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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 68 (FGE.68):

Consideration of cinnamyl alcohol and related flavouring agents evaluated by JECFA (55th meeting) structurally related to aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in FGE.15Rev1 (2008)[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

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SUMMARY

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

The JECFA has evaluated 55 substances in the group of cinnamyl alcohol and related substances at their 55th meeting. Twenty-six of these substances are alpha,beta-unsaturated aldehydes or precursors for such, which the Panel considers to be a structural alert for genotoxicity. The following 25 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.739 and 09.780] have initially been considered in FGE.214 with respect to genotoxicity. The Panel concluded that for these 25 substances the genotoxicity data available do not preclude their

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evaluation through the Procedure. For the remaining substance (of the 26 alpha,beta-unsaturated aldehydes or precursors for such), allyl cinnamate [FL-no: 09.741], which may be metabolised to allyl alcohol and further to acrolein, considered with respect to genotoxicity in subgroup 1.1.1 of FGE.19, a final conclusion as to its genotoxic properties could not be reached and additional data were requested. Accordingly, this substance will not be considered in the present FGE. This consideration therefore only deals with the 54 JECFA evaluated substances.

The Panel concluded that the 54 substances in the JECFA flavouring group of cinnamyl alcohol and related flavouring substances are structurally related to the group of nine aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in the Flavouring Group Evaluation 15, Revision 1 (FGE.15Rev1).

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the 54 substances considered in this FGE.

However for six substances [FL-no: 02.051, 05.094, 09.071, 09.084, 09.746 and 09.780] 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 54 substances 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 54 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 13 of the JECFA evaluated substances considered in this FGE. Information on stereoisomerism is lacking for 41 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.103, 05.118, 05.122, 06.013, 06.014, 08.022, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.780 and 09.782] and compositional information of mixture is lacking for four substances [FL-no 05.048, 05.094, 09.736 and 09.090].

Thus, in total, for 46 substances [FL-no: 02.017, 02.030, 02.051, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.094, 05.103, 05.118, 05.122, 06.013, 06.014, 08.022, 09.018, 09.026, 09.053, 09.071, 09.084, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.746, 09.780 and 09.782] the Panel has reservations (no European production volumes are available, preventing them to be evaluated using the Procedure, and/or missing data on stereoisomerism and/or compositional information of mixture).

For the remaining eight substances in the group of the JECFA evaluated cinnamyl alcohol and related substances [FL-no: 02.031, 05.080, 08.032, 09.032, 09.138, 09.428, 09.467 and 09.747] the Panel agrees with JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

KEY WORDS

Cinnamyl alcohol, cinnamyl derivatives, JECFA 55th meeting, FGE.15Rev1, aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives, food safety

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BACKGROUND

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

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

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

TERMS OF REFERENCE

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

ASSESSMENT

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

The following issues are of special importance.

Intake

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

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

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

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

As information on use levels for the flavouring substances has not been requested by the JECFA or 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 JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

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

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

At its 55th meeting the JECFA evaluated a group of 55 flavouring substances consisting of cinnamyl alcohol and related substances. Twenty-six of these substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.739, 09.741 and 09.780] are alpha,beta-unsaturated aldehydes or precursors for such. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b), they have been given special considerations in the Flavouring Group Evaluation 19 (FGE.19).

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

The present FGE.68 includes the consideration of 54 flavouring substances of which 25 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.739 and 09.780] were allocated to FGE.19 subgroup 3.1 and evaluated in FGE.214 (EFSA, 2009y) with respect to genotoxicity.

For the remaining substance, allyl cinnamate [FL-no: 09.741] (precursors of an alpha,beta-unsaturated aldehyde), considered with respect to genotoxicity in subgroup 1.1.1 of FGE.19 (EFSA, 2008b) as it may be metabolised to allyl alcohol and further to acrolein (prop-2-enal, [FL-no: 05.176]), a final conclusion as to its genotoxic properties could not be reached and additional data were requested.

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 55 flavouring substances consisting of cinnamyl alcohol and related substances.

1.1.2. EFSA Considerations

Twenty-six of the 55 substances in the group of cinnamyl alcohol and related substances evaluated by the JECFA (JECFA, 2001b) are alpha,beta-unsaturated aldehydes or precursors for alpha,beta-unsaturated aldehydes. As the alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity, these 26 substances have initially been considered with respect to genotoxicity (EFSA, 2008b).

Twenty-five of the alpha,beta-unsaturated cinnamyl derivatives [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.739 and 09.780] have been considered with respect to genotoxicity in FGE.214 (EFSA, 2009y), corresponding to subgroup 3.1 of FGE.19. For these substances the Panel concluded that although they have a structural alert for genotoxicity, the data available do not preclude to evaluate them through the Procedure.

For the remaining substance, allyl cinnamate [FL-no: 09.741] considered with respect to genotoxicity in subgroup 1.1.1 of FGE.19, and which may be metabolised to allyl alcohol and further to acrolein a final conclusion as to its genotoxic properties could not be reached and additional data were requested.

The present flavouring group consideration therefore only deal with 54 JECFA evaluated substances.

The Panel concluded that these 54 substances in the JECFA flavouring group of cinnamyl alcohol and related substances are structurally related to the group of aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in the Flavouring Group Evaluation 15 Revision 1 (FGE.15Rev1), (EFSA, 2008q).

1.2. Isomers

1.2.1. JECFA Status

Three of the substances in the group of the JECFA-evaluated cinnamyl alcohol and related substances have a chiral centre [FL-no: 05.103, 09.736 and 09.737] and 40 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 08.022,

09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.780 and 09.782] can exist as geometrical isomers due to presence and position of a double-bond.

1.2.2. EFSA Considerations

Information is lacking on the stereoisomerism for 41 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.103, 05.118, 05.122, 06.013, 06.014, 08.022, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.780 and 09.782].

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all substances (JECFA, 2002d; JECFA, 2001c). See Table 1.

1.3.2. EFSA Considerations

Specifications including complete purity criteria and identity are available for 13 substances. Information on the stereoisomerism is missing for 41 substances (see Section 1.2) and compositional information of mixture is lacking for four substances [FL-no 05.048, 05.094, 09.736 and 09.090].

2. Intake Estimations

2.1.1. JECFA Status

For 48 of the 54 substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining six substances [FL-no: 02.051, 05.094, 09.071, 09.084, 09.746 and 09.780] production figures are only available for the USA.

2.1.2. EFSA Considerations

As production figures are only available for the USA for the following six substances [FL-no: 02.051, 05.094, 09.071, 09.084, 09.746 and 09.780], MSDI values for the EU cannot be calculated for these.

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text Taken[4] from the JECFA (JECFA, 2001b)

In vitro

Cinnamaldehyde (trans- and unspecified stereochemistry), cinnamyl alcohol [FL-no: 02.017] (trans- and unspecified stereochemistry), cinnamic acid [FL-no: 08.022], alpha-methylcinnamaldehyde [FL-no: 05.050], cinnamyl acetate [FL-no: 09.018], benzyl cinnamate [FL-no: 09.738], cyclohexyl cinnamate [FL-no: 09.744], alpha-amylcinnamaldehyde [FL-no: 05.040], alpha-hexylcinnamaldehyde [FL-

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

no: 05.041], para-methoxy-alpha-methylcinnamaldehyde [FL-no: 05.051], and 3-phenylpropionaldehyde [FL-no: 05.080] generally did not cause reverse mutation in *Salmonella typhimurium* strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, and TA2637. The assays were performed at concentrations up to the level of cytotoxicity, both in the absence and presence of metabolic activation obtained from the livers of Aroclor 1254- or methylcholanthrene-induced Sprague-Dawley rats or Syrian hamsters (Dunkel & Simmon, 1980; Eder et al., 1980; Florin et al., 1980; Lijinsky & Andrews, 1980; Lutz et al., 1980; Eder et al., 1982a; Eder et al., 1982b) and (Kasamaki et al., 1982; Lutz et al., 1982; Prival et al., 1982; Sekizawa & Shibamoto, 1982; Neudecker et al., 1983; Wild et al., 1983; Ishidate et al., 1984) and (Huang et al., 1985; Marnett et al., 1985a; Mortelmans et al., 1986; Fujita & Sasaki, 1987; Tennant et al., 1987) and (Kato et al., 1989; Eder et al., 1991b; Dillon et al., 1992; Azizan & Blevins, 1995).

Weakly positive or positive results were reported for cinnamaldehyde [FL-no:05.014] in S. typhimurium strain TA100 with the pre-incubation method (Dillon et al., 1992; Ishidate et al., 1984), but most other studies in this strain, including a recent study with a prolonged pre-incubation time (120 min.) and others in which the standard plate incorporation method was used gave no evidence of mutagenicity (Sasaki & Endo, 1978; Lijinsky & Andrews, 1980; Eder et al., 1982a; Eder et al., 1982b; Kasamaki et al., 1982) and.

Negative or weakly positive results were obtained in *S. typhimurium* with pre-incubation with ortho-methoxycinnamaldehyde [FL-no: 05.048] (Eder et al., 1991b; Mortelmans et al., 1986). The weakly positive results in strain TA100 with metabolic activation were obtained with two different activation systems (Mortelmans et al., 1986). Negative results were obtained in strains TA1535, TA1537, and TA98 both with and without metabolic activation. In the study with strain TA100, negative results were reported in the absence of metabolic activation (Eder et al., 1991b). No standard plate incorporation assay was available for ortho-methoxycinnamaldehyde, which might be expected to behave similarly to the other cinnamyl compounds on the basis of structural and metabolic similarities.

The results of assays for mutation in *Escherichia coli* strains WP2uvrA, PQ37, and Sd-4-73, including several in which the pre-incubation method was used, were negative with cinnamaldehyde [FL-no: 05.014], cinnamyl alcohol [FL-no: 02.017], cinnamic acid [FL-no: 08.022], alpha-methylcinnamaldehyde [FL-no: 05.050], and alpha-amylcinnamaldehyde [FL-no: 05.040] (Szybalski, 1958; Sekizawa & Shibamoto, 1982; Ohta et al., 1986b; Yoo, 1986; Kato et al., 1989; Eder et al., 1991b; Eder et al., 1993). In the rec assay in *Bacillus subtilis*, positive results were reported with cinnamaldehyde [FL-no: 05.014] and cinnamyl alcohol [FL-no: 02.017], whereas cinnamic acid [FL-no: 08.022], ethyl cinnamate [FL-no: 09.730], methyl cinnamate [FL-no: 09.740], and benzyl cinnamate [FL-no: 09.738] gave negative results in all such tests (Oda et al., 1979; Sekizawa & Shibamoto, 1982; Kuroda et al., 1984a; Yoo, 1986).

Assays with isolated mammalian cells gave mixed but generally positive results for cinnamyl esters overall. Equivocal to positive results were obtained for cinnamaldehyde [FL-no: 05.014] in the assay for forward mutation in L5178Y mouse lymphoma cells with and without metabolic activation, but the reports of these tests did not provide sufficient detail of the method, concentrations tested, or cytotoxic effects to allow adequate evaluation of the results (Rudd et al., 1983; Palmer, 1984). In L1210 mouse lymphoma cells, DNA strand breaks were observed only at cytotoxic concentrations of cinnamaldehyde (Eder et al., 1993).

The results of tests for the induction of sister chromatid exchange in Chinese hamster ovary cells exposed to cinnamaldehyde [FL-no: 05.014] were negative at low concentrations and weakly positive at concentrations approaching cytotoxic levels, suggesting only weak activity (Galloway et al., 1987a; Sasaki et al., 1989). A dose-dependent increase in the frequency of sister chromatid exchange was reported only when cultures were pre-treated with mitomycin C (Sasaki et al., 1989); however, the activity in conjunction with mitomycin contributes little to an evaluation of potential sister chromatid exchange activity. Cinnamaldehyde at concentrations < 15 µg/ml was reported to induce chromosomal aberrations in Chinese hamster fibroblasts and B241 cells tested with and without metabolic activation

(Kasamaki et al., 1982; Ishidate et al., 1984; Kasamaki & Urasawa, 1985). However, higher concentrations did not induce chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of metabolic activation in a well-conducted, repeated assay (Galloway et al., 1987a).

The results of assays for cell transformation with cinnamaldehyde [FL-no: 05.014] were positive at near-cytotoxic concentrations or after multiple generations of growth and negative in human HAIN-55 cells (Kasamaki et al., 1987; Matthews et al., 1993). Subcutaneous injection of the transformed cells into nude mice led to the formation of nodules at the site of injection and neoplastic growth in the spleen (Kasamaki et al., 1987). Negative results were obtained with cinnamaldehyde [FL-no: 05.014] (No. 656) in Chinese hamster V79 cells (Fiorio & Bronzetti, 1994), while a weak increase in the incidence of micronucleated Hep-G2 cells was reported by (Sanyal et al., 1997).

The results obtained with the other cinnamyl compounds in isolated mammalian cells were, in general, comparable to those obtained with cinnamaldehyde [FL-no: 05.014]. Sister chromatid exchange was not observed in Chinese hamster ovary cells exposed to cinnamyl alcohol [FL-no: 02.017], cinnamic acid [FL-no: 08.022], ethyl cinnamate [FL-no: 09.730], methyl cinnamate [FL-no: 09.740], cinnamyl acetate [FL-no: 09.018], or 3-phenylpropionaldehyde [FL-no: 05.080]. Pretreatment with mitomycin C increased the incidence of sister chromatid exchange in assays with cinnamic acid [FL-no: 08.022], methyl cinnamate [FL-no: 09.740], and ethyl cinnamate [FL-no: 09.730] but not cinnamyl alcohol [FL-no: 02.017], cinnamyl acetate [FL-no: 09.018], or 3-phenylpropionaldehyde [FL-no: 05.080] (Sasaki et al., 1989; Palmer, 1984) reported reproducible, dose-related increases in the incidence of reversions in L5178Y mouse lymphoma cells, with and without metabolic activation, after treatment with cinnamyl alcohol [FL-no: 02.017], cinnamic acid [FL-no: 08.022], cinnamyl cinnamate [FL-no: 09.739], and ortho-methoxycinnamaldehyde [FL-no: 05.048].

The results of assays in L5178Y mouse lymphoma cells at the $Tk^{+/-}$ locus have yielded equivocal results. The positive results were seen at near-lethal concentrations in studies in which this was reported. The results of assays with simple aliphatic and aromatic substances were not consistent with the results of other, standard assays for genotoxicity (Tennant et al., 1987; Heck et al., 1989). Culture conditions of low pH and high osmolality, which may pertain with substances that have a potentially acidifying effect on the culture medium (aldehydes, carboxylic acids, lactones, and hydrolysed esters), have been shown to produce false-positive results in this and other assays (Heck et al., 1989). Other reports of positive responses in the mouse lymphoma cell assay lacked information on the concentration tested and on cytolethality (Rudd et al., 1983; Palmer, 1984).

In vivo

Most of the results of tests of the administration of cinnamyl compounds *in vivo* pertains to cinnamaldehyde [FL-no: 05.014]. An increase in the frequency of sex-linked recessive lethal mutations was reported when *Drosophila melanogaster* were injected with cinnamaldehyde at 20 000 mg/kg of diet, but no increase in the frequency of mutations was seen when *D. melanogaster* were fed 800 mg/kg of diet for 3 days. Reciprocal translocations were not observed in either assay (Woodruff et al., 1985). No increase in the frequency of unscheduled DNA synthesis was found in the hepatocytes of rats or mice given cinnamaldehyde at 1000 mg/kg bw by oral gavage (Mirsalis et al., 1989). The frequency of micronuclei was not increased when rats or mice were given 1700 mg/kg bw or 1100 mg/kg bw, respectively, of cinnamaldehyde by oral gavage (Mereto et al., 1994) or when mice were given 500 mg/kg bw by intraperitoneal injection (Hayashi et al., 1984; Hayashi et al., 1988). The frequency of micronucleated bone-marrow cells in mice that had been exposed to X-rays decreased after injection of 500 mg of cinnamaldehyde (Sasaki et al., 1990b).

An increase in the frequency of micronucleated cells was reported in rat and mouse hepatocytes and in rat (but not mouse) forestomach cells after the animals had received up to 1100 (rats) or 1700 (mice) mg/kg bw of cinnamaldehyde by oral gavage. No increase in the frequency of micronuclei in liver or forestomach was observed at doses ≥ 850 mg/kg bw, and no DNA fragmentation was observed in rat hepatocytes or gastric mucosal cells. The incidence and size of gamma-glutamyl transferase-positive

foci were increased in hepatocytes of rats pretreated with N-nitrosodiethylamine and then given cinnamaldehyde at 500 mg/kg bw per day by oral gavage for 14 days (Mereto et al., 1994).

The positive findings with cinnamaldehyde [FL-no: 05.014] in rat forestomach and in the livers of both rats and mice treated in vivo are not consistent with the results of the standard assays in bone marrow and were observed at doses that far exceeded those resulting from intake of cinnamaldehyde in foods. Cinnamaldehyde given at oral doses ≥ 500 mg/kg bw depleted hepatocellular glutathione concentrations (Swales & Caldwell, 1991; Swales & Caldwell, 1992; Swales & Caldwell, 1993), and the increases in micronucleus frequency were found at doses that appeared to affect cellular defence mechanisms, such as glutathione depletion. As the micronucleus formation was dose-dependent, induction of micronuclei may be a threshold phenomenon which occurs at intakes orders of magnitude greater than that of cinnamaldehyde as a flavouring agent. Furthermore, the bolus doses resulting from gavage probably resulted in much greater exposure of both the forestomach and the liver than administration in a dietary admixture. The author of the study in which these results were obtained (Mereto et al., 1994) acknowledged these facts and concluded that their data did not justify the conclusion that cinnamaldehyde is clastogenic. In view of the apparent threshold for micronucleus induction and the lack of activity in other studies in vivo, the effects induced by the bolus dose in the liver and forestomach are considered irrelevant to the evaluation of the safety of cinnamaldehyde when used as a flavouring agent.

Wild et al. (1983) reported negative results in tests for sex-linked recessive lethal mutation in D. melanogaster and in an assay for micronucleus formation in mouse bone-marrow cells after administration of alpha-methylcinnamaldehyde [FL-no: 05.050], alpha-amylcinnamyl alcohol [FL-no: 02.030], alpha-amylcinnamaldehyde [FL-no: 05.040], or alpha-hexylcinnamaldehyde [FL-no: 05.041] (Wild et al., 1983).

Conclusion

Cinnamyl alcohol [FL-no: 02.017] and related compounds lack direct mutagenic or genotoxic activity, as indicated by the negative results obtained in bacterial test systems. The mixed results in the assay for DNA repair and in various studies of antimutagenicity were associated with cytotoxicity, as noted by (Sekizawa & Shibamoto, 1982). Evidence of genotoxic activity was found in isolated mammalian cells, the cinnamyl compounds inducing chromosomal aberrations and/or mutations in the presence or absence of metabolic activation; however, the reported activity in vitro was not seen as mutagenic, clastogenic, or genotoxic activity *in vivo*.

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

3.2. Genotoxicity Studies - Text taken[5] from EFSA FGE.15Rev1 (EFSA, 2008q)

In vitro / in vivo

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

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

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

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

The five supporting substances [FL-no: 05.080, 08.022, 09.730, 09.738 and 09.744] have been tested for their ability to induce mutations in various strains of *Salmonella typhimurium* (e.g. TA92, TA94, TA98, TA100, TA1535, TA1537 and TA1538), in the presence or absence of an exogenous metabolic activation system. None of the compounds was mutagenic when tested at concentrations up to 5000 microgram/plate. Four of the substances, cinnamic acid [FL-no: 08.022], methyl cinnamate [FL-no: 09.740], ethyl cinnamate [FL-no: 09.730] and 3-phenylpropionaldehyde [FL-no: 05.080] were tested for induction of spontaneous SCEs in cultured CHO cells only in the absence of metabolic activation. For all the four substances no influence on cell cycle and SCE was observed. Ethyl cinnamate [FL-no: 09.730] in a study carried out in the absence of S9 activation did not induce chromosomal aberrations in Chinese hamster fibroblasts.

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

Conclusion on genotoxicity

Overall, the data available are not sufficient to evaluate the genotoxicity adequately and no *in vivo* genotoxicity data are available for the candidate or for the supporting substances, but the various studies carried out with supporting substances give no indication of a mutagenic activity in bacterial cells or of a direct clastogenic effect on mammalian cells. The limited genotoxicity data available do not preclude evaluating the nine candidate substances, using the Procedure."

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

3.3. Genotoxicity Studies and Conclusion on Genotoxicity and Carcinogenicity - Text taken[6] from FGE.214 (EFSA, 2009y)

"In subgroup 3.1 there are studies available for six of the substances.

For cinnamaldehyde [FL-no: 05.014] 19 *in vitro* studies (in total 27 tests) and four *in vivo* studies (5 different end points) have been evaluated. Only in one of the valid studies for reverse mutations in bacterial cells a positive result was obtained. However, the same test in the same strain provided negative results in other valid studies. Some positive results were obtained in bacterial tests for DNA repair (Rec and SOS-chromo assays), but these tests are not considered relevant for the evaluation of genotoxicity. A gene mutation study in mammalian cells provided also a negative result, but was considered too limited to be considered valid. In contrast, two studies which were considered as valid provided indications that cinnamaldehyde may induce chromosomal aberrations *in vitro* in Chinese hamster fibroblast or B241 cells. For the same endpoint also a valid negative study has been reported but a study in Hep-G2 cells provided a limited indication that cinnamaldehyde might induce micronuclei. Several studies reported cinnamaldehyde-induced Sister Chromatic Exchanges (SCEs), but this endpoint is considered of very limited relevance. A study with limited validity indicated induction of DNA strand breaks in mouse lymphoma cells at very high concentrations, which were clearly cytotoxic.

With several other candidate substances [FL-no: 05.050, 05.040, 05.041, 05.048 and 05.051] data from mutation tests with *S. typhimurium* have been reported. These studies did not indicate a mutagenic potential for these substances. However, for one substance a positive result has been reported [FL-no: 05.048].

In two of the *in vivo* studies with cinnamaldehyde an increase in hepatocellular micronuclei has been observed in rats and mice after gavage dosing. Although the tests were appropriately performed, the relevance of this effect is not clear as it was obtained in animals that had undergone 2/3 hepatectomy

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

and received the substance at 50% of the LD_{50}. In these animals, no DNA fragmentation was observed in hepatocytes and in stomach mucosal cells. Similarly, no increase in micronuclei frequency was observed in bone marrow cells from these animals. In another valid *in vivo* bone marrow assay with i.p. injection no increase in bone marow micronuclei formation was observed, either. From the few studies available with other substances [FL-no: 05.050, 05.040 and 05.041] also no indication of genotoxicity *in vivo* was obtained."

For validation and study results see Table 2.4 and 2.5.

Conclusion on Genotoxicity and Carcinogenicity

"Some concern could be raised by studies carried out with cinnamaldehyde [FL-no: 05.014], showing an ability to induce chromosomal damage *in vitro*, and by the positive result obtained for 2-methoxycinnamaldehyde [FL-no: 05.048] in an Ames test. For cinnamaldehyde the concern was not confirmed in *in vivo* studies. Thus it is concluded that cinnamaldehyde does not have a genotoxic potential *in vivo*. In addition, the carcinogenicity studies with *trans*-cinnamaldehyde did not indicate a carcinogenic potential.

The ring substituents (4-methyl, 4-hydroxy, 4-methoxy, 3-or 5-methoxy or 2-methoxy) are anticipated not to increase but rather decrease the reactivity of the alpha,beta-unsaturated aldehyde group. Therefore, the Panel concluded that the seven ring-substituted cinnamyl derivatives [FL-no: 05.048, 05.051, 05.118, 05.122, 05.154, 05.155 and 09.306] like the un-substituted cinnamyl derivatives were not of concern with respect to genotoxicity."

3.4. EFSA Considerations

Twenty-five of the 54 substances in FGE.68 are alpha,beta-unsaturated aldehydes or precursors of such aldehydes which are considered by the Panel to be structural alerts for genotoxicity. This was discussed in FGE.214, where the Panel concluded that data available do not preclude to evaluate the substances through the Procedure.

For the remaining 29 of the 54 substances from the JECFA group of cinnamyl alcohol and related substances not being alpa,beta-unsaturated substances, the Panel also concluded that the genotoxicity data available do not preclude to evaluate these substances through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 54 Cinnamyl Alcohol and Related Substances by JECFA (JECFA, 2001b)

According to the JECFA 48 of the substances belong to structural class I, and six to structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded for cinnamyl alcohol and 49 related substances at step A3 in the JECFA Procedure – i.e. the substances are expected to be metabolised to innocuous products (step 2) and the intakes for all substances are below the thresholds for their structural classes I and II (step A3).

For four substances it was concluded at step A5 – i.e. the intakes are above the thresholds for their structural classes, the substances are not endogenous, but a NOAEL is available that can provide an adequate margin of safety to the estimated intake of the substances [FL-no: 02.017, 05.014, 06.014 and 09.740].

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 54 substances are summarised in Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b).

4.2. Application of the Procedure to Nine Aryl-Substituted Saturated and Unsaturated Primary Alcohol/Aldehyde/Acid/Ester Derivatives by EFSA (EFSA, 2008q)

All nine candidate substances evaluated in FGE.15Rev1. are classified into structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The nine substances were concluded at step A3 – i.e. the substances are expected to be metabolised to innocuous products (step 2) and the estimated daily intake is below the threshold for the structural class (step A3).

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

The stepwise evaluations of the nine substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.15Rev1).

4.3. EFSA Considerations

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for all 54 substances in the group of cinnamyl alcohol and related substances.

However, the structural class have, based on EFSA considerations, been changed for the following flavouring substances:

- [FL-no: 06.013, 09.026 and 09.090 and 09.468] from structural class I to class II,
- [FL-no: 02.051] from structural class II to class I,
- [FL-no: 06.014] from structural class II to class III.

These changes in structural classes do not give rise to change in the outcome of the application of the Procedure.

For six substances [FL-no: 02.051, 05.094, 09.071, 09.084, 09.746 and 09.780] no European production figures were available and consequently no European exposure estimates could be calculated. Accordingly, the safety in use in Europe could not be assessed using the Procedure for these six substances.

5. Conclusion

The JECFA has evaluated 55 substances in the group of cinnamyl alcohol and related substances at their 55th meeting. Twenty-six of these substances are alpha,beta-unsaturated aldehydes or precursors for such, which the Panel considers to be a structural alert for genotoxicity. The following 25 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.118, 05.122, 06.013, 06.014, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.739 and 09.780] have initially been considered in FGE.214 with respect to genotoxicity. The Panel concluded that for these 25 substances the genotoxicity data available do not preclude their evaluation through the Procedure. For the remaining substance (of the 26 alpha,beta-unsaturated aldehydes or precursors for such), allyl cinnamate [FL-no: 09.741], which may be metabolised to allyl alcohol and further to acrolein, considered with respect to genotoxicity in subgroup 1.1.1 of FGE.19, a final conclusion as to its genotoxic properties could not be reached and additional data were requested.

Accordingly, this substance will not be considered in the present FGE. This consideration therefore only deals with 54 JECFA evaluated substances.

The Panel concluded that the 54 substances in the JECFA flavouring group of cinnamyl alcohol and related flavouring substances are structurally related to the group of nine aryl-substituted saturated and unsaturated primary alcohol/aldehyde/acid/ester derivatives evaluated by EFSA in FGE.15Rev1.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the 54 substances considered in this FGE.

However for six substances [FL-no: 02.051, 05.094, 09.071, 09.084, 09.746 and 09.780] 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 54 substances 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 54 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 13 of the JECFA evaluated substances considered in this FGE. Information on stereoisomerism is lacking for 41 substances [FL-no: 02.017, 02.030, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.103, 05.118, 05.122, 06.013, 06.014, 08.022, 09.018, 09.026, 09.053, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.780 and 09.782] and compositional information of mixture is lacking for four substances [FL-no 05.048, 05.094, 09.736 and 09.090].

Thus, in total, for 46 substances [FL-no: 02.017, 02.030, 02.051, 05.014, 05.039, 05.040, 05.041, 05.048, 05.050, 05.051, 05.094, 05.103, 05.118, 05.122, 06.013, 06.014, 08.022, 09.018, 09.026, 09.053, 09.071, 09.084, 09.085, 09.090, 09.133, 09.459, 09.468, 09.470, 09.708, 09.730, 09.731, 09.732, 09.733, 09.734, 09.736, 09.737, 09.738, 09.739, 09.740, 09.742, 09.743, 09.744, 09.745, 09.746, 09.780 and 09.782] the Panel has reservations (no European production volumes are available, preventing them to be evaluated using the Procedure, and/or missing data on stereoisomerism and/or compositional information of mixture).

For the remaining eight substances in the group of JECFA evaluated cinnamyl alcohol and related substances [FL-no: 02.031, 05.080, 08.032, 09.032, 09.138, 09.428, 09.467 and 09.747] the Panel agrees with JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY

Table 1: specifications summary for the JECFA evaluated substances in the present group (JECFA, 2001c; JECFA, 2000d)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

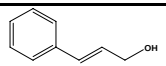
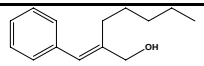
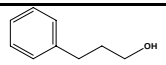
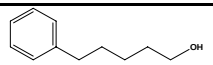
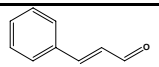
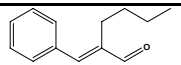
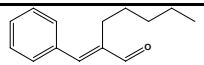
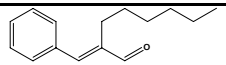
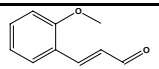
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.017 647	Cinnamyl alcohol 6)	 Trans form shown	2294 65 104-54-1	Solid $C_9H_{10}O$ 134.18	Insoluble to slightly soluble Moderately soluble	258 30 IR 98 %	n.a. n.a.	
02.030 674	alpha-Pentylcinnamyl alcohol 6)	 Trans form shown	2065 79 101-85-9	Liquid $C_{14}H_{20}O$ 204.31	Insoluble Miscible	141 (7 hPa) IR 95 %	1.533-1.540 0.954-0.962	
02.031 636	3-Phenylpropan-1-ol		2885 80 122-97-4	Liquid $C_9H_{12}O$ 136.19	Slightly soluble Miscible	235-236 IR 98 %	1.524-1.528 0.993-1.002	
02.051 675	5-Phenylpentan-1-ol		3618 674 10521-91-2	Liquid $C_{11}H_{16}O$ 164.25	Insoluble Miscible	155 (26 hPa) IR 98 %	1.514-1.521 0.970-0.977	
05.014 656	Cinnamaldehyde 6)	 Trans form shown	2286 102 104-55-2	Liquid C_9H_8O 132.16	Insoluble Miscible	248-250 IR 98 %	1.547-1.553 1.030-1.040	
05.039 684	alpha-Butylcinnamaldehyde 6)	 Trans form shown	2191 127 7492-44-6	Liquid $C_{13}H_{16}O$ 188.27	Insoluble Miscible	265 MS 98 %	1.539-1.547 0.977-0.984	
05.040 685	alpha-Pentylcinnamaldehyde 6)	 Trans form shown	2061 128 122-40-7	Liquid $C_{14}H_{18}O$ 202.30	Insoluble Miscible	284-287 IR 97 %	1.554-1.562 0.962-0.969	
05.041 686	alpha-Hexylcinnamaldehyde 6)	 Trans form shown	2569 129 101-86-0	Liquid $C_{15}H_{20}O$ 216.32	Insoluble Miscible	174-175 (20hPa) IR 95 %	1.547-1.553 0.950-0.961	
05.048 688	2-Methoxycinnamaldehyde 6)	 Trans form shown	3181 571 1504-74-1	Solid $C_{10}H_{10}O_2$ 162.19	Slightly soluble Miscible	160-161(16 hPa) 45-46 IR 94 %	n.a. n.a.	According to JECFA: Min. assay value is "94 (min. 95% combined aldehyde and corresponding acid)" and

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

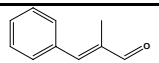
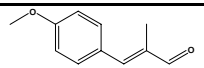
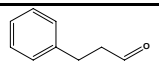
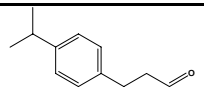
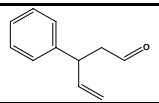
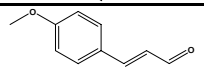
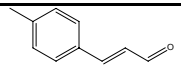
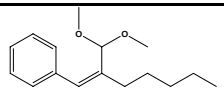
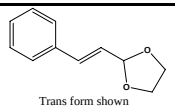
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
								"o-methoxycinnamic acid <3%".
05.050 683	alpha-Methylcinnamaldehyde 6)	 Trans form shown	2697 578 101-39-3	Liquid $C_{10}H_{10}O$ 146.19	Insoluble Miscible	148 (35 hPa) IR 95 %	1.598-1.607 1.034-1.040	
05.051 689	3-(4-Methoxyphenyl)-2-methylprop-2-enal 6)	 Trans form shown	3182 584 65405-67-6	Liquid $C_{11}H_{12}O_2$ 176.21	Insoluble Miscible	106-109(0.1hPa) MS 95 %	1.625-1.632 0.989-0.996	
05.080 645	3-Phenylpropanal		2887 2013 104-53-0	Liquid $C_9H_{10}O$ 134.18	Insoluble Miscible	222 IR 95 %	1.518-1.528 1.008-1.018	
05.094 680	3-(4-Isopropylphenyl)propionaldehyde		2957 2261 7775-00-0	Liquid $C_{12}H_{16}O$ 176.26	Insoluble Miscible	270 MS 90 %	1.503-1.508 0.946-0.952	According to JECFA: Min. assay value is "90 (min. 95 % combined o- and p-isomers)".
05.103 679	3-Phenylpent-4-enal 6)		3318 10378 939-21-9	Liquid $C_{11}H_{12}O$ 160.22	Insoluble Miscible	140 (26 hPa) MS 95 %	1.526-1.532 1.003-1.009	
05.118 687	4-Methoxycinnamaldehyde 6)	 Trans form shown	3567 11919 1963-36-6	Solid $C_{10}H_{10}O_2$ 162.18	Insoluble Moderately soluble	277 57-58 IR 96 %	n.a. n.a.	
05.122 682	p-Methylcinnamaldehyde 6)	 Trans form shown	3640 10352 1504-75-2	Solid $C_{10}H_{10}O$ 146.19	Insoluble Moderately soluble	154 (33 hPa) 41 IR 95 %	n.a. n.a.	
06.013 681	alpha-Pentylcinnamaldehyde dimethyl acetal 6)	 Trans form shown	2062 47 91-87-2	Liquid $C_{16}H_{24}O_2$ 248.36	Slightly soluble Miscible	300 IR 97 %	1.504-1.511 0.954-0.963	
06.014 648	Cinnamaldehyde ethylene glycol acetal 6)	 Trans form shown	2287 48 5660-60-6	Liquid $C_{11}H_{12}O_2$ 176.22	Insoluble Miscible	265 NMR 90 %	1.561-1.570 1.095-1.103	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

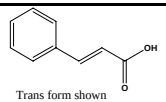
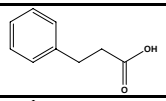
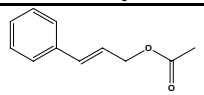
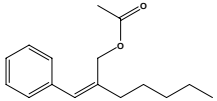
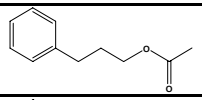
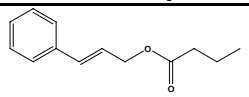
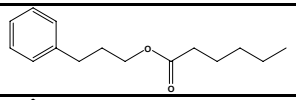
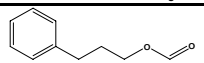
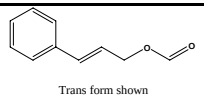
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
08.022 657	Cinnamic acid 6)	 Trans form shown	2288 22 621-82-9	Solid $C_9H_8O_2$ 148.16	Insoluble Slightly soluble	300 132 IR 98 %	n.a. n.a.	
08.032 646	3-Phenylpropionic acid		2889 32 501-52-0	Solid $C_9H_{10}O_2$ 150.18	Slightly soluble Moderately soluble	280 43 IR 97 %	n.a. n.a.	
09.018 650	Cinnamyl acetate 6)	 Trans form shown	2293 208 103-54-8	Liquid $C_{11}H_{12}O_2$ 176.22	Insoluble Miscible	262-265 IR 98 %	1.539-1.544 1.047-1.054	
09.026 677	alpha-Pentylcinnamyl acetate 6)	 Trans form shown	2064 216 7493-78-9	Liquid $C_{16}H_{22}O_2$ 246.35	Miscible	291 IR 97 %	1.487-1.495 0.953-0.961	
09.032 638	3-Phenylpropyl acetate		2890 222 122-72-5	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	244-245 IR 98 %	1.494-1.498 1.011-1.020	
09.053 652	Cinnamyl butyrate 6)	 Trans form shown	2296 279 103-61-7	Liquid $C_{13}H_{16}O_2$ 204.27	Insoluble Miscible	300 IR 98 %	1.525-1.530 1.010-1.020	
09.071 642	3-Phenylpropyl hexanoate		2896 321 6281-40-9	Liquid $C_{15}H_{22}O_2$ 234.34	Insoluble Miscible	292 IR 99 %	1.482-1.488 0.947-0.960	
09.084 637	3-Phenylpropyl formate		2895 351 104-64-3	Liquid $C_{10}H_{12}O_2$ 164.20	Insoluble Miscible	238 MS 97 %	1.494-1.499 1.012-1.019	
09.085 649	Cinnamyl formate 6)	 Trans form shown	2299 352 104-65-4	Liquid $C_{10}H_{10}O_2$ 162.19	Insoluble Miscible	250 IR 95 %	1.550-1.556 1.075-1.082	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

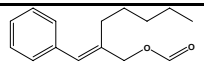
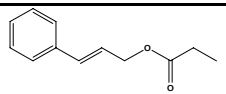
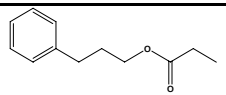
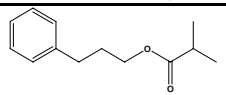
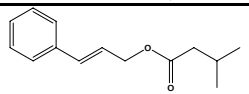
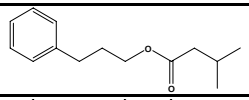
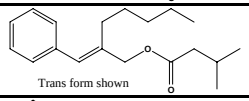
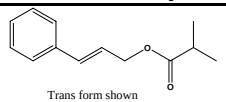
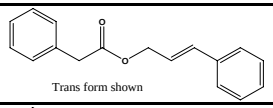
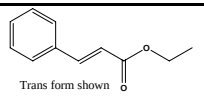
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.090 676	alpha-Pentylcinnamyl formate 6)	 Trans form shown	2066 357 7493-79-0	Liquid $C_{15}H_{20}O_2$ 232.32	Miscible	277 IR 85 %	1.516-1.526 0.980-0.999	According to JECFA: Min. assay value is "85 % (97 % total of the formate and the parent alcohol)".
09.133 651	Cinnamyl propionate 6)	 Trans form shown	2301 414 103-56-0	Liquid $C_{12}H_{14}O_2$ 190.24	Insoluble Miscible	289 IR 98 %	1.532-1.537 1.029-1.034	
09.138 639	3-Phenylpropyl propionate		2897 419 122-74-7	Liquid $C_{12}H_{16}O_2$ 192.26	Insoluble Miscible	265 MS 99 %	1.488-1.495 0.995-1.005	
09.428 640	3-Phenylpropyl isobutyrate		2893 303 103-58-2	Liquid $C_{13}H_{18}O_2$ 206.28	Insoluble Miscible	258 IR 98 %	1.483-1.493 0.975-0.981	
09.459 654	Cinnamyl isovalerate 6)	 Trans form shown	2302 454 140-27-2	Liquid $C_{14}H_{18}O_2$ 218.30	Insoluble Miscible	313 IR 95 %	1.517-1.524 0.990-0.996	
09.467 641	3-Phenylpropyl isovalerate		2899 462 5452-07-3	Liquid $C_{14}H_{20}O_2$ 220.31	Insoluble Miscible	280 IR 98 %	1.482-1.489 0.962-0.971	
09.468 678	alpha-Pentylcinnamyl isovalerate 6)	 Trans form shown	2067 463 7493-80-3	Liquid $C_{19}H_{28}O_2$ 288.43	Insoluble Miscible	171 (5 hPa) IR 97 %	1.498-1.508 0.939-0.950	
09.470 653	Cinnamyl isobutyrate 6)	 Trans form shown	2297 496 103-59-3	Liquid $C_{13}H_{16}O_2$ 204.27	Insoluble Miscible	254 IR 96 %	1.520-1.528 1.005-1.014	
09.708 655	Cinnamyl phenylacetate 6)	 Trans form shown	2300 235 7492-65-1	Liquid $C_{17}H_{16}O_2$ 252.31	Insoluble Miscible	333-335 IR 96 %	1.575-1.581 1.089-1.095	
09.730 659	Ethyl cinnamate 6)	 Trans form shown	2430 323 103-36-6	Liquid $C_{11}H_{12}O_2$ 176.22	Insoluble Miscible	271-272 IR 99 %	1.558-1.562 1.044-1.051	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

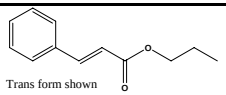
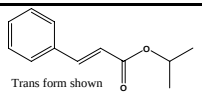
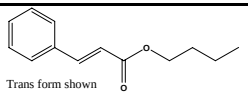
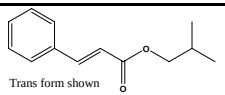
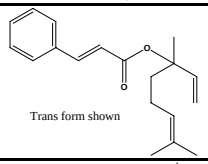
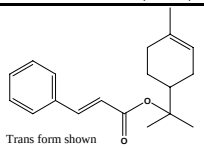
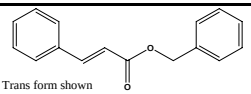
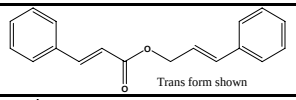
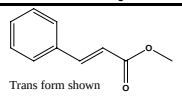
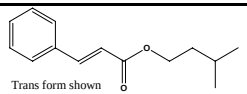
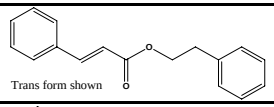
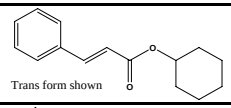
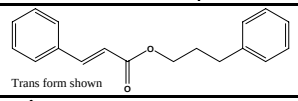
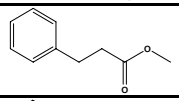
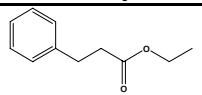
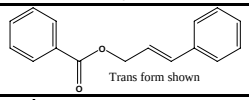
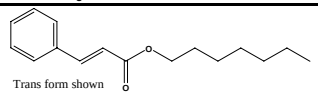
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.731 660	Propyl cinnamate 6)	 Trans form shown	2938 324 7778-83-8	Liquid $C_{12}H_{14}O_2$ 190.24	Insoluble Miscible	283-284 IR 98 %	1.547-1.553 1.030-1.040	
09.732 661	Isopropyl cinnamate 6)	 Trans form shown	2939 325 7780-06-5	Liquid $C_{12}H_{14}O_2$ 190.24	Insoluble Miscible	268-270 MS 98 %	1.541-1.548 1.020-1.027	
09.733 663	Butyl cinnamate 6)	 Trans form shown	2192 326 538-65-8	Liquid $C_{13}H_{16}O_2$ 204.27	Slightly soluble to Insoluble Miscible	287 IR 98 %	1.539-1.545 1.008-1.014	
09.734 664	Isobutyl cinnamate 6)	 Trans form shown	2193 327 122-67-8	Liquid $C_{13}H_{16}O_2$ 204.27	Insoluble Miscible	287 IR 97 %	1.538-1.542 1.001-1.005	
09.736 668	Linalyl cinnamate 6)	 Trans form shown	2641 329 78-37-5	Liquid $C_{19}H_{24}O_2$ 284.40	Insoluble Miscible	353 IR 94 %	1.540-1.545 0.985-0.995	According to JECFA: Min. assay value is "94 %" and secondary components "linalool".
09.737 669	Terpinyl cinnamate 6)	 Trans form shown	3051 330 10024-56-3	Liquid $C_{19}H_{24}O_2$ 284.40	Insoluble Miscible	360 NMR 95 %	1.548-1.552 0.991-0.999	CASrn in Register refers to (S)-isomer. Register name to be changed to (S)-Terpinyl cinnamate and in accordance with geometric isomerism.
09.738 670	Benzyl cinnamate 6)	 Trans form shown	2142 331 103-41-3	Solid $C_{16}H_{14}O_2$ 238.29	Insoluble Very soluble	350 25 IR 98 %	n.a. n.a.	
09.739 673	Cinnamyl cinnamate 6)	 Trans form shown	2298 332 122-69-0	Solid $C_{18}H_{16}O_2$ 264.32	Insoluble Moderately soluble	370 42 IR 95 %	n.a. n.a.	
09.740 658	Methyl cinnamate 6)	 Trans form shown	2698 333 103-26-4	Solid $C_{10}H_{10}O_2$ 162.19	Insoluble Moderately soluble	262-263 33 IR 98 %	n.a. n.a.	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Cinnamyl Alcohol and Related Substances (JECFA, 2001c)

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
09.742 665	Isopentyl cinnamate 6)	 Trans form shown	2063 335 7779-65-9	Liquid $C_{14}H_{18}O_2$ 218.30	Insoluble Miscible	310 IR 97 %	1.533-1.541 0.992-0.997	
09.743 671	Phenethyl cinnamate 6)	 Trans form shown	2863 336 103-53-7	Solid $C_{17}H_{16}O_2$ 252.31	Insoluble Moderately soluble	170 (1 hPa) 54 IR 98%	n.a. n.a.	
09.744 667	Cyclohexyl cinnamate 6)	 Trans form shown	2352 337 7779-17-1	Liquid $C_{15}H_{18}O_2$ 230.31	Insoluble Miscible	195 (16 hPa) MS 95 %	1.558-1.564 1.047-1.056	
09.745 672	3-Phenylpropyl cinnamate 6)	 Trans form shown	2894 338 122-68-9	Liquid $C_{18}H_{18}O_2$ 266.34	Insoluble Miscible	190 (0.3 hPa) IR 98 %	1.583-1.588 1.074-1.080	
09.746 643	Methyl 3-phenylpropionate		2741 427 103-25-3	Liquid $C_{10}H_{12}O_2$ 164.20	Insoluble Miscible	238-239 IR 98 %	1.499-1.505 1.037-1.045	
09.747 644	Ethyl 3-phenylpropionate		2455 429 2021-28-5	Liquid $C_{11}H_{14}O_2$ 178.23	Insoluble Miscible	247-249 IR 98 %	1.492-1.497 1.009-1.017	
09.780 760	Cinnamyl benzoate 6)	 Trans form shown	 743 5320-75-2	Solid $C_{16}H_{14}O_2$ 238.29	Insoluble Miscible	335 31 IR 98 %	n.a. n.a.	
09.782 666	Heptyl cinnamate 6)	 Trans form shown	2551 2104 10032-08-3	Liquid $C_{16}H_{22}O_2$ 246.35	Insoluble Miscible	185 (16 hPa) IR 97 %	1.528-1.530 0.982-0.990	

1) Solubility in water, if not otherwise stated.
2) Solubility in 95% ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.
6) Stereoisomeric composition not specified.

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (in vitro / in vivo) for 54 Cinnamyl Alcohol and Related Flavouring Substances (JECFA, 2001b)

Table 2.1: Summary of Genotoxicity Data of 54 Cinnamyl Alcohol and Related Substances Evaluated by the JECFA

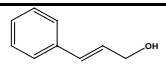
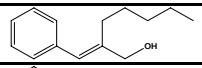
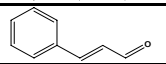
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
02.017 647	Cinnamyl alcohol		Reverse mutation[c]	*S. typhimurium* TA1537, TA1535	3000 µg/plate	Negative[a]	(Sekizawa & Shibamoto, 1982)
			DNA repair	*B. subtilis* M45 (rec-) and H17 (rec$^+$)	21 µg/disc	Negative[b]	(Oda et al., 1979)
			DNA repair	*B. subtilis* M45 (rec-) and H17 (rec$^+$)	1.0 mg/disc (1000 µg/disc)	Positive[a]	(Sekizawa & Shibamoto, 1982)
			DNA repair	*B. subtilis* M45 (rec-) and H17 (rec$^+$)	10 µl/disc (10 400 µg/disc)	Positive[b]	(Yoo, 1986)
			Mutation	*E. coli* WP2 uvrA	3000 µg/plate	Negative[b]	(Sekizawa & Shibamoto, 1982)
			Mutation	*E. coli* WP2 uvrA	4.0 mg/plate (4000 µg/plate)	Negative[b]	(Yoo, 1986)
			Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (4468 µg)	Negative[b]	(Sasaki et al., 1989)
02.030 674	alpha-Pentylcinnamyl alcohol		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)
05.014 656	Cinnamaldehyde						
		Cinnamaldehyde	Reverse mutation[c]	*S. typhimurium* TA1537, TA1538, TA98, TA100, TA1535	600 µg/plate	Negative[a]	(Sekizawa & Shibamoto, 1982)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA1537, TA98, TA100, TA1535	10 mg/plate (10,000 µg/plate)	Negative[a]	(Prival et al., 1982)
		Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA104 (with preincubation)	0.8 µmol (105 µg)	Negative[a]	(Marnett et al., 1985a)
		Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA1537, TA92, TA94, TA98, TA100, TA1535 (with preincubation)	0.5 mg/plate (500 µg/plate)	Positive[a,d]	(Ishidate et al., 1984)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA1537, TA92, TA94, TA98, TA100, TA1535 (with plate incorporation and preincubation)	500 µg/plate	Negative[a]	(Lijinsky & Andrews, 1980)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA1537, TA1538, TA98, TA100, TA1535 (with plate incorporation and preincubation)	500 µg/plate	Negative[a]	(Kasamaki et al., 1982)

Table 2.1: Summary of Genotoxicity Data of 54 Cinnamyl Alcohol and Related Substances Evaluated by the JECFA

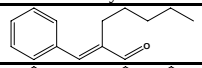
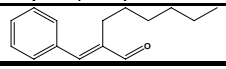
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
		Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA97, TA98, TA100 (with preincubation)	1 mg/ml (1000 µg/ml)	Negative[a]	(Azizan & Blevins, 1995)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA98, TA100, TA104 (with preincubation)	Not reported	Negative[a]	(Kato et al., 1989)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA1537, TA98, TA100, TA1535 (with preincubation)	100 µg/plate	Negative[a]	(Mortelmans et al., 1986)
		trans-Cinnamaldehyde	Reverse mutation	*S. typhimurium* TA100 (with preincubation)	5 µmol/plate (661 µg/plate)	Negative[a]	(Neudecker et al., 1983)
		Cinnamaldehyde	Mutation	*E. coli* WP2 uvrA	600 µg/plate	Negative[b]	(Sekizawa & Shibamoto, 1982)
		Cinnamaldehyde	Mutation	*E. coli* WP2 uvrA	0.8 mg/plate (800 µg/plate)	Negative[b]	(Yoo, 1986)
		Cinnamaldehyde	DNA repair	*B. subtilis* M45 (rec^-)	0.2 mg/disk (200 µg/disc)	Positive[b]	(Sekizawa & Shibamoto, 1982)
		Cinnamaldehyde	DNA repair	*B. subtilis* M45 (rec^-) and H17 (rec^+)	10 µl/disc (10,500 µg/disc)	Positive[b]	(Yoo, 1986)
		Cinnamaldehyde	DNA repair	*B. subtilis* M45 (rec^-) and H17 (rec^+)	10 µl/disc (10,500 µg/disc)	Positive[a]	(Kuroda et al., 1984a)
		Cinnamaldehyde	DNA repair	*B. subtilis* M45 (rec^-) and H17 (rec^+)	21 µg/disc	Negative[b]	(Oda et al., 1979)
		Cinnamaldehyde	Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (4401 µg)	Negative[b]	(Sasaki et al., 1987)
		Cinnamaldehyde	Chromosomal aberration	Chinese hamster fibroblasts	0.015 mg/ml (15 µg/ml)	Positive[b]	(Ishidate et al., 1984)
		Cinnamaldehyde	Chromosomal aberration	Chinese hamster B241 cells	20 nmol/L (2.6 µg)	Positive[b]	(Kasamaki & Urasawa, 1985)
		Cinnamaldehyde	Chromosomal aberration	Chinese hamster B241 cells	10 nmol/L (1.3 µg)	Positive[a]	(Kasamaki et al., 1982)
		trans-Cinnamaldehyde	Chromosomal aberration	Chinese hamster ovary cells	18.3 µg/ml 100 µg/ml	Negative[b] Negative[c]	(Galloway et al., 1987a)
		trans-Cinnamaldehyde	Sister chromatid exchange	Chinese hamster ovary cells	6.8 µg/ml 91.8 µg/ml	Positive[b] Positive[c]	(Galloway et al., 1987a)
		Cinnamaldehyde	DNA strand breaks	Mouse L1210 lymphoma cells	500 µmol (66 080 µg)	Positive[b]	(Eder et al., 1993)
		Cinnamaldehyde	Cytotoxicity	Mouse L1210 lymphoma cells	10 µg/ml	Positive[b]	(Moon & Pack, 1983)
		Cinnamaldehyde	Mutation	Chinese hamster V79 cells	100 µmol/L (13 216 µg)	Negative[b]	(Fiorio & Bronzetti, 1994)
		Cinnamaldehyde	Micronucleus formation	Hep-G2 cells	500 µg/ml	Positive[b]	(Sanyal et al., 1997)
05.040 685	alpha-Pentylcinnamaldehyde		Reverse mutation	*S. typhimurium* TA97, TA102 (with preincubation)	1.0 mg/plate (1000 µg/plate)	Negative[a]	(Fujita & Sasaki, 1987)
05.041 686	alpha-Hexylcinnamaldehyde		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)

Table 2.1: Summary of Genotoxicity Data of 54 Cinnamyl Alcohol and Related Substances Evaluated by the JECFA

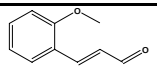
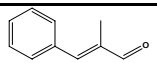
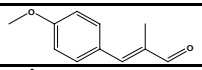
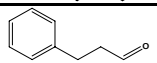
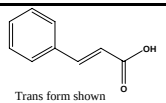
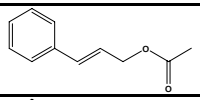
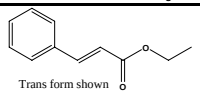
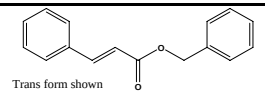
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
05.048 688	2-Methoxycinnamaldehyde		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 (with preincubation)	666 µg/plate	Positive[a]	(Mortelmans et al., 1986)
05.050 683	alpha-Methylcinnamaldehyde		Reverse mutation	*S. typhimurium* TA100(with preincubation)	4 µmol/plate (585 µg/plate)	Negative[a]	(Neudecker et al., 1983)
			Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 (with preincubation)	500 µg/plate	Negative[a]	(Mortelmans et al., 1986)
			Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)
			Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)
05.051 689	3-(4-Methoxyphenyl)-2-methylprop-2-enal		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)
05.080 645	3-Phenylpropanal		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol/plate (402 µg/plate)	Negative[a]	(Florin et al., 1980)
			Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (4468 µg)	Negative[b]	(Sasaki et al., 1989)
08.022 657	Cinnamic acid	 Trans form shown	Reverse mutation	*S. typhimurium* TA1537, TA1538, TA98, TA100, TA1535 (with plate incorporation and preincubation)	1000 µg	Negative[a]	(Lijinsky & Andrews, 1980)
			DNA repair	*B. subtilis* M45 (rec$^-$) and H17 (rec$^+$)	25 µg/disc	Negative[b]	(Oda et al., 1979)
			DNA repair	*B. subtilis* M45 (rec$^-$) and H17 (rec$^+$)	2.0 mg/disc (2000 µg/disc)	Negative[b]	(Yoo, 1986)
			Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (4934 µg)	Positive[b]	(Sasaki et al., 1989)
09.018 650	Cinnamyl acetate		Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (5868 µg)	Negative[b]	(Sasaki et al., 1989)
09.730 659	Ethyl cinnamate	 Trans form shown	Reverse mutation	*S. typhimurium* TA1537, TA92, TA94, TA98, TA100,TA1535 (with preincubation)	5.0 mg/plate (5000 µg/plate)	Negative[a]	(Ishidate et al., 1984)
			Chromosomal aberration	Chinese hamster fibroblasts	0.063 mg/ml (63 µg/ml)	Equivocal[b]	(Ishidate et al., 1984)
			DNA repair	*B. subtilis* M45 (rec$^-$) and H17 (rec$^+$)	20 µg/disc	Negative[b]	(Oda et al., 1979)
			Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (5868 µg)	Positive[b]	(Sasaki et al., 1989)
09.738 670	Benzyl cinnamate	 Trans form shown	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol/plate (715 µg/plate)	Negative[a]	(Florin et al., 1980)
			DNA repair	*B. subtilis* M45 (rec$^-$) and H17 (rec$^+$)	1.0 mg/disc (1000 µg/disc)	Negative[b]	(Yoo, 1986)

Table 2.1: Summary of Genotoxicity Data of 54 Cinnamyl Alcohol and Related Substances Evaluated by the JECFA

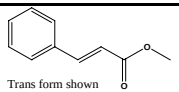
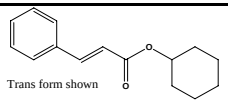
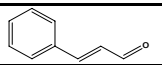
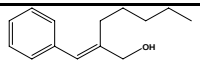
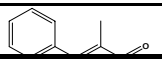
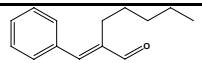
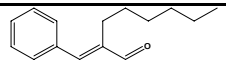
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
09.740 658	Methyl cinnamate	 Trans form shown	DNA repair	*B. subtilis* M45 (rec$^-$) and H17 (rec$^+$)	20 µg/disc	Negative[b]	(Oda et al., 1979)
			Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (5401 µg)	Positive[b]	(Sasaki et al., 1989)
09.744 667	Cyclohexyl cinnamate	 Trans form shown	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	3.6 mg/plate (3600 µg/plate)	Negative[a]	(Wild et al., 1983)
In vivo							
05.014 656	Cinnamaldehyde						
		trans-Cinnamaldehyde	Sex-linked recessive lethal mutation	D. melanogaster	800 mg/kg in diet (800 µg/g)	Negative	(Woodruff et al., 1985)
		Cinnamaldehyde	Unscheduled DNA synthesis	Rat and mouse hepatocytes	1000000 µg/kg bw	Negative	(Mirsalis et al., 1989)
		Cinnamaldehyde	Micronucleus formation	Mouse bone-marrow cells	500000 µg/kg bw	Negative	(Hayashi et al., 1984) (Hayashi et al., 1988)
		trans-Cinnamaldehyde	Micronucleus formation	Rat and mouse hepatocytes	1700000 µg/kg bw (mice) 1100000 µg/kg bw (rats)	Positive	(Mereto et al., 1994)
		trans-Cinnamaldehyde	Micronucleus formation	Rat and mouse bone marrow	1700000 µg/kg bw (mice) 1100000 µg/kg bw (rats)	Negative	(Mereto et al., 1994)
		Cinnamaldehyde	Nuclear anomalies[f]	Rat and mouse fore- stomach mucosal cells	1700000 µg/kg bw (mice)	Negative	(Mereto et al., 1994)
					1100000 µg/kg bw (rats)	Positive	
		trans-Cinnamaldehyde	DNA fragmentation	Rat hepatocytes and gastric mucosal cells	1100000 µg/kg bw	Negative	(Mereto et al., 1994)
		Cinnamaldehyde	Hyperplastic foci	Rat hepatocytes	500000 µg/kg bw per dayg	Positive	(Mereto et al., 1994)
02.030 674	alpha-Pentylcinnamyl alcohol		Sex-linked recessive lethal mutation	D. melanogaster	45 mmol/L (9194000 µg)	Negative	(Wild et al., 1983))
			Micronucleus formation	Mouse bone-marrow cells	510000 µg/kg bw	Negative	(Wild et al., 1983)
05.050 683	alpha-Methylcinnamaldehyde		Sex-linked recessive lethal	D. melanogaster	5 mmol/L	Negative	(Wild et al., 1983)

Table 2.1: Summary of Genotoxicity Data of 54 Cinnamyl Alcohol and Related Substances Evaluated by the JECFA

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
			mutation		(731000 µg)		
			Micronucleus formation	Mouse bone-marrow cells	438000 µg/kg bw	Negative	(Wild et al., 1983)
05.040 685	alpha-Pentylcinnamaldehyde		Sex-linked recessive lethal mutation	D. melanogaster	10 mmol/L (2023000 µg)	Negative	(Wild et al., 1983)
			Micronucleus formation	Mouse bone-marrow cells	1213000 µg/kg bw	Negative	(Wild et al., 1983)
05.041 686	alpha-Hexylcinnamaldehyde		Sex-linked recessive lethal mutation	D. melanogaster	10 mmol/L (2163000 µg)	Negative	(Wild et al., 1983)
			Micronucleus formation	Mouse bone-marrow cells	657000 µg/kg bw	Negative	(Wild et al., 1983)

[a] With and without metabolic activation.
[b] Without metabolic activation.
[c] With metabolic activation.

Table 2.2: Genotoxicity Data (in vitro) EFSA / FGE.15Rev1 (EFSA, 2008q)

Substances listed in brackets are the JECFA evaluated supporting substances in FGE.15Rev1

Table 2.2: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(3-Phenylpropionaldehyde [05.080]) syn. 3-Phenylpropanal	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmoles/plate (403 µg/plate)[14]	Negative[1]	(Florin et al., 1980)	Published non-GLP study. Qualitative screening in a spot-test only. Precipitates of substance reported. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study not considered adequate for the evaluation of mutagenic activity.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100µM (0, 0.134, 0.443, 1.34, 4.43, 13.4 µg/ml)[7, 14]	Negative[2, 8, 15]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Cinnamic acid [08.022])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1-1000 µg	Negative[1]	(Lijinsky & Andrews, 1980)	Published non-GLP study of acceptable quality. Limited report of detailed results (for controls only).
	Rec assay	*B. subtilis* M45 (rec-), H17 (rec+)	25 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Rec assay	*B. subtilis* M45 (rec-), H17 (rec+)	2.0 mg/plate (2000 µg/plate)	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100 µM (0, 0.148, 0.489, 1.482, 4.933, 14.82 µg/ml)[4, 7]	Negative[2, 8, 9]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
4-Hydroxy-3,5-dimethoxycinnamic acid [08.088]	Mutation assay	*E. coli* B/r WP2	1000 µg/plate	Negative[2, 5]	(Shimoi et al., 1985)	Published non-GLP study. Study designed for the determination of effects on UV-induced mutagenesis. Experimental details of the assessment of direct mutagenic activity not reported and results not shown. Thus, the validity of these data cannot be evaluated.
4-Hydroxy-3-methoxycinnamic acid [08.089]	Ames reverse mutation assay	*S. typhimurium* TA98, TA100	NR[6]	Negative[1, 3]	(Matsuda et al., 1992)	Published non-GLP study. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study designed for the determination of ozonation products of 4-hydroxy-3-methoxy-cinnamic acid (and other structural components of humic substances). Thus only results of negative control (not ozonated) are of relevance in this evaluation.
	Mutation assay	*E. coli* B/r WP2	1000 µg/plate	Negative[2, 5]	(Shimoi et al., 1985)	Published non-GLP study. Study designed for the determination of effects on UV-induced mutagenesis. Experimental details of the assessment of direct mutagenic activity not reported and results not shown. Thus, the validity of these data cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 3.3, 10, 33.3, 100, 333 µM (0, 0.641, 1.94, 6.41, 19.4, 64.1 µg/ml)[7, 12]	Negative[2, 8, 9, 13]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-, UV- and X-ray-induced SCEs.

Table 2.2: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(Ethyl cinnamate [09.730])	Ames reverse mutation assay (preincubation method)	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537,	Up to 5000 µg/plate[17]	Negative[1]	(Ishidate et al., 1984)	Published non-GLP study of acceptable quality.
	Chromosomal aberration assay	Chinese hamster fibroblasts	Up to 63 µg/ml[18]	Equivocal[2, 19] Negative[2, 19]	(Ishidate et al., 1984)	Published non-GLP study of limited quality.
	Rec assay	*B. subtilis* M45 (rec$^-$), H17 (rec$^+$)	20 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3 µM (0, 0.176, 0.581, 1.76, 5.81 µg/ml) [11, 7]	Negative[2, 8, 9]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Benzyl cinnamate [09.738])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmoles/plate (715 µg/plate)[16]	Negative[1]	(Florin et al., 1980)	Published non-GLP study. Qualitative screening in a spot-test only. Precipitates of substance reported. Limited report of experimental details and results. Validity of the study cannot be evaluated. Study not considered adequate for the evaluation of mutagenic activity.
	Rec assay	*B. subtilis* M45 (rec$^-$), H17 (rec$^+$)	1.0 mg/disk (1000 µg/plate)	Negative	(Yoo, 1986)	Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
(Methyl cinnamate [09.740])	Rec assay	*B. subtilis* M45 (rec$^-$), H17 (rec$^+$)	20 µg/plate	Negative	(Oda et al., 1979)	Study published in Japanese without English abstract. Data extracted from tables. Validity of the study cannot be evaluated.
	Sister chromatid exchange	Chinese hamster ovary cells	0, 1.0, 3.3, 10, 33.3, 100 µM (0, 0.162, 0.535, 1.62, 5.40, 16.2 µg/ml)[10, 7]	Negative[2, 8, 9]	(Sasaki et al., 1989)	Published non-GLP study of limited quality. Study designed to investigate the influence on spontaneous as well as on mitomycin-induced SCEs.
(Cyclohexyl cinnamate [09.744])	Ames reverse mutation assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Up to 3600 µg/plate[20]	Negative[1]	(Wild et al., 1983)	Published non-GLP study. No detailed results reported. However, as experimental details and evaluation criteria including results of positive controls are sufficiently reported the study is considered valid.

NR = Not reported
1 With and without S9 metabolic activation.
2 Without S9 metabolic activation.
3 Ozonated samples gave a positive result (more than three times compared to spontaneous mutation) with tester strain TA100 with metabolic activation and weakly positive result (1.5-3 times) without metabolic activation possibly due to formed ozonation products (aldehydes, ketones and carboxylic acids such as formaldehyde, acetaldehyde, glyoxal and methylglyoxal as identified in the same study after ozonation of p-hydroxybenzaldehyde).
4 Calculated based on molecular weight = 148.15.
5 Negative result reported for both direct mutagenic activitäy and enhancement of UV-induced mutagenesis.
6 Unquantified samples of 4-hydroxy-3-methoxy-cinnamic acid were ozonated at a ratio of sample to ozone of 1:0 (control), 1:0.5, 1:1 and 1:6 (by weight) and then tested for mutagenicity.
7 The highest concentration was reported to be toxic.
8 The substance did not influence cell cycle (data not shown) and spontaneous SCEs at the concentrations used.
9 Posttreatment of mitomycin-treated cells with the substance increased the frequency of induced SCEs in a dose-related manner. The effect was statistically significant ($p<0.001$) at the two highest nontoxic concentrations.
10 Calculated based on molecular weight = 162.15.
11 Calculated based on molecular weight = 176.21.
12 Calculated based on molecular weight = 194.19.
13 The frequency of SCEs induced by UV was significantly increased by treatment with 4-hydroxy-3-methoxy-cinnamic acid at 10 ($0.001<p<0.01$), 33.3 and 100 µM ($p<0.001$) in a dose-related manner. On the contrary, X-ray induced SCEs were significantly reduced by treatment with 4-hydroxy-3-methoxy-cinnamic acid at 10 ($0.01<p<0.05$), 33.3 and 100 µM ($p<0.001$). The effect was also dose-related.
14 Calculated based on molecular weight = 134.17.
15 Posttreatment of mitomycin-treated cells with the substance did not influence the frequency of induced SCEs.

16 Calculated based on molecular weight = 238.27.
17 Six different concentrations used (single concentrations not reported).
18 Three different doses used (single doses not reported).
19 Negative result with respect to chromosomal aberrations; equivocal result considering the observed polyploidization effect.
20 Five different concentrations used (single concentrations not reported).

Table 2.3: Genotoxicity Data (in vitro) for alpha,beta-Unsaturated Cinnamyl Derivatives from FGE.214 (EFSA, 2009y)

Table 2.3: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments[e]
Cinnamaldehyde [05.014]	Reverse mutationc	*S. typhimurium* TA1537, TA1538, TA98, TA100, TA1535	600 µg/plate	Negative[a]	(Sekizawa & Shibamoto, 1982)	Valid. Published non-GLP study with sufficient details; the result is considered valid.
	Reverse mutation	*S. typhimurium* TA1537, TA98, TA100, TA1535	10 mg/plate (10,000 µg/plate)	Negative[a]	(Prival et al., 1982)	Validity cannot be evaluated. Published non-GLP study with insufficient documentation (no figures); the validity cannot be evaluated.
	Reverse mutation	*S. typhimurium* TA104 (with preincubation)	0.8 µmol (105 µg)	Negative[a]	(Marnett et al., 1985a)	Valid. Published non-GLP study carried out with only one strain and only without S9; however, for the purpose og the study, the result is considered valid.
	Reverse mutation	*S. typhimurium* TA98, TA100	Up to 0.5 mg/plate (500 µg/plate)	Positive[a,d]	(Ishidate et al., 1984)	Valid. According to current guidelines (in TA 100 with and without metabolic activation)[a,b].
	Reverse mutation	*S. typhimurium* TA1537, TA92, TA94, TA98, TA100, TA1535 (with plate incorporation and preincubation)	500 µg/plate	Negative[a]	(Lijinsky & Andrews, 1980)	Valid.
	Reverse mutation	*S. typhimurium* TA98, TA100 (with plate incorporation and preincubation)	0.05 - 500 µg/plate	Negative[a]	(Kasamaki et al., 1982)	Limited validity (only two strains tested).
	Reverse mutation	*S. typhimurium* TA97, TA98, TA100 (with preincubation)	1 mg/ml (1000 µg/ml)	Negative[a]	(Azizan & Blevins, 1995)	Validity cannot be evaluated. Published non-GLP study with insufficient documentation (no figures); the validity cannot be evaluated.
	Reverse mutation	*S. typhimurium* TA98, TA100, TA104 (with preincubation)	Not reported	Negative[a]	(Kato et al., 1989)	Validity cannot be evaluated. Abstract – limited data reported.
	Reverse mutation	*S. typhimurium* TA1537, TA98, TA100, TA1535 (with preincubation)	100 µg/plate	Negative[a]	(Mortelmans et al., 1986)	Valid.
	Reverse mutation	*S. typhimurium* TA100 (with preincubation)	5 µmol/plate (661 µg/plate)	Negative[a]	(Neudecker et al., 1983)	Limited validity. Only in one strain.
	Reverse mutation	*S. typhimurium* TA98, TA100 (with plate incorporation)	0, 165, 330 and 660 µg/plate	Negative[a]	(Stammati et al., 1999)	Limited validity only in two strains. *trans*-cinnamaldehyde was tested. [1)]
	Mutation	*E. coli* WP2 uvrA	0.8 mg/plate (800 µg/plate)	Negative[b]	(Yoo, 1986)	Validity cannot be evaluated. Only in Japanese (insufficient documentation).
	DNA repair	*B. subtilis* M45 (rec-)	0.2 mg/disk (200 µg/disc)	Positive[b]	(Sekizawa & Shibamoto, 1982)	Insufficient validity. The test system used is considered inappropriate, not relevant for the evaluation.
	DNA repair	*B. subtilis* M45 (rec-) and H17 (rec+)	10 µl/disc (10,500 µg/disc)	Positive[b]	(Yoo, 1986)	Insufficient validity. Rec assay not considered relevant for evaluation of genotoxicity.
Cinnamaldehyde [05.014]	DNA repair	*B. subtilis* M45 (rec-) and H17 (rec+)	10 µl/disc (10,500 µg/disc)	Positive[a]	(Kuroda et al., 1984a)	Insufficient valitidy (Rec assay not considered relevant for evaluation of gentoxicity).
	DNA repair	*B. subtilis* M45 (rec-) and H17 (rec+)	21 µg/disc	Negative[b]	(Oda et al., 1979)	Validity cannot be evaluated (relevance for evaluation of genotoxicity uncertain).

Table 2.3: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments[e]
	DNA repair.	*E. coli*, WP2 uvrA and CM871 strains	0 – 8 µmol/disk	Positive	(Stammati et al., 1999)	Test with limited relevance and low predictive value for genotoxicity. Probably only tested in absence of metabolicactivation *trans*-cinnamaldehyde was tested. [1)]
	Sister chromatid exchange	Chinese hamster ovary cells	33.3 µmol/L (4401 µg)	Negative[b]	(Sasaki et al., 1987)	Validity cannot be evaluated (relevance for evaluation of genotoxicity uncertain).
	Chromosomal aberration	Chinese hamster fibroblasts	Up to 0.015 mg/ml (15 µg/ml)	Positive[b]	(Ishidate et al., 1984)	Valid.
	Chromosomal aberration	Chinese hamster B241 cells	20 nmol/L (2.6 µg)	Positive[b]	(Kasamaki & Urasawa, 1985)	Valid (unusual cell line).
	Chromosomal aberration	Chinese hamster B241 cells	10 nmol/L (1.3 µg)	Positive[a]	(Kasamaki et al., 1982)	Limited validity (limited documentation; results for only one test concentration reported; long incubation period of 24 hrs; unusual cell line).
	Chromosomal aberration	Chinese hamster ovary cells	18.3 µg/ml 100 µg/ml	Negative[b] Negative[c]	(Galloway et al., 1987a)	Valid.
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 6.8 µg/ml	Positive[b]	(Galloway et al., 1987a)	Valid. Weakly positive without S9.
	Sister chromatid exchange	Chinese hamster ovary cells	91.8 µg/ml	Positive[c]	(Galloway et al., 1987a)	Valid, however, the result (obtained in the presence of S9) is considered equivocal.
	DNA strand breaks	Mouse L1210 lymphoma cells	500 µmol / 4 ml (16.5 mg/ml)	Positive[b]	(Eder et al., 1993)	Limited validity. Positive at cytotoxic levels.
	Nuclear fragmentation	Hep-2 larynx carcinoma cell line	*ca.* 3.5, 5.4, 7.4, 8.2, 11 and 22 µM	Positive	(Stammati et al., 1999)	Irrelevant test. The effect was indicative for apoptosis. rather than for substance-induced chromosomal breaks. Probably only tested in absence of metabolicactivation.. *trans*-cinnamaldehyde was tested. [1)]
	SOS chromo	?	?	Negative	(Eder et al., 1993)	Limited validity. Results poorly reported – relevance questionable.
	SOS chromotest	*E. coli*, PQ37	0 – 0.01 µmol/	Negative	(Stammati et al., 1999)	Test with limited relevance and low predictive value for genotoxicity. Probably only tested in absence of metabolicactivation. *trans*-cinnamaldehyde was tested. [1)]
	Mutation (HGPRT)	Chinese hamster V79 cells	100 µmol/L (13 216 µg)	Negative[b]	(Fiorio & Bronzetti, 1994)	Insufficient validity (only one concentration and only without S9 tested).
	Micronucleus formation	Hep-G2 cells	500 µg/ml	POSITIVE	(SANYAL ET AL., 1997)	Limited validity. Published non-GLP study, not according with standard, conventional guidelines; the moderate increase observed only at the highest concentration is considered of limited validity.
alpha-Methylcinnamaldehyde [05.050]	Reverse mutation	*S. typhimurium* TA100(with preincubation)	4 µmol/plate (585 µg/plate)	Negative[a]	(Neudecker et al., 1983)	Limited validity (only one strain tested).
	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535,	500 µg/plate	Negative[a]	(Mortelmans et al.,	Valid.

Table 2.3: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments[e]
		TA1537 (with preincubation)			1986)	
	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations up to cytotoxicity, or max. 3600 µg/plate	Negative[a]	(Wild et al., 1983)	Valid.
	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations up to cytotoxicity, or max. 3600 µg/plate	Negative[a]	(Wild et al., 1983)	Valid.
alpha-Pentylcinnamaldehyde [05.040]	Reverse mutation	*S. typhimurium* TA97, TA102 (with preincubation)	1.0 mg/plate (1000 µg/plate)	Negative[a]	(Fujita & Sasaki, 1987)	Validity cannot be evaluated.
alpha-Hexylcinnamaldehyde [05.041]	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations up to cytotoxicity, or max. 3600 µg/plate	Negative[a]	(Wild et al., 1983)	Valid.
2-Methoxycinnamaldehyde [05.048]	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 (with preincubation)	666 µg/plate	Positive[a]	(Mortelmans et al., 1986)	Valid.
3-(4-Methoxyphenyl)-2-methylprop-2-enal [05.051]	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations up to cytotoxicity, or max. 3600 µg/plate	Negative[a]	(Wild et al., 1983)	Valid.

[a] With and without metabolic activation.
[b] Without metabolic activation.
[c] With metabolic activation.
[d] Positive results in strain TA100 only.
e:Validity of genotoxicity studies:
Valid.
Limited validity (e.g. if certain aspects are not in accordance with OECD guidelines or current standards and / or limited documentation).
Insufficient validity (e.g. if main aspects are not in accordance with any recognised guidelines (e.g. OECD) or current standards and/or inappropriate test system).
Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).
[1)]This study is not mentioned in FGE.214.

Table 2.4: Genotoxicity Data (in vivo) for alpha,beta-Unsaturated Cinnamyl Derivatives from FGE.214 (EFSA, 2009y)

Table 2.4: GENOTOXICITY (*in vivo*)

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments [a]
Cinnamaldehyde [05.014]	Sex-linked recessive lethal mutation	*Drosophila melanogaster*	800 mg/kg od diet (800 µg/g)		Negative	(Woodruff et al., 1985)	Limited validity. Published study carried out within NTP. The moderate increase observed only at highest doses by injection and not by feeding is considered of limited validity.
	Unscheduled DNA synthesis	Rat hepatocytes	Oral (gavage)	0, 50, 200, 1000 mg/kg bw	Negative	(Mirsalis et al., 1989)	Valid. According to current guidelines.
	Micronucleus formation	Mouse bone-marrow cells	Intraperitoneal	500 000 µg/kg bw	Negative	(Hayashi et al., 1984)	Valid. Published non-GLP pilot study with too few animals but positive for controls. It should be considered together with Hayashi et al. (1988). Taking into account the results of both studies, the final result is considered valid.
	Micronucleus formation	Mouse hepatocytes	Gavage	0-2 550 000 µg/kg bw	Positive	(Mereto et al., 1994)	Valid. After 2/3 hepatectomy. The highest dose cause 100% mortality. Relevance not clear.
	Micronucleus formation	Rat hepatocytes	Gavage	0-1 650 000 µg/kg bw	Positive	(Mereto et al., 1994)	Valid. After 2/3 hepatectomy. The highest dose cause 100% mortality. Relevance not clear.
	Micronucleus formation	Mouse bone marrow	Gavage	0-2 550 000 µg/kg bw	Negative	(Mereto et al., 1994)	Limited validity. PCE/NCE ratios were not affected , at the highest dose tested 100% lethality.
	Micronucleus formation	Rat bone marrow	Gavage	0-1 650 000 µg/kg bw	Negative	(Mereto et al., 1994)	Limited validity. PCE/NCE ratios were not affected , at the highest dose tested 100% lethality.
	Nuclear anomalies	Mouse fore- stomach mucosal cells	Gavage	0-2 550 000 µg/kg bw	Negative	(Mereto et al., 1994)	Validity cannot be evaluated (meaning of endpoint for genotoxicity is unclear, at the highest dose tested 100% lethality).
	Nuclear anomalies	Rat fore- stomach mucosal cells	Gavage	0 - 1 650 000 µg/kg bw	Positive	(Mereto et al., 1994)	Validity cannot be evaluated. Mainly karyorrhexis and pyknosis which are signs of cytotoxiciy. The meaning of this endpoint for genotoxicity is questionable, at the highest dose tested 100% lethality.
	DNA fragmentation	Rat hepatocytes and gastric mucosal cells	Gavage	1 100 000 µg/kg bw	Negative	(Mereto et al., 1994)	Valid. Alkaline elution assay.
alpha-Methylcinnamaldehyde [05.050]	Sex-linked recessive lethal mutation	*Drosophila melanogaster*	Feed	5 mM	Negative	(Wild et al., 1983)	Limited validity (limited reporting, test system considered of limited relevance).
	Micronucleus formation	Mouse, bone marrow	Intraperitoneal	146, 292, 438 mg/kg bw	Negative	(Wild et al., 1983)	Limited validity (only analysis at one time point; no PCE/NCE ratio reported.
alpha-Pentylcinnamaldehyde [05.040]	Sex-linked recessive lethal mutation	*Drosophila melanogaster*	Feed	10 mM	Negative	(Wild et al., 1983)	Limited validity (limited reporting, test system considered of limited relevance).
	Micronucleus formation	Mouse, bone marrow	Intraperitoneal	405, 809, 1313 mg/kg bw	Negative	(Wild et al., 1983)	Limited validity (only analysis at one time point; no PCE/NCE ratio reported lethality at highest dose

							level).
alpha-Hexylcinnamaldehyde [05.041]	Sex-linked recessive lethal mutation	*Drosophila melanogaster*	Feed	10 mM	Negative	(Wild et al., 1983)	Limited validity (limited reporting, test system considered of limited relevance).
		Mouse, bone marrow	Intraperitoneal	324, 540, 756 mg/kg bw	Negative	(Wild et al., 1983)	Limited validity (only analysis at one time point; no PCE/NCE ratio reported).

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

TABLE 3: SUMMARY OF SAFETY EVALUATIONS

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

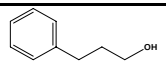
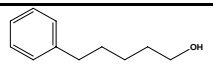
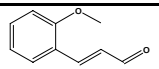
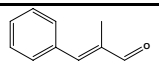
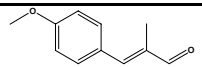
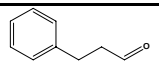
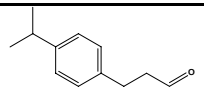
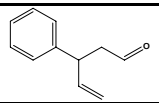
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.031 636	3-Phenylpropan-1-ol		51 31	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
02.051 675	5-Phenylpentan-1-ol		ND 0.1	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.
05.048 688	2-Methoxycinnamaldehyde	 Trans form shown	0.49 71	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition and composition of mixture to be specified.
05.050 683	alpha-Methylcinnamaldehyde	 Trans form shown	2.4 390	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.051 689	3-(4-Methoxyphenyl)-2-methylprop-2-enal	 Trans form shown	0.012 0.05	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.080 645	3-Phenylpropanal		16 19	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
05.094 680	3-(4-Isopropylphenyl)propionaldehyde		ND 0.1	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure. Composition of mixture to be specified.
05.103 679	3-Phenylpent-4-enal		0.73 2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

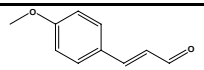
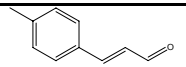
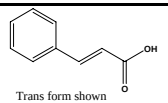
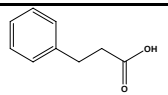
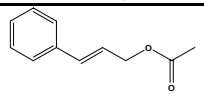
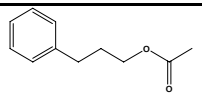
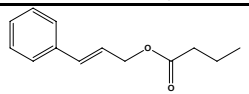
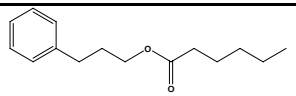
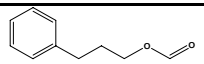
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
05.118 687	4-Methoxycinnamaldehyde	 Trans form shown	0.037 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.122 682	p-Methylcinnamaldehyde	 Trans form shown	0.012 0.9	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
08.022 657	Cinnamic acid	 Trans form shown	28 44	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
08.032 646	3-Phenylpropionic acid		20 0.5	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.018 650	Cinnamyl acetate	 Trans form shown	180 300	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.032 638	3-Phenylpropyl acetate		35 9	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.053 652	Cinnamyl butyrate	 Trans form shown	2.6 2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.071 642	3-Phenylpropyl hexanoate		ND 0.4	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.
09.084 637	3-Phenylpropyl formate		ND 0.8	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

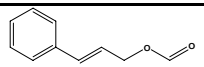
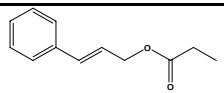
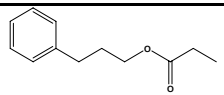
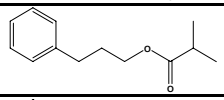
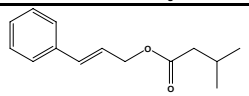
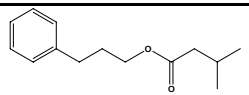
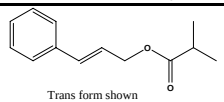
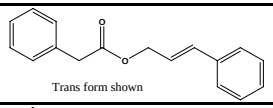
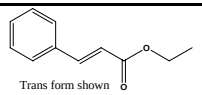
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.085 649	Cinnamyl formate	 Trans form shown	1.8 17	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.133 651	Cinnamyl propionate	 Trans form shown	3.7 25	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.138 639	3-Phenylpropyl propionate		0.12 0.3	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.428 640	3-Phenylpropyl isobutyrate		3.7 16	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.459 654	Cinnamyl isovalerate	 Trans form shown	3.9 8	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.467 641	3-Phenylpropyl isovalerate		0.012 0.1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.470 653	Cinnamyl isobutyrate	 Trans form shown	11 22	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.708 655	Cinnamyl phenylacetate	 Trans form shown	0.0024 1	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.730 659	Ethyl cinnamate	 Trans form shown	89 70	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

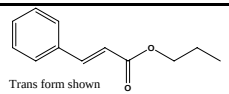
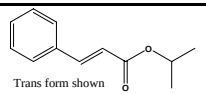
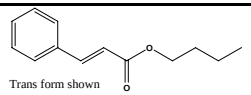
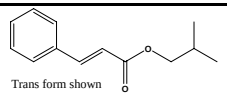
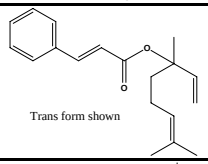
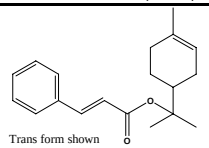
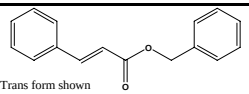
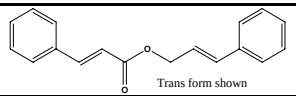
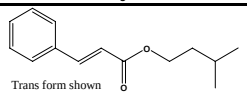
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.731 660	Propyl cinnamate	 Trans form shown	0.32 4	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.732 661	Isopropyl cinnamate	 Trans form shown	16 3	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.733 663	Butyl cinnamate	 Trans form shown	0.37 0.2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.734 664	Isobutyl cinnamate	 Trans form shown	1.2 3	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.736 668	Linalyl cinnamate	 Trans form shown	6.0 3	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition and composition of mixture to be specified.
09.737 669	Terpinyl cinnamate	 Trans form shown	0.012 0.5	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified Register name to be changed to S-Terpinyl cinnamate.
09.738 670	Benzyl cinnamate	 Trans form shown	38 69	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.739 673	Cinnamyl cinnamate	 Trans form shown	1.3 36	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.742 665	Isopentyl cinnamate	 Trans form shown	6.9 6	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

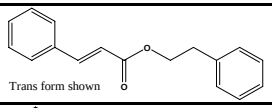
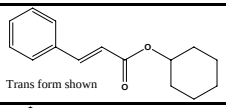
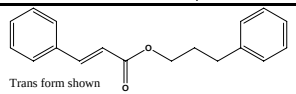
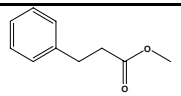
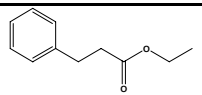
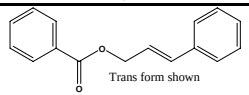
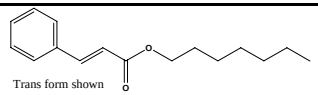
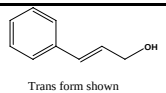
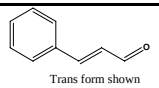
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.743 671	Phenethyl cinnamate	 Trans form shown	4.9 50	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.744 667	Cyclohexyl cinnamate	 Trans form shown	0.37 0.04	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.745 672	3-Phenylpropyl cinnamate	 Trans form shown	0.49 37	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.746 643	Methyl 3-phenylpropionate		ND 3	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure.
09.747 644	Ethyl 3-phenylpropionate		1.2 0.07	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.
09.780 760	Cinnamyl benzoate	 Trans form shown	ND 1	Class I A3: Intake below threshold	4)	No European production volumes available, preventing them to be evaluated using the Procedure.	No European production volumes available, preventing them to be evaluated using the Procedure. Stereoisomeric composition to be specified.
09.782 666	Heptyl cinnamate	 Trans form shown	1.5 52	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
02.017 647	Cinnamyl alcohol	 Trans form shown	1500 1900	Class I A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.014 656	Cinnamaldehyde	 Trans form shown	2100 59000	Class I A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

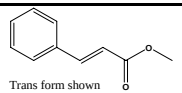
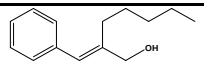
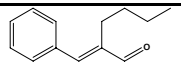
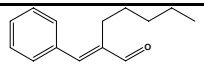
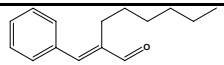
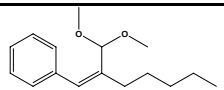
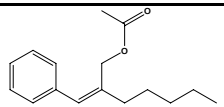
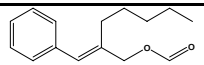
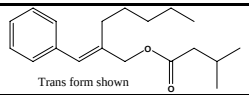
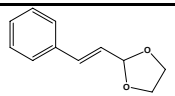
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.740 658	Methyl cinnamate	 Trans form shown	2400 830	Class I A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
02.030 674	alpha-Pentylcinnamyl alcohol	 Trans form shown	3.3 1	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.039 684	alpha-Butylcinnamaldehyde	 Trans form shown	0.012 0.07	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.040 685	alpha-Pentylcinnamaldehyde	 Trans form shown	22 23	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
05.041 686	alpha-Hexylcinnamaldehyde	 Trans form shown	74 11	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
06.013 681	alpha-Pentylcinnamaldehyde dimethyl acetal	 Trans form shown	0.012 0.007	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.026 677	alpha-Pentylcinnamyl acetate	 Trans form shown	2.4 260	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.
09.090 676	alpha-Pentylcinnamyl formate	 Trans form shown	1.2 0.5	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition and composition of mixture to be specified to be specified.
09.468 678	alpha-Pentylcinnamyl isovalerate	 Trans form shown	0.012 0.5	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

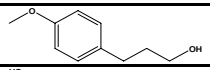
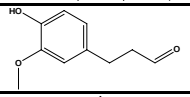
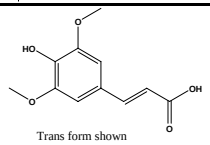
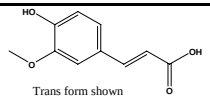
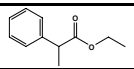
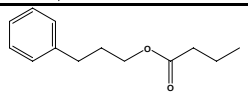
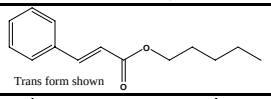
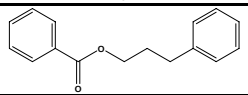
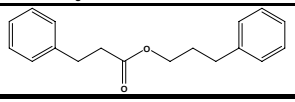
Table 3.1: Summary of Safety Evaluation of Cinnamyl Alcohol and Related Substances (JECFA, 2001b)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
06.014 648	Cinnamaldehyde ethylene glycol acetal	 Trans form shown	590 0.007	Class III A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake as flavouring substance based on the MSDI approach.	Stereoisomeric composition to be specified.

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
ND: not determined.

Table 3.2: Nine Aryl-Substituted Saturated and Unsaturated Primary Alcohol/Aldehyde/Acid/Ester Derivatives by EFSA in FGE.15Rev1 (EFSA, 2008q)

Table3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.173	3-(4-Methoxyphenyl)propan-1-ol		0.061	Class I A3: Intake below threshold	4)	6)	
05.156	3-(4-Hydroxy-3-methoxyphenyl)propanal		0.12	Class I A3: Intake below threshold	4)	6)	
08.088	4-Hydroxy-3,5-dimethoxycinnamic acid	 Trans form shown	0.012	Class I A3: Intake below threshold	4)	7)	
08.089	4-Hydroxy-3-methoxycinnamic acid	 Trans form shown	0.097	Class I A3: Intake below threshold	4)	7)	
09.364	Ethyl 2-phenylpropionate		0.0024	Class I A3: Intake below threshold	4)	7)	
09.690	3-Phenylpropyl butyrate		0.012	Class I A3: Intake below threshold	4)	6)	
09.735	Pentyl cinnamate	 Trans form shown	0.012	Class I A3: Intake below threshold	4)	7)	
09.836	3-Phenylpropyl benzoate		0.37	Class I A3: Intake below threshold	4)	6)	
09.837	3-Phenylpropyl 3-phenylpropionate		0.012	Class I A3: Intake below threshold	4)	6)	

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
6) No safety concern at estimated level of intake 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 and/or information on stereoisomerism.

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

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ABBREVIATIONS

CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DNA	Deoxyribonucleic acid
DTU-NFI	Danish Technical University – National Food Institute
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practise
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
ISS	Istituto Superiore di Sanita
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NCE	Normochromatic erythrocyte
No	Number
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
PCE	Polychromatic erythrocyte
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food

US EPA United States Environmental Protection Agency

WHO World Health Organisation