

## SCIENTIFIC OPINION

### Flavouring Group Evaluation 70 (FGE.70):

**Consideration of aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters evaluated by JECFA (61<sup>st</sup> meeting)**

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

(Question No EFSA-Q-2008-054)

**Adopted on 23 July 2009**

#### PANEL MEMBERS

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#### SUMMARY

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

The JECFA at their 61<sup>st</sup> meeting evaluated 26 flavouring substances consisting of aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters. Two of the JECFA evaluated substances are not in the Register [(E,E)-2,4-octadien-1-ol and (E,Z)-2,6-nonadien-1-ol acetate, (JECFA-no: 1180 and 1188)]. Seventeen substances are alpha,beta-unsaturated aldehydes or precursors for such considered by the Panel to be of concern for genotoxicity and are considered together with other alpha,beta-unsaturated aldehydes and precursors in FGE.200 (EFSA, 2008b) and FGE.203 (EFSA, 2009v). This consideration therefore only deals with seven dienoic and trienoic acids or esters hereof.

The Panel concluded that no supporting FGE was available for the substances in the present FGE.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for all seven dienoic and trienoic acids or esters thereof dealt with in this Opinion. However, for three substances [FL-no: 08.085, 09.371 and 09.639] the JECFA evaluation is only based on Maximised Survey-derived Daily Intake (MSDI) values derived from production figures from the USA. Accordingly, the safety in use in Europe could not be assessed using the Procedure, so EU production figures are needed for these three substances in order to finalise the evaluation of these three substances.

For all seven substances evaluated through the Procedure use levels are needed to calculate the modified Theoretical Added Maximum Daily Intake (mTAMDI) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the seven 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 four of the seven JECFA evaluated substances [FL-no: 08.085, 09.194, 09.260 and 09.300]. For two substances [FL-no: 09.371 and 09.840] information on stereoisomerism has not been provided and for two substances [FL-no: 09.639 and 09.840] further information on the composition of the mixture is requested.

Thus, for four substances [FL-no: 08.085, 09.371, 09.639 and 09.840] the Panel has reservations (no European production volumes available, preventing them to be evaluated using the Procedure, and/or missing data on stereoisomerism and/or compositional information of mixture). For the remaining three substances [FL-no: 09.194, 09.260 and 09.300] in the group of the JECFA evaluated aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances”, based on the MSDI approach.

## **KEYWORDS**

Flavourings; food safety; aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters; dienoic and trienoic acids or esters thereof; JECFA; 61<sup>st</sup> meeting.

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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 flavouring substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 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 55<sup>th</sup>, 57<sup>th</sup>, 59<sup>th</sup>, 61<sup>st</sup>, 63<sup>rd</sup>, 65<sup>th</sup>, 68<sup>th</sup> and 69<sup>th</sup> 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.

## ACKNOWLEDGEMENT

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## ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the “EFSA Procedure”. This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the “JECFA Procedure”. The 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 considerations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance.

#### Intake

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

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

When the Panel examined the information provided by the European 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 65<sup>th</sup> meeting, considered "how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods" (JECFA, 2006c).

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

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

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

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

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

that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure (“Do the condition of use result in an intake greater than 1.5 microgram per day?”) (JECFA, 1999b).

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

### Genotoxicity

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

### Specifications

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

### Structural Relationship

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

## **1. Presentation of the Substances in the JECFA Flavouring Group**

### 1.1. Description

#### 1.1.1. JECFA Status

The JECFA has evaluated a group of 26 flavouring substances consisting of aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters at the 61<sup>st</sup> meeting (JECFA, 2004b).

#### 1.1.2. EFSA Considerations

Two of the JECFA evaluated substances are not in the Register [(E,E)-2,4-octadien-1-ol and (E,Z)-2,6-nonadien-1-ol acetate, (JECFA-no: 1180 and 1188)]. Seventeen substances are alpha,beta-unsaturated aldehydes or precursors for such considered by the Panel to be of concern for genotoxicity and are considered together with other alpha,beta-unsaturated aldehydes and precursors in FGE.200 (EFSA, 2008b) and FGE.203 (EFSA, 2009v). This consideration therefore only deals with seven dienoic and trienoic acids or esters hereof.

The Panel concluded that no supporting FGE was available for the substances in the present FGE.

The Panel noted that one of the substances evaluated in the present FGE, hexa-2,4-dienoic acid [FL-no: 08.085] (synonyms: 2,4-hexadienoic acid and sorbic acid), together with its calcium, sodium and potassium salts, has been allocated a group ADI of 25 mg/kg body weight (expressed as sorbate) by the JECFA (JECFA, 1986a).

## 1.2. Isomers

### 1.2.1. *JECFA Status*

All seven substances [FL-no: 08.085, 09.194, 09.260, 09.300, 09.371, 09.639 and 09.840] can exist as geometrical isomers.

### 1.2.2. *EFSA Considerations*

Information is lacking about the stereoisomerism for two substances [FL-no: 09.371 and 09.840]. For the remaining substances [FL-no: 08.085, 09.194, 09.260, 09.300 and 09.639] the CAS register number (CASrn) specifies the stereoisomerism.

## 1.3. Specifications

### 1.3.1. *JECFA Status*

The JECFA specifications are available for all seven substances (JECFA, 2003b). See Table 1.

### 1.3.2. *EFSA Considerations*

The available specifications are considered adequate for four substances [FL-no: 08.085, 09.194, 09.260 and 09.300]. Information on isomerism is lacking for two substances [FL-no: 09.371 and 09.840] (see Section 1.2) and compositional information of mixture is lacking for two substances [FL-no: 09.639 and 09.840].

## 2. **Intake Estimations**

### 2.1. JECFA Status

For four substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining three substances [FL-no: 08.085, 09.371 and 09.639] production figures are only available for the USA.

### 2.2. EFSA Considerations

As production figures are only available for the USA for three substances, MSDI values for the EU cannot be calculated for these [FL-no: 08.085, 09.371 and 09.639].

## 3. **Genotoxicity Data**

### 3.1. Genotoxicity Studies – Information Taken from the JECFA (JECFA, 2004b)

The JECFA text (JECFA, 2004b) on the genotoxicity of the aliphatic, alicyclic, linear, di- and trienals and related alcohols, acids and esters includes information on the genotoxicity of the alpha,beta-unsaturated aldehydes or precursors thereof, evaluated by the JECFA in this group. Since these substances are considered by the Panel to be of concern for genotoxicity, they are considered together with other alpha,beta-unsaturated aldehydes and precursors in FGE.200 (EFSA, 2008b) and FGE.203 (EFSA, 2009v). Accordingly, in the following only text from the JECFA which includes information related to the seven dienoic or trienoic acids or esters thereof dealt with in this Opinion has been taken and modifications have thus been made to the text to provide clarity.



### *In vitro*

Testing for genotoxicity *in vitro* has been performed with hexa-2,4-dienoic acid and ethyl deca-2,4,7-trienoate [FL-no: 08.085 and 09.371] as representative members of the group of dienoic and trienoic acids and esters used as flavouring agents.

Negative results were reported in assays for mutagenicity when *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were incubated with up to 5000 µg of ethyl 2,4,7-decatrienoate [FL-no: 09.371]/plate, with and without metabolic activation (Thompson, 1996b).

JECFA reported that sodium and potassium 2,4-hexadienoic acid produced cell cycle alterations in V79 Chinese hamster ovary cells at levels < 2500 µg/ml (Schlatter et al., 1992), indicative of weak aneugenic activity (JECFA, 2004b).

### *In vivo*

Testing for the genotoxic potential of sodium and potassium 2,4-hexadienoic acid in somatic cells of *Drosophila melanogaster* after a 48-h feeding, yielded negative results at respective concentrations of 3.35 and 3.75 mg/ml (Schlatter et al., 1992).

The potential genotoxicity of repeated doses of 2,4-hexadienoic acid [FL-no: 08.085] was investigated in a test for chromosomal aberrations in mouse bone marrow. Groups of 10 Swiss albino male mice were given 2,4-hexadienoic acid at a daily dose of 0 (control) or 15 mg/kg bw by gavage for 30 days. Although there was an increase in the mitotic index, there was no significant increase in structural chromosomal aberrations as compared with the control group (Banerjee & Giri, 1986).

In a later study, groups of eight Swiss albino male mice were given 2,4-hexadienoic acid [FL-no: 08.085] in a single intraperitoneal injection containing a dose of 0, 25, 50, 75, 100, or 150 mg/kg bw (Mukherjee et al., 1988). A significant increase in sister chromatid exchanges ( $p < 0.05$ ) was observed in animals receiving 2,4-hexadienoic acid at a dose of >75 mg/kg bw per day. In a concurrent assay, groups of four mice were sacrificed at 24 h or 48 h, and the incidence of micronucleated cells per 500 polychromatic erythrocytes was recorded per animal, after administration of 2,4-hexadienoic acid at an acute intraperitoneal dose of 0, 2.5, 20, or 150 mg/kg bw. Micronucleated polychromatic erythrocytes were significantly increased ( $p < 0.05$ ) at the highest dose evaluated (150 mg/kg bw). It is important to note that the positive findings *in vivo* resulted from intraperitoneal administration, which has no relevance to human consumption of flavouring agents. In studies using administration by gavage, there was no genotoxic activity.

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

### 3.2. EFSA Considerations

Ethyl 2,4,7-decatrienoate [FL-no: 09.371] gave negative results in a bacterial mutagenicity assay at levels of up to 5000 µg/plate of ethyl 2,4,7-decatrienoate, with and without metabolic activation (Thompson, 1996b). While sodium and potassium 2,4-hexadienoic acid caused cell cycle alterations in V79 cells *in vitro* (Schlatter et al., 1992), a negative result was obtained in somatic cells of *Drosophila melanogaster* (Schlatter et al., 1992). Hexa-2,4-dienoic acid [FL-no: 08.085] (synonyms: 2,4-hexadienoic acid, sorbic acid) was not considered to induce chromosomal aberrations in mouse bone marrow *in vivo* (Banerjee & Giri, 1986), while a statistically significant increase in sister chromatid exchanges ( $p < 0.05$ ) was seen *in vivo* in mice receiving 2,4-hexadienoic



acid at a dose of >75 mg/kg bw per day by intraperitoneal injection, and an increase in micronuclei ( $p < 0.05$ ) was detected at 150 mg/kg bw (Mukherjee et al., 1988). The Panel noted however that the studies by Banerjee & Giri (1986) and Mukherjee et al. (1988) were of limited validity, since they did not meet the criteria of OECD guidelines 475 and 474, respectively. The study of Banerjee & Giri (1986) deviated from the guideline 475 with respect to dosing and sampling times. There was only one dose tested and the results were not reported in detail. In the study of Mukherjee et al. (1988) on the induction of micronuclei, only four animals per group were used (instead of five per sex per group), only 500 polychromatic cells were scored (instead of 2000), the PCE/NCE ratio was not determined and the results were not reported for individual animals.

A study not considered by the JECFA, in their evaluation of the genotoxicity of the aliphatic, alicyclic, linear, di- and trienals and related alcohols, acids and esters, examined the effect of potassium sorbate and sodium benzoate on a genetically modified *Saccharomyces cerevisiae*, lacking the Pdr12 plasma membrane transporter protein (Piper, 1999). Cells lacking this protein are hypersensitive to short-chain water-soluble monocarboxylic acids such as sorbate and benzoate, due to severe oxidative stress developing in the presence of such acids (Piper et al., 1998). The respiratory capability of these mutant *S. cerevisiae* cells was measured in a halo assay in the presence of either sorbate or benzoate. The author concluded that the test substances produced an increased number of respiratory-deficient yeast cells under aerobic conditions, indicating that damage was occurring to the mitochondrial DNA in the yeast cells (Piper, 1999). The study has been evaluated by several expert committees including the UK Committee on Mutagenicity (COM).

The COM concluded that direct extrapolation of these results from mutant yeast cells *in vitro* to mammalian cells *in vivo* was not possible (COM, 2007). The COM considered that “mammalian mitochondria *in vivo* have sufficient anti-oxidant and DNA repair mechanisms to deal with any oxidative stress that may be attributed to the action of these preservatives in addition to that normally seen through the normal respiratory activities of the cell. The superoxide dismutase (SOD) mutant cells used in the study by Piper have a significantly attenuated anti-oxidant and DNA repair response and therefore had a greater susceptibility to oxidative DNA damage.” The COM noted the evaluation of sorbates and benzoates by the JECFA and the large package of toxicology data, including rodent carcinogenicity studies, and concluded that the study in *S. cerevisiae* did not suggest a need for a full re-evaluation of the mutagenicity data on benzoates and sorbates. On the basis of this conclusion, COM considered that no further *in vivo* mutagenicity testing of these two preservatives was necessary at that time.

The Panel agrees with the views of the COM. The Panel noted that there was no evidence of any carcinogenic effect of hexa-2,4-dienoic acid (sorbic acid) in rats (Gaunt et al., 1975) or mice (Hendy et al., 1976) fed diets containing up to 10 % sorbic acid for 2 years and 80 weeks, respectively. These dietary levels were equivalent to an intake of up to 5 g/kg bw/day in rats and 13 g/kg bw/day in mice (Gold, 2007). Similarly, the potassium salt of hexa-2,4-dienoic acid (potassium sorbate) administered to groups of 6 rats at 0.1 % in the diet or 0.3 % in drinking water for up to 100 weeks did not result in the induction of tumours (Dickens et al., 1968). Ishizawa et al. (1980) reported that very high dietary levels of sorbic acid (15 % in the diet, approximately 20 g/kg bw/day) resulted in formation of liver cell tumours in mice in the presence of liver cell hypertrophy (Ishizawa et al., 1980). The Panel concluded that this finding was of no relevance in the evaluation of the safety of hexa-2,4-dienoic acid, given the propensity of certain mouse strains to develop liver cell tumours and the very high dose level used in the study.

The Panel therefore concluded overall that available genotoxicity and carcinogenicity data on the dienoic and trienoic acids or esters in this FGE, including hexa-2,4-dienoic acid [FL-no: 08.085] (synonyms: 2,4-hexadienoic acid and sorbic acid), do not preclude taking them through the Procedure.

#### 4. Application of the Procedure

##### 4.1. Application of the Procedure to Seven Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters by the JECFA (JECFA, 2004b)

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

The JECFA concluded all seven dienoic and trienoic acids and esters 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 substances from structural class I (step A3).

In conclusion the JECFA evaluated all seven 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 seven dienoic and trienoic acids and esters are summarised in Table 3.1: Summary of Safety Evaluation of Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters (JECFA, 2004b).

##### 4.2. EFSA Considerations

Following hydrolysis of the esters in the gastrointestinal tract, the resulting carboxylic acids will participate in normal fatty acid metabolism including beta-oxidation and citric acid cycle, which finally leads to the total oxidation of these substances as described for the mono-unsaturated, shorter chain carboxylic acids evaluated in FGE.05 Revision 1 (Annex III of FGE.05Rev.1 (EFSA, 2008j)). The Panel therefore agrees with the conclusion of the JECFA, that the substances in this FGE will be metabolised to innocuous products and can be evaluated via the A-side of the Procedure.

The Panel agrees with the way that the application of the Procedure has been performed by the JECFA for all seven substances. However, for three substances [FL-no: 08.085, 09.371 and 09.369] 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 three substances.

The Panel notes that for one of these substances hexa-2,4-dienoic acid [FL-no: 08.085] (synonyms: 2,4-hexadienoic acid and sorbic acid), together with its calcium, sodium and potassium salts, has been allocated a group ADI of 25 mg/kg body weight (expressed as sorbate) by the JECFA (JECFA, 1986a).

## 5. Conclusion

The JECFA has evaluated a group of 26 flavouring substances consisting of aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters.

Two of the JECFA evaluated substances are not in the Register [(E,E)-2,4-octadien-1-ol and (E,Z)-2,6-nonadien-1-ol acetate, (JECFA-no: 1180 and 1188)]. Seventeen substances are alpha,beta-unsaturated aldehydes or precursors for such considered by the Panel to be of concern for genotoxicity and are considered together with other alpha,beta-unsaturated aldehydes and precursors in FGE.200 (EFSA, 2008b) and FGE.203 (EFSA, 2009v). This consideration therefore only deals with seven dienoic and trienoic acids or esters hereof.

The Panel concluded that no supporting FGE was available for the substances in the present FGE.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the seven dienoic and trienoic acids or esters thereof dealt with in this Opinion. However, for three substances [FL-no: 08.085, 09.371 and 09.639] the JECFA evaluation is only based on MSDI values derived from production figures from the USA. Accordingly, the safety in use in Europe could not be assessed using the Procedure, so EU production figures are needed for these three substances in order to finalise their evaluation.

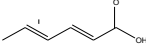
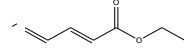
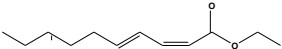
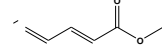
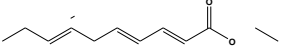
For the four remaining substances [FL-no: 09.194, 09.260, 09.300 and 09.840], intakes are below the threshold for the structural class, based on the MSDI approach.

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

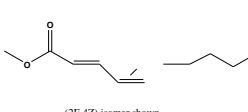
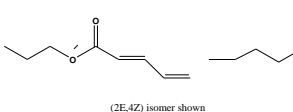
In order to determine whether the conclusion for the seven JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity are available for four of the seven JECFA evaluated substances [FL-no: 08.085, 09.194, 09.260 and 09.300]. For two substances [FL-no: 09.371 and 09.840] information on stereoisomerism has not been provided and for two substances [FL-no: 09.639 and 09.840] further information on the composition of the mixture is requested. Thus, for these four substances [FL-no: 08.085, 09.371, 09.639 and 09.840] the Panel has reservations (no European production volumes available, preventing them to be evaluated using the Procedure, and/or missing data on stereoisomerism and/or compositional information of mixture).

For the remaining three substances [FL-no: 09.194, 09.260 and 09.300] in the group of the JECFA evaluated aliphatic, alicyclic, linear, alpha,beta-unsaturated, di- and trienals and related alcohols, acids and esters the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances”, based on the MSDI approach.

**TABLE 1: SPECIFICATION SUMMARY FOR JECFA EVALUATED SUBSTANCES IN THE PRESENT GROUP (JECFA, 2004B)**

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters (JECFA, 2004b)								
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
08.085 1176	Hexa-2,4-dienoic acid		3921 110-44-1	Solid C <sub>6</sub> H <sub>8</sub> O <sub>2</sub> 112.13	Slightly soluble Soluble	n.a. 132-135 IR NMR 99 %	n.a. n.a.	The JECFA evaluated (E,E)-2,4-hexadienoic acid (CASrn as in Register). CASrn in Register refers to the (E,E)-isomer. Register name to be changed to (E,E)-Hexa-2,4-dienoic acid.
09.194 1178	Ethyl hexa-2,4-dienoate		2459 635 2396-84-1	Liquid C <sub>8</sub> H <sub>12</sub> O <sub>2</sub> 140.18	Slightly soluble Soluble	195-196 IR MS 98 %	1.491-1.498 0.936-0.939	The JECFA evaluated ethyl sorbate (CASrn as in Register). CASrn in Register refers to the (E,E)-enantiomer. Register name to be changed to Ethyl (E,E)-hexa-2,4-dienoic acid.
09.260 1192	Ethyldeca-2(cis),4(trans)-dienoate		3148 10574 3025-30-7	Liquid C <sub>12</sub> H <sub>20</sub> O <sub>2</sub> 196.29	Insoluble	120 (9hPa) NMR 90%	1.480-1.1486 0.917-0.920	The JECFA evaluated ethyl trans-2-cis-4-decadienoate (CASrn as in Register). CASrn in Register refers to the (2E,4Z)-enantiomer. Register name to be changed to Ethyl (E,Z)-deca-2,4-dienoate.
09.300 1177	Methyl hexa-2,4-dienoate		3714 689-89-4	Liquid C <sub>7</sub> H <sub>10</sub> O <sub>2</sub> 126.16	Slightly soluble Soluble	180 IR NMR 99 %	1.501-1.505 0.933-0.938	The JECFA evaluated methyl sorbate (CASrn as in Register). CASrn in Register refers to the (E,E)-enantiomer. Register name to be changed to Methyl (E,E)-hexa-2,4-dienoic acid.
09.371 1193	Ethyl deca-2,4,7-trienoate 6)		3832 10576 78417-28-4	Liquid C <sub>12</sub> H <sub>18</sub> O <sub>2</sub> 194.28	Soluble Soluble	134 (18 hPa) IR NMR 95 %	1.547-1.554 0.933-0.939	

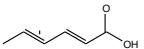
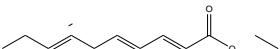
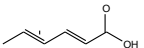
**Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters (JECFA, 2004b)**

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
09.639 1191	Methyl deca-2,4-dienoate	 (2E,4Z) isomer shown	3859 4493-42-9	Liquid C <sub>11</sub> H <sub>18</sub> O <sub>2</sub> 182.26	Insoluble Soluble	67 (1 hPa) IR NMR 93.5	1.488-1.494 0.917-0.923	According to the JECFA: Min. assay value is "93 %" and secondary components "(E,E) methyl 2,4-decadienoate". CASrn in Register refers to the (2E,4Z)-enantiomer. Register name to be changed to Methyl (E,Z)-deca-2,4-dienoate.
09.840 1194	Propyl-2,4-decadienoate 6)	 (2E,4Z) isomer shown	3648 10889 84788-08-9	Liquid C <sub>13</sub> H <sub>22</sub> O <sub>2</sub> 210.32	Insoluble Soluble	110 (0.5 hPa) NMR 95 %	1.468-1.475 0.913-0.919	According to the JECFA: Min. assay value is "95 % (sum of isomers)". Register name to be changed to Propyl 2,4-decadienoate and in accordance with the actual stereoisomeric composition.

- 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 Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters (JECFA, 2004b) Table 2.1: Summary of Genotoxicity Data of Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters evaluated by JECFA**

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
<b><i>In vitro</i></b>							
08.085 1176	Hexa-2,4-dienoic acid		Cell cycle alterations	V79 Chinese hamster cells	≤2500 µg/ml	Positive <sup>a</sup>	(Schlatter et al., 1992)
			Cell cycle alterations	V79 Chinese hamster cells	≤2500 µg/ml	Positive <sup>a,b</sup>	(Schlatter et al., 1992)
09.371 1193	Ethyl deca-2,4,7-trienoate		Reverse mutation	<i>S. typhimurium</i> TA100, TA1535, TA1538, TA98 and TA1537	1.5–5000 µg/plate	Negative <sup>c</sup>	(Thompson, 1996b)
<b><i>In vivo</i></b>							
08.085 1176	Hexa-2,4-dienoic acid		Somatic mutation and recombination	<i>Drosophila melanogaster</i>	3.35-3.75 mg/ml	Negative <sup>d</sup>	(Schlatter et al., 1992)
			Chromosome aberration	Mouse	15 mg/kg bw	Positive <sup>e,f</sup>	(Banerjee & Giri, 1986)
			Micronucleus formation	Mouse	2.5, 20 mg/kg bw	Negative <sup>g</sup>	(Mukherjee et al., 1988)
					150 mg/kg bw	Positive <sup>g</sup>	
			Sister chromatid exchange	Mouse	25 to 50 mg/kg bw	Negative <sup>g</sup>	(Mukherjee et al., 1988)
		75, 100, or 150 mg/kg bw	Positive <sup>g</sup>				

<sup>a</sup> Pattern of positive effects is suggestive of weak aneugenic activity.

<sup>b</sup> Positive effects observed only with stored solutions (28-days old).

<sup>c</sup> With and without metabolic activation.

<sup>d</sup> Administered orally.

<sup>e</sup> Administered by gavage for 30 days.

<sup>f</sup> Positive effects limited to spindle activity; no effects observed on structural chromosome aberrations.

<sup>g</sup> Administered as a single intraperitoneal injection.



**TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES**

**Table 3.1: Summary of Safety Evaluation of Aliphatic, Alicyclic, Linear, alpha,beta-Unsaturated, Di- and Trienals and Related Alcohols, Acids and Esters (JECFA, 2004b)**

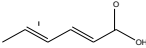
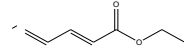
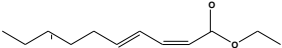
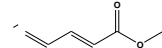
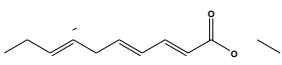
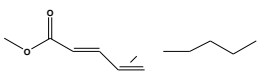
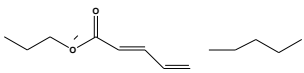
<b>Table 3.1: Summary of Safety Evaluation of the JECFA-evaluated Substances (JECFA, 2004b)</b>							
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI ( $\mu\text{g}/\text{capita}/\text{day}$ )	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
08.085 1176	Hexa-2,4-dienoic acid		ND 6	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. Register name to be changed to (E,E)-Hexa-2,4-dienoic acid.
09.194 1178	Ethyl hexa-2,4-dienoate		50 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. Register name to be changed to Ethyl (E,E)-hexa-2,4-dienoic acid.
09.260 1192	Ethyldeca-2(cis),4(trans)-dienoate		29 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. Register name to be changed to Ethyl (E,Z)-deca-2,4-dienoate.
09.300 1177	Methyl hexa-2,4-dienoate		0.097 ND	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. Register name to be changed to Methyl (E,E)-hexa-2,4-dienoic acid.

Table 3.1: Summary of Safety Evaluation of the JECFA-evaluated Substances (JECFA, 2004b)							
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI ( $\mu\text{g}/\text{capita}/\text{day}$ )	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
09.371 1193	Ethyl deca-2,4,7-trienoate		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. Stereoisomeric composition to be specified.
09.639 1191	Methyl deca-2,4-dienoate	 (2E,4Z) isomer 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. Composition of mixture to be specified. Register name to be changed to Methyl (E,Z)-deca-2,4-dienoate.
09.840 1194	Propyl-2,4-decadienoate	 (2E,4Z) isomer shown	0.77 ND	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. Composition of mixture to be specified. Register name to be changed to Propyl 2,4-decadienoate and in accordance with the actual stereoisomeric composition.

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) =  $\mu\text{g}/\text{capita}/\text{day}$ .

2) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90  $\mu\text{g}/\text{person}/\text{day}$ .

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

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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