Flavouring Group Evaluation 88, (FGE.88)\textsuperscript{1}

Consideration of Phenol and Phenol Derivatives

evaluated by JECFA (55\textsuperscript{th} meeting)

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

(EFSA-Q-2008-081)

Adopted on 6 March 2008

PANEL MEMBERS


SUMMARY

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

The Panel has considered three substances in the JECFA flavouring group of phenol and phenol derivatives. The Panel concluded that no corresponding Flavouring Group Evaluation (FGE) is available.

Considering the EU Risk Assessment Report on phenol, the Panel concluded that the available data do not preclude the evaluation of phenol [FL-no: 04.041] and its two esters, phenol acetate [FL-no: 09.688] and phenyl salicylate [FL-no: 09.689] through the Procedure. However, the Panel did not fully agree with the application of the Procedure as performed by the JECFA for the three substances considered in this FGE. Due to the possible formation of

Flavouring Group Evaluation 88, (FGE.88) Phenol and Phenol Derivatives

The Panel considered that phenol and its two esters could not be predicted to be metabolised to innocuous products. Accordingly, the evaluation proceeded via the B-side while JECFA has evaluated them via the A-side.

The Panel considered that on the basis of the default Maximised Survey-derived Daily Intake (MSDI) approach the three substances [FL-no: 04.041, 09.688 and 09.689], which have been evaluated using the Procedure, would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

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

Specifications including complete purity criteria and identity tests are available for two of the three JECFA evaluated substances. For one substance [FL-no: 09.689] an identity test is lacking.

Thus, for phenyl salicylate [FL-no: 09.689] the Panel has a reservation (a missing identity test). For the remaining two of the three JECFA evaluated substances, phenol and phenyl acetate [FL-no: 04.041 and 09.688] the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

KEYWORDS

Flavourings, safety, phenol, phenol esters, JECFA, 55th meeting, European Union Risk Assessment Report Phenol.
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 flavouring substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2006/252/EC (EC, 2006). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

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

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

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

TERMS OF REFERENCE

EFSA is requested to consider the JECFA 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.

ACKNOWLEDGEMENTS

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food wishes to thank Vibe Beltoft, Frederikke Bentzen, Jørn Gry, Rainer Gürtler, Pia Lund and Karin Nørby for their contribution to the draft Opinion.
ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000), hereafter named the “EFSA Procedure”. This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the “JECFA Procedure”. The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance.

Intake

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

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

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

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

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

Threshold of 1.5 Microgram/Person/Day (Step B5) Used by the JECFA
The JECFA uses the threshold of concern of 1.5 microgram/person/day as part of the evaluation procedure:

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

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has evaluated a group of 48 flavouring substances consisting of phenol and phenol derivatives.

1.1.2. EFSA Considerations

One of the JECFA evaluated substances, 2-phenylphenol [JECFA-no: 735], is not in the Register, and 44 of the phenol derivatives were considered in 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)”. The remaining unsubstituted phenol [FL-no: 04.041] and the two esters of phenol, phenol acetate [FL-no: 09.688] and phenyl salicylate [FL-no: 09.689], will be dealt with in this FGE. In contrast to phenol the formation of toxic metabolites like hydroquinones and quinones is not expected to be of significance for the ring-substituted phenols in FGE.22 at their estimated levels of intake as...
flavouring substances (EFSA, 2006h). Therefore, the Panel concluded that FGE.22 should not be used as a supporting group and that there was no other corresponding FGE available.

1.2. Isomers

1.2.1. JECFA Status
None of the three substances dealt with in this FGE, from the JECFA flavouring group of 48 substances, has a chiral centre.

1.2.2. EFSA Considerations
No comments.

1.3. Specifications

1.3.1. JECFA Status
JECFA specifications are available for the three substances (JECFA, 2001b). See Table 1.

1.3.2. EFSA Considerations
Specifications are considered adequate for two of the three substances. For one substance [FL-no: 09.689] an identity test is lacking.

2. Intake Estimations

2.1. JECFA Status
For all three substances evaluated through the JECFA Procedure intake data based on production volumes (MSDI approach) are available for the EU.

2.2. EFSA Considerations
No comments.

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text Taken from the 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 phenol at concentrations up to 9400 µg/plate (Florin et al., 1980; Gocke et al., 1981; Pool & Lin, 1982; Haworth et al., 1983; Aeschbacher et al., 1989; Massey et al., 1994) and phenyl salicylate at up to 333 µg (Zeiger et al., 1987), 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). At concentrations of 470-9400 µg/plate, phenol caused reverse mutation only in strain TA98 in the presence of metabolic activation. Negative results with phenol at doses up to 3333 µg/plate were reported in another study when Vogel-Bonner medium was used (Haworth et al., 1983).

Forward mutation was not induced in mouse lymphoma L5178Y*TK^+/−* cells by phenol at concentrations of 100-3200 µg/ml without metabolic activation (McGregor et al., 1988c).
However, positive results were reported with phenol at concentrations of 5-42 µg/ml with activation and 178-887 µg/ml without activation (Wangenheim & Bolcsfoldi, 1988).

Sister chromatid exchange was not induced in human lymphocytes by phenol at concentrations up to 188 µg/ml (Jansson et al., 1986; Jansson et al., 1988). Phenol at 19 µg/ml also did not induce sister chromatid exchange in human lymphocytes, but positive results were reported when the concentration was increased to 94 µg/ml (Morimoto & Wolff, 1980). This concentration greatly exceeds that which induces cytotoxicity (47 µg/ml), as estimated by the authors. Genotoxic effects observed in conjunction with cytotoxicity may be artefacts of lysosome breakdown and release of DNase. Such action leads to DNA single- and double-strand breaks, sister chromatid exchange, and chromosomal aberration (Bradley et al., 1987).

Sister chromatid exchange was induced by phenol at doses of 300-400 µg/ml in Chinese hamster ovary cells without metabolic activation, and weakly positive results were reported at 1670-3000 µg/ml with metabolic activation. Cytotoxic effects, including cell cycle delay, were also observed at these doses (Ivett, 1989).

No chromosomal aberrations were induced when Chinese hamster ovary cells were incubated with phenol at 600-800 µg/ml without metabolic activation (Ivett, 1989). However, positive results were reported when a metabolic activation system was added and the phenol concentration was increased to 2000-3000 µg/ml (Ivett, 1989). The authors did not determine the cytotoxic threshold or the pH of the test media. Mammalian cells in situ rely on complex regulatory mechanisms to maintain homeostatic conditions, and those in culture are not equipped to respond to environmental changes. The pH of the culture media used in mammalian cell assays must be maintained at approximately 6.8-7.5, because lower values or changes in osmolality due to acidic or ionizing test substances (e.g. phenol) may result in false-positive results, especially with metabolic activation systems. Acidity facilitates the breakdown of the components of such systems into mutagenic agents (Brusick, 1986). Micronuclei were not induced in human lymphocytes exposed to phenol at a concentration of 94 µg/ml without metabolic activation (Robertson et al., 1991).

No evidence of DNA strand breaks was found in Chinese hamster ovary cells incubated with phenol at a dose of 94 and 110 µg/ml (Sze et al., 1996).

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 phenol of doses of 40-188 mg/kg bw (Barale et al., 1990; Shelby et al., 1993; Marrazzini et al., 1994; Chen & Eastmond, 1995 [three doses of 50-100 mg/bw administered 24 h apart]). Increased frequencies of micronuclei were reported in mice given intraperitoneal injections of phenol at 120-180 mg/kg bw (Shelby et al., 1993; Marrazzini et al., 1994; Chen & Eastmond, 1995 [three doses of 160 mg/kg bw administered 24 h apart]) or a single oral dose of 250 mg/kg bw (Karim et al., 1986).

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

3.2. Genotoxicity Studies

No FGE with structurally related substances is available. The available genotoxicity data on phenol have been described in an EU Risk Assessment Report that has been prepared in the context of Council Regulation (EEC) No 793/93 on the evaluation and control of existing substances (EU-RAR, 2006). Summary and conclusion of that Risk Assessment Report is quoted in section 3.3.
3.3. EFSA Considerations


Summary and conclusion of the RAR on phenol concerning mutagenicity (RAR page 111):
“Phenol did not induce gene mutations in bacteria. In mammalian cell cultures positive effects were found for chromosomal aberrations, micronuclei, and gene mutations (hprt locus; Na+/K+ locus) in mouse lymphoma assays and in several indicator tests. A test for induction of aneuploidy was negative.

In vivo in rodents, negative results were found for chromosomal aberrations, DNA strand breaks and DNA adducts. Also Drosophila tests were negative.

Results from in vivo micronucleus tests were weakly positive or negative. The frequency of micronuclei is extremely low even in doses which correspond to the LD50. The induction of micronuclei at high doses may be based on an indirect mode-of-action.

The EU Classification and Labelling Working Group decided in 2001 to classify phenol as a category 3 mutagen.

Based on the available evidence, it is considered that this classification still stands and that phenol should still be regarded as a somatic cell mutagen. It is noted that although the high dose positive micronuclei results being secondary to phenol-induced hypothermia is a plausible hypothesis, no definite conclusions about this mechanism can be drawn due to the limited nature of the available data (abstract form and lack of a confirmatory test showing that prevention of hypothermia by maintaining the animals body heat also prevents the induction of micronuclei).

Furthermore, it is deemed that the available in vivo genotoxicity data are unable to address remaining concerns about mutagenicity at the initial site of contact following inhalation or dermal exposure.”

Summary and conclusion of the RAR on phenol concerning carcinogenicity (RAR page 128):
“Oral long term studies on rats and mice revealed no effect of phenol on tumour induction. A medium-term study on a transgenic mouse model did not give any indication on treatment-related proliferative responses. Phenol was shown to act as a promoter in skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10 % solution of phenol in benzene (without initiation), but was considered less relevant. The test solution was strongly irritative, and contained the carcinogen benzene. However, there is some concern on the basis of weakly positive in vivo mutagenicity data and from the phenol metabolite hydroquinone classified as a suspected carcinogen (Category 3). This concern is considered to be of minor significance, as long term studies revealed no relevant indication for carcinogenicity. However, in conclusion, phenol is considered not to be a carcinogen in animals.

There are no data revealing an association of phenol exposure to increased tumour rates in humans. No firm conclusion on risk levels could be drawn from a case-control study on respiratory cancer of workers exposed to phenol.”

The Panel concluded that the data available on genotoxicity and carcinogenicity do not preclude evaluation of phenol and its two esters through the Procedure.
4. **Application of the Procedure**

4.1. **Application of the Procedure by the JECFA (JECFA, 2001b):**

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

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

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

The evaluations of the three substances are summarised in Table 3: Summary of Safety Evaluation of phenol and the two esters hereof (JECFA, 2001b).

4.2. **EFSA Considerations**

Considering the EU Risk Assessment Report on phenol (EU-RAR, 2006) the Panel agrees with the conclusion on phenol and concluded that the available data do not preclude the evaluation of phenol and its two esters through the Procedure. However, the Panel did not fully agree with the application of the Procedure as performed by the JECFA for phenol and the two phenol derivatives. As the formation of toxic metabolites such as hydroquinones and quinones cannot be excluded, the Panel concluded that the three substances should be evaluated via the B-side.

**Step 1**

Phenol and its two esters were assigned to structural class I using the decision tree approach presented by Cramer *et al.* (1978).

**Step 2**

Due to the possible formation of toxic metabolites like hydroquinones and quinones, phenol and its two esters could not be predicted to be metabolised to innocuous products. Accordingly, the evaluation proceeds via the B-side.

**Step B3**

Phenol and its two esters have estimated daily *per capita* intakes from their use as flavouring substances in the range from 0.012 to 7.3 microgram. These intakes are below the threshold of concern of 1800 microgram/person/day for structural class I substances.

**Step B4**

There are several repeated oral dose toxicity studies as described in the EU Risk Assessment Report on phenol (EU-RAR, 2006), including short and long term studies. The most sensitive adverse effect identified in the Risk Assessment Report was a significantly reduced number of erythrocytes (-32%) in mice administered 1.8 mg phenol/kg bw per day in drinking water for 28 days (Hsieh *et al.*, 1992).

Based on a total daily *per capita* phenol intake of 10.6 microgram (equivalent to 0.18 microgram/kg bw/day assuming a body weight of 60 kg) and the Low Observed Adverse Effect Level (LOAEL) of 1.8 mg/kg bw/day phenol derived from a 28-day drinking water study in mice, the margin of exposure would be 10000.
However, the Panel noted that in long-term toxicity and carcinogenicity studies on phenol in mice and rats at daily doses in drinking water up to 1200 mg/kg bw (mice) and 500 mg/kg bw (rats) (which did not reveal effect of phenol on tumor production), there were no indications of apparent hematotoxic effects which should have been seen after prolonged exposure (EU-RAR, 2006). Therefore, despite the fact that the margin of exposure of 10000 calculated above is based on a LOAEL rather that a No Observed Adverse Effect Level (NOAEL), it is considered to be a conservative value and its large magnitude is reassuring.

The Panel considered that on the basis of the default MSDI approach phenol and the two related phenol esters [FL-no: 04.041, 09.688 and 09.689], which have been evaluated using the Procedure, would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

CONCLUSION

The Panel has considered three substances in the JECFA flavouring group of phenol and phenol derivatives. The Panel concluded that no corresponding FGE is available.

Considering the EU Risk Assessment Report on phenol, the Panel concluded that the available data do not preclude the evaluation of phenol [FL-no: 04.041] and its two esters, phenol acetate [FL-no: 09.688] and phenyl salicylate [FL-no: 09.689], through the Procedure. However, the Panel did not fully agree with the application of the Procedure as performed by the JECFA for the three substances considered in this FGE. Due to the possible formation of toxic metabolites like hydroquinones and quinones, the Panel considered that phenol and its two esters could not be predicted to be metabolised to innocuous products. Accordingly, the evaluation proceeded via the B-side while JECFA has evaluated them via the A-side.

The Panel considered that on the basis of the default MSDI approach the three substances [FL-no: 04.041, 09.688 and 09.689], which have been evaluated using the Procedure, would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

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

Specifications, including complete purity criteria and identity, are available for two of the three JECFA evaluated substances. For one substance [FL-no: 09.689] an identity test is lacking.

Thus, for phenyl salicylate [FL-no: 09.689] the Panel has reservation (a missing identity test). For the remaining two of the three JECFA evaluated substances, phenol [FL-no: 04.041] and phenyl acetate [FL-no: 09.688], the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

The Panel considered that on the basis of the default MSDI approach phenol and the two related phenol esters [FL-no: 04.041, 09.688 and 09.689], which have been evaluated using the Procedure, would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.
**Table 1: Specification Summary for JECFA Evaluated Substances in the Present Group**

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>FEMA no</th>
<th>CoE no</th>
<th>CAS no</th>
<th>Phys. form</th>
<th>Mol. formula</th>
<th>Mol. weight</th>
<th>Solubility 1)</th>
<th>Solubility in ethanol 2)</th>
<th>Boiling point, °C 3)</th>
<th>Melting point, °C</th>
<th>ID test</th>
<th>Assay minimum</th>
<th>Refrac. Index 4)</th>
<th>Spec. gravity 5)</th>
<th>EFSA comments</th>
</tr>
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<tbody>
<tr>
<td>04.041 690</td>
<td>Phenol</td>
<td></td>
<td>3223 11811 108-95-2</td>
<td>Solid</td>
<td>C₆H₆O</td>
<td>94.11</td>
<td>Soluble</td>
<td>Very soluble</td>
<td></td>
<td></td>
<td>182</td>
<td>40-43</td>
<td>IR</td>
<td>98 %</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>09.688 734</td>
<td>Phenyl acetate</td>
<td></td>
<td>3958 10878 122-79-2</td>
<td>Liquid</td>
<td>C₈H₈O₂</td>
<td>136.15</td>
<td>Insoluble</td>
<td>Miscible</td>
<td></td>
<td></td>
<td>195-196</td>
<td>IR</td>
<td>97 %</td>
<td></td>
<td>1.500-1.506</td>
<td>1.073-1.079</td>
<td></td>
</tr>
<tr>
<td>09.689 736</td>
<td>Phenyl salicylate</td>
<td></td>
<td>3960 11814 118-55-8</td>
<td>Solid</td>
<td>C₁₃H₁₀O₃</td>
<td>214.22</td>
<td>Insoluble</td>
<td>Moderately soluble</td>
<td></td>
<td></td>
<td>172-173 (16hPa)</td>
<td>41-43</td>
<td>99 %</td>
<td>n.a.</td>
<td>n.a.</td>
<td>ID 6)</td>
<td></td>
</tr>
</tbody>
</table>

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) ID: Missing identification test.
## TABLE 2: GENOTOXICITY DATA

Table 2: Genotoxicity Data (*in vitro/in vivo*) for Phenol and Two Phenol Derivatives (JECFA, 2001b)

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>JECFA name</th>
<th>Structural formula</th>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>04.041</td>
<td>Phenol</td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA98, TA100, TA102</td>
<td>6.59-6587 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Aeschbacher et al., 1989)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA98, TA100, TA1535, TA1537, TA1538</td>
<td>3 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Florin et al., 1980)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA98, TA100, TA1535, TA1537, TA1538</td>
<td>0-9400 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Gocke et al., 1981)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S. typhimurium TA98</td>
<td>470-9400 µg/plate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Positive</td>
<td>(Gocke et al., 1981)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S. typhimurium TA100, TA1535, TA1537, TA1538</td>
<td>0-9400 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Gocke et al., 1981)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA1535, TA1537, TA98, TA100</td>
<td>33-3333 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Haworth et al., 1983)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA98, TA100</td>
<td>5 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Massey et al., 1994)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA98, TA100, TA1535, TA1537, TA1538</td>
<td>5000 µg/plate&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Negative</td>
<td>(Pool &amp; Lin, 1982)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Forward mutation</td>
<td>Mouse lymphoma cells</td>
<td>100-3200 µg/ml&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Negative</td>
<td>(McGregor et al., 1988c)</td>
</tr>
</tbody>
</table>
Table 2: Summary of Genotoxicity Data for Phenol and Two Phenol Derivatives Evaluated by the JECFA

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JECFA-no</td>
<td>JECFA name</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Forward mutation</td>
<td>Mouse lymphoma cells</td>
<td>178-887 µg/ml(^a) 5-42 µg/ml(^b)</td>
<td>Positive</td>
<td>(Wangenheim &amp; Bolcsfoldi, 1988)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sister chromatid exchange</td>
<td>Human lymphocytes</td>
<td>0-188 µg/ml</td>
<td>Negative</td>
<td>(Jansson et al., 1986)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sister chromatid exchange</td>
<td>Human lymphocytes</td>
<td>0-188 µg/ml</td>
<td>Negative</td>
<td>(Jansson et al., 1988)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sister chromatid exchange</td>
<td>Human lymphocytes</td>
<td>19 µg/ml 94 µg/ml</td>
<td>Negative Positive</td>
<td>(Morimoto &amp; Wolff, 1980)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary cells</td>
<td>300-400 µg/ml(^a) 1670-3000 µg/ml(^b)</td>
<td>Positive Weakly positive</td>
<td>(Ivett, 1989)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chromosomal aberration</td>
<td>Chinese hamster ovary cells</td>
<td>600-800 µg/ml(^a) 2000-3000 µg/ml(^b)</td>
<td>Negative Positive</td>
<td>(Ivett, 1989)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DNA strand breaks</td>
<td>Chinese hamster ovary cells</td>
<td>94, 110 µg/ml</td>
<td>Negative</td>
<td>(Sze et al., 1996)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Micronucleus formation</td>
<td>Human lymphocytes</td>
<td>94 µg/ml(^a)</td>
<td>Negative</td>
<td>(Robertson et al., 1991)</td>
</tr>
<tr>
<td>09.689</td>
<td>Phenyl salicylate</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Reverse mutation</td>
<td>S. typhimurium TA97, TA98, TA100, TA1535, TA1537</td>
<td>3-333 µg/plate(^a)</td>
<td>Negative</td>
<td>(Zeiger et al., 1987)</td>
</tr>
</tbody>
</table>

\(^a\) Without metabolic activation.

\(^b\) With metabolic activation.
## Table 3: Summary of Safety Evaluation of Phenol and Phenol Derivatives (JECFA, 2001b)

<table>
<thead>
<tr>
<th>FL-No</th>
<th>JECFA-No</th>
<th>EU Register Name</th>
<th>Structural Formula</th>
<th>EU MSDI 1) (μg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3)</th>
<th>Outcome on the named compound [4) or 5])</th>
<th>EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)</th>
<th>EFSA conclusion on the material of commerce</th>
</tr>
</thead>
<tbody>
<tr>
<td>04.041</td>
<td>690</td>
<td>Phenol</td>
<td><img src="image" alt="Phenol Structural Formula" /></td>
<td>5.2</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>09.688</td>
<td>734</td>
<td>Phenyl acetate</td>
<td><img src="image" alt="Phenyl Acetate Structural Formula" /></td>
<td>0.012 0.01</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td></td>
</tr>
<tr>
<td>09.689</td>
<td>736</td>
<td>Phenyl salicylate</td>
<td><img src="image" alt="Phenyl Salicylate Structural Formula" /></td>
<td>7.3</td>
<td>Class I A3: Intake below threshold</td>
<td>4) No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.</td>
<td>ID-test is missing.</td>
<td></td>
</tr>
</tbody>
</table>

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.
REFERENCES


