CM561	2000 µg/ml	Negative	(Mikulasova & Bohovicova, 2000)	17.

GI = Growth inhibition.

IP = Intraperitoneal.

1) Without metabolic activation.

2) With metabolic activation.

3) Presumably non-mutagenic but solubility did not allow testing in amounts that result in lethality.

4) Negative results in TA100, with and without S9 metabolic activation.

5) Positive results in TA98, with and without metabolic activation.

6) The use of metabolic activation was not reported.

7) The concentrations selected for this assay corresponded to 0.5, 0.25, and 0.125 of the concentration causing 50 % growth inhibition (this concentration was not specified) as determined from a cytotoxicity assay.

8) Test substance was negative in a short-term assay without S9 metabolic activation and in a long-term assay (48 hrs.) with and without S9 metabolic activation. The test substance gave positive results in the short-term assay with S9 metabolic activation.

9) Tested quantitatively with TA100. Substance was cytotoxic at 30 µmol/plate.

10) 5000 µg/plate resulted in cytotoxicity which was defined as a thinning of the background lawn.

11) Tested quantitatively with TA98. Substance was cytotoxic at 30 µmol/plate.

12) The presentation of the result in the publication obviously led the petitioner to the interpretion that the substance was positive in TA1530 but this is not correct. From the footnotes of the publication it becomes clear that the substance was tested in TA100 and TA1530 and that the result was negative. However, as only two strains were used the quality of the study must be considered insufficient for the purpose of this Flavouring Group Evaluation.

13) Antimutagenicity study. Sesamol greatly reduced the mutagenic effects of t-*BOOH.*

14) Test with both rat and mouse S-9 metabolic activation.

15) Negative response for gene conversion (strain D7) and a positive response for reversion (strain XV185-14C).

16) Dose level was the highest non-toxic dose level examined. At 2500 µg/ml cytotoxicity was observed.

17) Summarised by JECFA, 55th meeting (JECFA, 2001b).

Table 2.3: Genotoxicity (*in vivo*) EFSA / FGE.22

Substances listed in brackets are JECFA evaluated substances in FGE.22

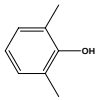
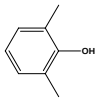
Table 2.3: Summary of Genotoxicity Data (*in vivo*) EFSA / FGE.22

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
(2-Methylphenol [04.027])	*In vivo* Sister chromatid exchange	Mouse bone marrow cells, alveolar macrophages, and regenerating liver cells	IP injection	0, 200 mg/kg	Negative	(Cheng & Kligerman, 1984)	1 Limited quality since only two animals were used and only 20 metaphases were analysed for each cell type from each animal. Only one dose tested.
	In vivo Sex- linked recessive lethal test	*D. melanogaster*	Oral	0, 100, 500, 1000 µg/ml	Negative	(Sernau, 1989)	1 Acceptable quality. GLP study generally in accordance with OECD 477 (1984).
(3-Methylphenol [04.026])	*In vivo* Sister chromatid exchange	Mouse bone marrow cells, alveolar macrophages, and regenerating liver cells	IP injection	0, 200 mg/kg	Negative	(Cheng & Kligerman, 1984)	1 Limited quality since only three animals were used and only 20 metaphases were analysed for each cell type from each animal. Only one dose tested.
	In vivo Chromosome aberration assay	Mouse bone marrow	Oral (gavage)	0, 96, 320, 960 mg/kg	Negative	(Ivett et al., 1989)	1 GLP study in accordance with OECD guideline 475 (1984). However, the validity of the result cannot be evaluated as all pages with results in table format are lacking.
(4-Methylphenol [04.028])	*In vivo* Sister chromatid exchange	Mouse bone marrow cells, alveolar macrophages, and regenerating liver cells	IP injection	0, 75 mg/kg	Negative	(Cheng & Kligerman, 1984)	1 Limited quality since only three animals were used and only 20 metaphases were analysed for each cell type from each animal. Only one dose tested.
(Carvacrol [04.031])	*In vivo* Spot test	*D. melanogaster* BINSC; Oregon-R		1.40 ppm; 0.35 ppm	Negative	(Kono et al., 1995)	1 Validity cannot be evaluated. Publication is in Japanese with a short summary in English. Results reported only for two doses in table format. Not clear if control groups were treated concomitantly.
4-Methoxyphenol [04.077]	*In vivo* Chromosome aberration assay	Rat	Oral (gavage)	0, 100, 333, 1000 mg/kg bw	Negative	(Esber, 1986)	The study design was in accordance with OECD guideline 475 (1984). The study was incompletely reported, however, the study report contained sufficient details to conclude that the outcome of the study is negative.

1) Summarised by JECFA, 55th meeting (JECFA, 2001b).

Table 2.4: Additional Genotoxicity Studies (*in vitro / in vivo*) not Included in JECFA Evaluation

Table 2.4: Additional Genotoxicity Studies (*in vitro/ in vivo*) not Included in JECFA Evaluation

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
04.042 707	2,6-Dimethylphenol		Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	10, 33.3, 100, 333, 1000, 2500, 5000 µg/plate[a]	Negative	(Poth, 1994b)
			Chromosomal aberration	V79 Chinese hamster cells	30, 100, 300 µg/ml (18 hours)[b], 600 µg/ml (28 hours)[b]	Positive	(Völkner, 1994)
			Chromosomal aberration	V79 Chinese hamster cells	10, 30, 100 µg/ml (18 hours)[c], 100 µg/ml (28 hours)[c]	Negative	(Völkner, 1994)
			HPRT assay	V79 Chinese hamster cells	30, 300, 350, 400 µg/ml[c] 30, 100, 200, 300, 600 µg/ml[b]	Negative	(Poth, 1994a)
In vivo							
04.042 707	2,6-Dimethylphenol		Chromosomal aberration	Rat bone marrow	350, 700, 1400 mg/kg bw[d] 300, 600, 1200 mg/kg bw[e]	Negative	(Gudi & Putman, 1966)

a With and without metabolic activation.

b With metabolic activation.

c Without metabolic activation.

d Male rats.

e Female rats.

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 44 Phenol Derivatives (JECFA, 2001a)

Table 3.1: Summary of Safety Evaluation of 44 JECFA Evaluated Phenol Derivatives (JECFA, 2001a)

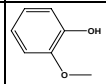
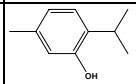
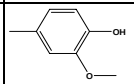
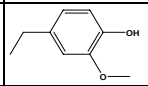
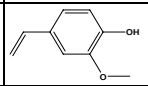
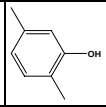
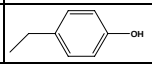
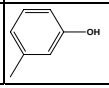
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
04.005 713	2-Methoxyphenol		44 16	Class I A3: Intake below threshold	4)	6)	6)
04.006 709	Thymol		51 160	Class I A3: Intake below threshold	4)	6)	6)
04.007 715	2-Methoxy-4-methylphenol		31 3	Class I A3: Intake below threshold	4)	6)	6)
04.008 716	4-Ethylguaiacol		6.9 0.4	Class I A3: Intake below threshold	4)	6)	6)
04.009 725	2-Methoxy-4-vinylphenol		2.6 1	Class I A3: Intake below threshold	4)	6)	6)
04.019 706	2,5-Dimethylphenol		0.49 0.03	Class I A3: Intake below threshold	4)	6)	6)
04.022 694	4-Ethylphenol		3.5 0.1	Class I A3: Intake below threshold	4)	6)	6)
04.026 692	3-Methylphenol		0.12 0.1	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 44 JECFA Evaluated Phenol Derivatives (JECFA, 2001a)

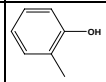
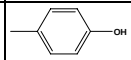
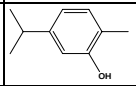
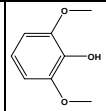
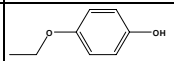
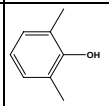
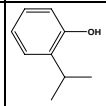
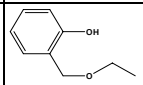
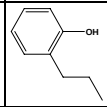
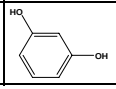
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
04.027 691	2-Methylphenol		250 0.1	Class I A3: Intake below threshold	4)	6)	6)
04.028 693	4-Methylphenol		0.97 1	Class I A3: Intake below threshold	4)	6)	6)
04.031 710	Carvacrol		14 0.3	Class I A3: Intake below threshold	4)	6)	6)
04.036 721	2,6-Dimethoxyphenol		5.4 12	Class I A3: Intake below threshold	4)	6)	6)
04.037 720	4-Ethoxyphenol		ND 0.4	Class I A3: Intake below threshold	4)	7)	7)
04.042 707	2,6-Dimethylphenol		1.7 1	Class I A3: Intake below threshold	4)	6)	6)
04.044 697	2-Isopropylphenol		14 0.3	Class I A3: Intake below threshold	4)	6)	6)
04.045 714	2-(Ethoxymethyl)phenol		1.5 0.01	Class I A3: Intake below threshold	4)	6)	6)
04.046 695	2-Propylphenol		0.12 1	Class I A3: Intake below threshold	4)	6)	6)
04.047 712	Benzene-1,3-diol		1.2 0.3	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 44 JECFA Evaluated Phenol Derivatives (JECFA, 2001a)

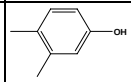
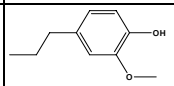
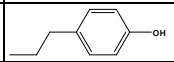
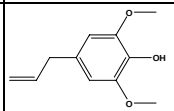
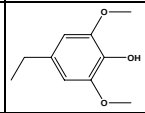
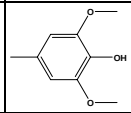
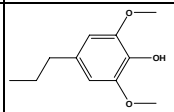
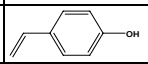
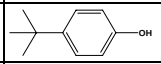
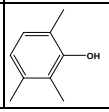
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
04.048 708	3,4-Dimethylphenol		5.7 1	Class I A3: Intake below threshold	4)	6)	6)
04.049 717	2-Methoxy-4-propylphenol		180 0.1	Class I A3: Intake below threshold	4)	6)	6)
04.050 696	4-Propylphenol		0.049 0.1	Class I A3: Intake below threshold	4)	6)	6)
04.051 726	4-Allyl-2,6-dimethoxyphenol		0.012 6	Class I A3: Intake below threshold	4)	6)	6)
04.052 723	4-Ethyl-2,6-dimethoxyphenol		ND 1	Class I A3: Intake below threshold	4)	7)	7)
04.053 722	4-Methyl-2,6-dimethoxyphenol		ND 0.04	Class I A3: Intake below threshold	4)	7)	7)
04.056 724	2,6-Dimethoxy-4-propylphenol		ND 0.1	Class I A3: Intake below threshold	4)	7)	7)
04.057 711	4-Vinylphenol		0.12 6	Class I A3: Intake below threshold	4)	6)	6)
04.064 733	4-(1,1-Dimethylethyl)phenol		0.012 0.01	Class I A3: Intake below threshold	4)	6)	6)
04.085 737	2,3,6-Trimethylphenol		0.24 0.3	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 44 JECFA Evaluated Phenol Derivatives (JECFA, 2001a)

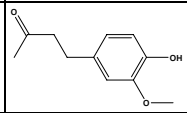
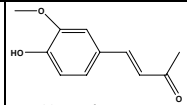
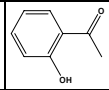
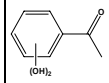
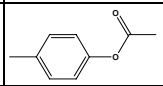
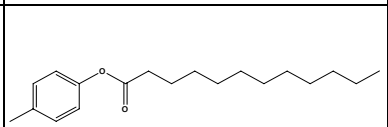
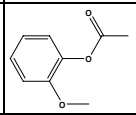
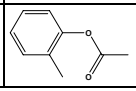
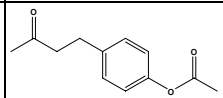
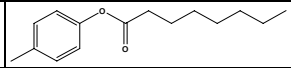
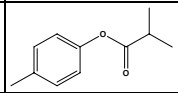
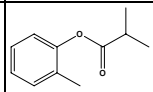
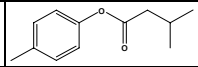
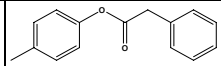
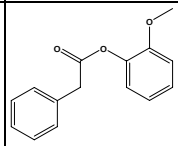
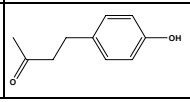
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
07.005 730	Vanillyl acetone		34 83	Class I A3: Intake below threshold	4)	6)	6)
07.046 732	Vanillylidene acetone	 (E)-isomer shown	ND 0.1	Class I A3: Intake below threshold	4)	7)	7) CASrn does not specify stereoisomers. Stereoisomeric composition to be specified.
07.124 727	2-Hydroxyacetophenone		0.12 0.01	Class I A3: Intake below threshold	4)	6)	6)
07.135 729	2,4-Dihydroxyacetophenone		0.012 0.1	Class I A3: Intake below threshold	4)	6)	CASrn does not specify position of hydroxy groups, incompletely defined substance. Composition of mixture to be specified
09.036 699	p-Tolyl acetate		ND 70	Class I A3: Intake below threshold	4)	7)	7)
09.102 704	p-Tolyl dodecanoate		ND 0.3	Class I A3: Intake below threshold	4)	7)	7) According to JECFA: Min. assay value is "90" and secondary components "p-Tolyl tetradecanoate, p-Tolyl decanoate, p-Tolyl hexadecanoate". Composition of mixture to be specified.
09.174 718	2-Methoxyphenyl acetate		0.012 0.1	Class I A3: Intake below threshold	4)	6)	6)
09.228 698	o-Tolyl acetate		0.12 40	Class I A3: Intake below threshold	4)	6)	6)

Table 3.1: Summary of Safety Evaluation of 44 JECFA Evaluated Phenol Derivatives (JECFA, 2001a)

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
09.288 731	4-(4-Acetoxyphenyl)butan-2-one		ND 0.1	Class I A3: Intake below threshold	4)	7)	7)
09.301 703	p-Tolyl octanoate		0.024 1	Class I A3: Intake below threshold	4)	6)	6)
09.429 701	p-Tolyl isobutyrate		0.037 0.01	Class I A3: Intake below threshold	4)	6)	6)
09.480 700	o-Tolyl isobutyrate		0.024 0.1	Class I A3: Intake below threshold	4)	6)	6)
09.518 702	4-Methylphenyl isovalerate		0.37 0.1	Class I A3: Intake below threshold	4)	6)	6)
09.709 705	p-Tolyl phenylacetate		0.61 0.1	Class I A3: Intake below threshold	4)	6)	6)
09.711 719	Guaiacyl phenylacetate		0.37 2	Class I A3: Intake below threshold	4)	6)	6)
07.055 728	4-(p-Hydroxyphenyl)butan-2-one		2400 3800	Class I A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	6)	6)

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

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

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

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

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

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

7) MSDI based on USA production figure.

ND: not determined

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.22)

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

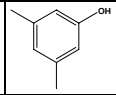
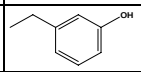
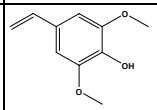
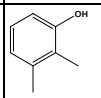
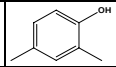
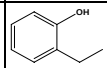
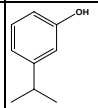
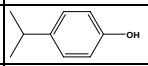
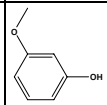
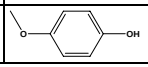
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
04.020	3,5-Dimethylphenol		0.037	Class I A3: Intake below threshold	4)	6)	
04.021	3-Ethylphenol		0.073	Class I A3: Intake below threshold	4)	6)	
04.061	2,6-Dimethoxy-4-vinylphenol		1.2	Class I A3: Intake below threshold	4)	6)	
04.065	2,3-Dimethylphenol		0.013	Class I A3: Intake below threshold	4)	6)	
04.066	2,4-Dimethylphenol		0.011	Class I A3: Intake below threshold	4)	6)	
04.070	2-Ethylphenol		0.037	Class I A3: Intake below threshold	4)	6)	
04.072	3-Isopropylphenol		0.0012	Class I A3: Intake below threshold	4)	6)	
04.073	4-Isopropylphenol		0.24	Class I A3: Intake below threshold	4)	6)	
04.076	3-Methoxyphenol		0.011	Class I A3: Intake below threshold	4)	6)	
04.077	4-Methoxyphenol		0.12	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)

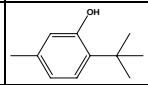
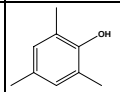
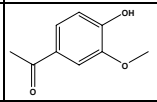
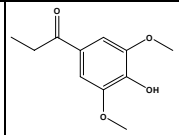
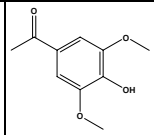
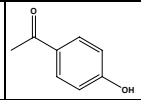
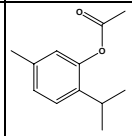
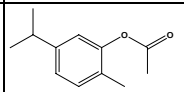
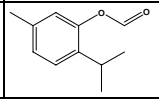
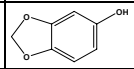
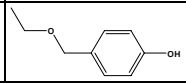
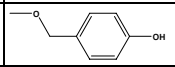
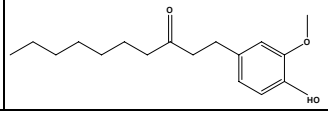
FL-no	EU Register name	Structural formula	MSDI 1) (μg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
04.078	5-Methyl-2-(tert-butyl)phenol		0.061	Class I A3: Intake below threshold	4)	6)	
04.095	2,4,6-Trimethylphenol		0.0097	Class I A3: Intake below threshold	4)	6)	
07.142	Acetovanillone		2.2	Class I A3: Intake below threshold	4)	6)	
07.154	1-(3,5-Dimethoxy-4-hydroxyphenyl)propan-1-one		0.026	Class I A3: Intake below threshold	4)	6)	
07.164	4-Hydroxy-3,5-dimethoxyacetophenone		0.24	Class I A3: Intake below threshold	4)	6)	
07.243	4-Hydroxyacetophenone		0.016	Class I A3: Intake below threshold	4)	6)	
09.253	2-Isopropyl-5-methylphenyl acetate		1.1	Class I A3: Intake below threshold	4)	6)	
09.337	Carvacryl acetate		0.61	Class I A3: Intake below threshold	4)	6)	
09.893	2-Isopropyl-5-methylphenyl formate		0.52	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
04.080	3,4-Methylenedioxyphenol		1.7	Class I No evaluation			a)
04.091	Ethyl 4-hydroxybenzyl ether		0.0012	Class II A3: Intake below threshold	4)	6)	
04.092	4-Hydroxybenzyl methyl ether		0.61	Class II A3: Intake below threshold	4)	6)	
07.234	5-Paradol		0.012	Class II 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.

a) Evaluation deferred pending further genotoxicity data

REFERENCES:

Aeschbacher, H.U., Wolleb, U., Loliger, J., Spadone, J.C., Liardon, R., 1989. Contribution of coffee aroma constituents to the mutagenicity of coffee. Food Chem. Toxicol. 27(4), 227-232.

Azizan, A., Blevins, R.D., 1995. Mutagenicity and antimutagenicity testing of six chemicals associated with the pungent properties of specific spices as revealed by the ames salmonella/microsomal assay. Arch. Environ. Contam. Toxicol. 28, 248-258.

Bartsch, H., Malaveille, C., Camus, A.M., Martel-Planche, G., Brun, G., Hautefeuille, A., Sabadie, N., Barbin, A., Kuroki, T., Drevon, C., Piccoli, C., Montesano, R., 1980. Validation and comparative studies on 180 chemicals with S. typhimurium strains and V79 Chinese hamster cells in the presence of various metabolizing systems. Mutat. Res. 76, 1-50.

Canter, D.A., 1981. Letter from Dept of Health and Human services to U S EPA regarding Salmonella assays performed on cresols, with attachments. EPA Doc. 40-8160101, microfiche no. OTS0517549. Date 2/10/81. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Castle, L., Larsen, J.C., 1997, Food Contact Material Constituent Summary Safety Data Sheet for 2,6-Dimethylphenol, EU-SCF WG-FCM 72nd Meeting, 17-19 November 1997.

Cheng, M., Kligerman, A.D., 1984. Evaluation of the genotoxicity of cresols using sisterchromatid exchange (SCE). Mutat. Res. 137(1), 51-55.

Cifone, M.A., 1988a. Mutagenicity test on meta-cresol in a rat primary hepatocyte unscheduled DNA Synthesis assay with cover letter dated 07/06/88. Chemical Manufacturers Association. EPA Doc. 40-8860250, microfiche no. OTS0517692. Date 6/28/88. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Claxton, L.D., 1985. Assessment of bacterial mutagenicity methods for volatile and semivolatile compounds and mixtures. Environ. Int. 11, 375-383.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard - a decision tree approach. Food Cosmet. Toxicol. 16(3), 255-276.

Crowley, J.P., Margard, W., 1978. Determination of mutagenic/carcinogenic and cytotoxic potential of four chemical compounds (summary report). Sherwin Williams Co. EPA Doc. 40-7860090, microfiche no. OTS0517540. Date 10/31/78. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Daugherty, J.P., Franks, H., 1986. Effect of monocyclic derivatives on DNA repair in human lymphocytes. Res. Commun. Chem. Pathol. Pharmacol. 54,133-136.

Dean, B.J., Brooks, T.M., Hodson-Walker, G., Hutson, D.H., 1985. Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153, 57-77.

Douglas, G.R., Nestmann, E.R., Betts, J.L., Mueller, J.C., Lee, E.G.H., Stich, H.F.,San, H.C., Brouzes, R.J.P., Chmelauskas, A.L., Paavila, H.D., Walden, C.C., 1980. Mutagenic activity in pulp mill effluents. In: Jolley, R. L., Brungs, W.A., Cumming, R.B., Jacobs, V.A., (Eds.). Water Chlorination: Environmental Impact and Health Effects. vol. 3. Ann Arbor Science Publishers Inc., Ann Arbor, MI, pp. 865-880.

EC, 1996. Regulation No 2232/96 of the European Parliament and of the Council of 28 October 1996. Official Journal of the European Communities 23.11.1996, L 299, 1-4.

EC, 1999a. Commission Decision 1999/217/EC of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs. Official Journal of the European Communities 27.3.1999, L 84, 1-137.

EC, 2000. Commission Regulation No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) no. 2232/96. Official Journal of the European Communities 19.7.2000, L 180, 8-16.

EC, 2006. Commission Decision 2006/252/EC of 27 March 2006 amending Decision 1999/217/EC as regards the register of flavouring substances used in or on foodstuffs. Official Journal of the European Union 29.3.2006, L 91, 48.

EFSA, 2006h. Opinion of the Scientific Panel AFC related to Flavouring Group Evaluation 22 (FGE.22): Ring-substituted phenolic substances from chemical groups 21 and 25 (Commission Regulation (EC) No 1565/2000 of 18 July 2000).Adopted on 27 September 2006. EFSA-Q-2003-165.

Epler, J.L., Rao, T.K., Guerin, M.R., 1979. Evaluation of feasibility of mutagenic testing of shale oil products and effluents. Environ. Health Perspect. 30, 179-184.

Esber, H.J., 1986. In vivo cytogenetics study in rats - compound W1188.01 with cover letter dated 08/17/92. Proctor & Gamble Co. EPA Doc. 88-920007233, microfiche no. OTS0545546. Date 7/09/86. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18, 219-232.

Fukuda, S., 1987. Assessment of the carcinogenic hazard of 6 substances used in dental practices. I.Morphological transformations, DNA damage and SCE in cultured Syrian hamster embryo cells induced by camphor, eugenol, thymol, EDTA, benzalkonium chloride and benzethonium chloride. Shigaku 74(6), 1365-1383. (In Japanese)

Galloway, S.M., Brusick, D.J., 1980. Mutagenicity evaluation of sample containing 33 1/3% each ortho-, meta-, and para-cresol in sister chromatid exchange assay with Chinese hamster ovary (CHO) cells. Final report. Cresol Task Force. EPA Doc. FYI-OTS-0780-0079, microfiche no. OTS0000079-0. Date 060180. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Galloway, S.M., Brusick, D.J., 1981. Sister chromatid exchange assay, Ames assay, mouse lymphoma forward mutation assay, and cell transformation on o-cresol. Pepper, Hamilton & Scheetz. EPA Doc. 40-8160079, microfiche no. OTS0517531. Date 5/01/81. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Gocke, E., King, M.-T., Eckhardt, K., Wild, D., 1981. Mutagenicity of cosmetics ingredients licensed by the European Communities. Mutat. Res. 90, 91-109.

Gudi, R., Putman, D.L., 1966. In vivo rat bone marrow cytogenetic assay with 2,6-dimethylphenol, Microbiological Associates, Inc., 5221 River Road, Bethesda, Maryland 20826 and 9900 Blackwell Road, Rockville, Maryland 20850, Report: G95CA85.105, February 22.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutag. Suppl. 1, 3-142.

Honma, M., Zhang, L.-S., Sakamoto, H., Ozaki, M., Takeshita, K., Momose, M., Hayashi, M., Sufuni, T., 1999. The need for long-term treatment in the mouse lymphoma assay. Mutagenesis 14(1), 23-29.

Ivett, J.L., Brown, B.M., Rodgers, C., Anderson, B.E., Resmick, M.A., Zeiger, E., 1989. Chromosomal aberrations and sister chromatid exchange tests in chinese hamster ovary cells in vitro. IV. Results with 15 chemicals. Environ. Mol. Mutag. 14, 165-187.

Jansson, T., Curvall, M., Hedin, A., Enzell, C., 1986. In vitro studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid in human lymphocytes by weakly acidic, semivolatile constituents. Mutat. Res. 169, 129-139.

Jansson, T., Curvall, M., Hedin, A., Enzell, C., 1988. In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke. Mutat. Res. 206, 17-24.

JECFA, 1995. Evaluation of certain food additives and contaminants. Forty-fourth Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, no. 859. Geneva.

JECFA, 1996a. Toxicological evaluation of certain food additives. The forty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives and contaminants. WHO Food Additives Series: 35. IPCS, WHO, Geneva.

JECFA, 1997a. Evaluation of certain food additives and contaminants. Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 6-15 February 1996. WHO Technical Report Series, no. 868. Geneva.

JECFA, 1999b. Evaluation of certain food additives and contaminants. Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. Rome, 17-26 June 1997. WHO Technical Report Series, no. 884. Geneva.

JECFA, 2000d. Compendium of food additive specifications. Addendum 8. Joint FAO/WHO Expert Commitee of Food Additives. 55th meeting. Geneva, 6-15 June 2000. FAO Food and Nutrition paper 52 Add. 8.

JECFA, 2001a. Evaluation of certain food addtives and contaminants. Fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, no. 901. Geneva, 6-15 June 2000.

JECFA, 2001b. Safety evaluation of certain food additives and contaminants. Fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 46. IPCS, WHO, Geneva.

JECFA, 2006c. Joint FAO/WHO Expert Committee on Food Additives. Sixty-seventh meeting Rome, 20-29 June 2006, Summary and Conclusions. issued 7 July 2006

Kaur, I.P., Saini, A., 2000. Sesamol exhibits antimutagenic activity against oxygen species mediated mutagenicity. Mutat. Res. 470(1), 71-76.

Kono, M., Yoshida, Y., Itaya, Y., Shimobo, K., Yoshikawa, K., Terashita, T., Shishiyama, J., 1995. Antimicrobial activity and mutagenicity of allyl isothiocyanates and several essential oils from spices. Mem. Fac. Agri. Kinki Univ. 28, 11-19. (In Japanese)

Kusakabe, H., Yamakage, K., Wakuri, S., Sasaki, K., Nakagawa, Y., Watanabe, M., Hayashi, M., Sofuni, T., Ono, H., Tanaka, N., 2002. Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals. Mutat. Res. 517, 187-198.

Longfellow, D., 1985/1986. Mutagenicity studies. Sesamol. Short-term test program sponsored by the Division of Cancer Etiology, National Cancer Institute. As cited in Chemical Carcinogenesis Research Information System (CCRIS), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) on July 1, 2004.

Massey, I.J., Aitken, M.D., Ball, L.M., Heck, P.E., 1994. Mutagenicity screening of reaction products from the enzyme-catalyzed oxidation of phenolic pollutants. Environ. Toxicol. Chem. 13(11), 1743-1752.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C., Caspary, W.J., 1988a. Responses of the L5178Y tk+/tk- mouse lymphona cell forward mutation assay: III. 72 coded chemicals. Environ. Mol. Mutag. 12, 85-153.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Caspary, W.J., 1988b. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay II: 18 coded chemicals. Environ. Mol. Mutag. 11, 91-118.

McMahon, R.E., Cline, J.C., Thompson, C.Z., 1979. Assay of 855 test chemicals in ten tester strains using a new modification of the ames test for bacterial mutagens. Cancer Res. 39, 682-693.

Mikulasova, M., Bohovicova, I., 2000. Genotoxic effect of vanillin derivatives. Biologia (Bratislava) 55(3), 229-234.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. Salmonella mutagenicity tests II. Results from the testing of 270 chemicals. Environ. Mol. Mutag. 8(Suppl. 7), 1-119.

Myhr, B.C., Brusick, D.J., 1980. Evaluation of ortho-,meta-,and para-cresol 33 1/3% each in primary rat hepatocyte unscheduled DNA synthesis assay, draft report. Cresol Task Force. EPA Doc. FYI-OTS-0980-0079, microfiche no. OTS0000079-0. Date 080180. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Nestmann, E.R., Lee, E.G.H., 1983. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of Saccharomyces cerevisiae. Mutat. Res. 119, 273-280.

Nestmann, E.R., Lee, E.G., Matula, T.I., Douglas, G.R., Mueller, J.C., 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79, 203-212.

NTP, 1986e. NTP technical report on the toxicology and carcinogenesis studies of ortho-phenylphenol (CAS no. 90-43-7) alone and with 7,12-dimethylbenz(a)anthracene (CAS no. 57-97-6) in in swiss CD-1 mice (dermal studies). NTP-TR 301. NIH Publication no. 86-2557.

Nuodex Inc., 1980a. Mutagenicity studies ON R-1044. EPA Doc. 878211352, microfiche no. OTS0206261. Date 032780. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Nuodex Inc., 1980b. Evaluation of R-1044 in the E. coli DNA repair - suspension assay. EPA Doc. 878211353, microfiche no. OTS0206261. Date 032780. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Pepper Hamilton and Scheetz, 1980. Evaluation of R-1044 In the E. coli DNA repair suspension assay with cover letter to EPA dated 10/11/83. EPA Doc. 40-8360166, microfiche no. OTS0507480. Date 032780. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Pfuhler, S., Stehrer-Schmid, P., Dorsch, W., Wagner, H., Wolf, H.U., 1995. Investigation of genotoxic effects of the anti-asthmatic and anti-inflammatory drugs apocyninand acetosyringenin in the Salmonella typhimurium mutagenicity assay and the SCE-test with human lymphocytes. Phytomedicine 1(4), 319-322.

Pool, B.L., Lin, P.Z., 1982. Mutagenicity testing in the Salmonella typhimurium assay of phenolic compounds and phenolic fractions obtained from smokehouse condensates. Food Chem. Toxicol. 20, 383-391.

Poth, A., 1994a. Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79/HPRT) with 2,6-dimethylphenol, Cytotest Research Gmbh & Co. KG, D-64380 Rossdorf, F.R.G., CCR/RCC report: 441802/360966, July 07.

Poth, A., 1994b. Salmonella typhimurium Reverse Mutation Assay with 2,6-dimethylphenol, Cytotest Cell Research Gmbh & Co. KG, D-64380 Rossdorf, F.R.G., CCR/RCC report: 441801/360955, July 07.

Putman, D.L., 1986. Initial submission: In vitro cytogenicity study with 4-methoxyphenol in Chinese Hamster Ovary (CHO) Cells (final report) with cover letter dated 08/17/92. Proctor & Gamble Co. EPA Doc. 88-920007112, microfiche no. OTS0545451. Date 8/06/86. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Rogers-Back, A., 1986. Initial submission: L5178Y: Mouse lymphoma assay with cover letter dated 08/17/92. Proctor & Gamble Company. EPA Doc. 88-920007210, microfiche no. OTS0545512. Date 8/13/86. Selected pages. Unpublished report submitted by EFFA to FLAVIS Secretariat.

SCF, 1999. Opinion on a programme for the evaluation of flavouring substances (expressed on 2 December 1999). Scientific Committee on Food. SCF/CS/FLAV/TASK/11 Final 6/12/1999. Annex I the minutes of the 119th Plenary meeting. European Commission, Health & Consumer Protection Directorate-General.

Schechtman, L.M., Curren, R.D., Parmar, A.S., Sinsky, P.M., 1980. Activity of T1570 in the Salmonella/microsomal assay for bacterial mutagenicity with attachments and cover letter dated 11/21/91. EPA Doc. 86-920000183, microfiche no. OTS0534388. Date 5/13/80. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Sernau, D., 1989. Mutagenicity tests on ortho- and para-cresol: drosophila melanogaster sex-linked recessive lethal test (final report) with attachments and cover letter dated 03/21/89. Chemical Manufacturers Association. EPA Doc. 40-8960320, microfiche no. OTS0529221. Date 2/22/89. pp. 1-33. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Smith, R.L., Newberne, P., Adams, T.B., Ford, R.A., Hallagan, J.B., FEMA Expert Panel, 1996. 17. GRAS Substances. Food Technol. 50(10), 72-78, 80-81. (With correction table for use levels for sodium (±)2-(4-methoxyphenoxy)propanoate. Food Technol. 51(2), 32).

Stammati, A., Bonsi, P., Zucco, F., Moezelaar, R., Alakomi, H.L., von Wright, A., 1999. Toxicity of selected plant volatiles in microbial and mammalian short-term assays. Food Chem. Toxicol. 37(8), 813-823.

Völkner, W., 1994. Support: Letter from General Elec Co. to US EPA re: Chromosome aberration assay in Chinese hamster V79 cells In vitro with 2, 6-dimethylphenol with attachments and cover letter dated 06/01/94. General Elec Co. EPA Doc. 8EHQ-0694-1027, microfiche no. OTS0527745-2. Date 06/01/94. Unpublished report submitted by EFFA to FLAVIS Secretariat.

Wild, D., King, M.T., Eckhardt, K., Gocke, E., 1981. Mutagenic activity of aminophenols, and diphenols, and relations with chemical structure. Mutat. Res. 85(6), 456.

Xu, J., Whong, W.-Z., Ong, T.-M., 1984. Validation of the Salmonella (SV50)-arabinoseresistant forward mutation assay system with 26 compounds. Mutat. Res. 130(2), 79-86.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutag. 19(21), 2-141.

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ACKNOWLEDGEMENT

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food wishes to thank Jørn Gry, Vibe Beltoft, Frederikke Bentzen, Karin Nørby and Trine Klein Reffstrup for their contribution to the draft opinion