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Flavouring Group Evaluation 62 (FGE.62)

Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

and to straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters evaluated by EFSA in FGE.06 (2004)

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

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

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

(Adopted on 3 July 2007)

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SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) is asked to advise the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular the Scientific Panel is requested to consider 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 present consideration concerns 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by the JECFA (61st meeting) and will be considered in relation to the European Food Safety Authority (EFSA) evaluations of esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated in the Flavouring Group Evaluation 05 (FGE.05) and straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters evaluated in the Flavouring Group Evaluation 06 (FGE.06).

The Panel concluded that the 19 substances in the JECFA flavouring group of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters are structurally related to the group of esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 and related to straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters evaluated by EFSA in FGE.06.

One additional substance ((E)-3-(Z)-6-nonadien-1-ol acetate) considered by the JECFA is not in the Register and was therefore not evaluated in this FGE.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances considered in this FGE.

For two substances [FL-no: 02.189 and 02.243] the JECFA evaluation is only based on Maximised Survey-derived Daily Intake (MSDI) values derived from production figures from the USA. EU production figures are needed in order to finalise the evaluation of these substances

For all 19 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 19 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications are available for 12 of the 19 JECFA evaluated substances. For six substances [FL-no: 05.192, 08.075, 09.566, 09.568, 09.571 and 09.846] information of the isomeric composition is lacking and for three substances additional information on the composition is requested [FL-no: 05.192, 09.568 and 09.922].

Thus, for nine substances [FL-no: 02.189, 02.243, 05.192, 08.075, 09.566, 09.568, 09.571, 09.846 and 09.922] the Panel has reservations (only USA production volumes available and/or missing data on specifications and/or isomerism/composition). For the remaining ten substances [FL-no: 02.249, 05.139, 09.559, 09.563, 09.564, 09.655, 09.917, 09.918, 09.921 and 09.932] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

Key words:

Linear-chain, branched-chain, aliphatic, unsaturated, unconjugated, alcohols, aldehydes, acids, esters, JECFA, FGE.05, FGE.06, 61st meeting.

Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

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BACKGROUND

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

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

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

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

TERMS OF REFERENCE

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

ASSESSMENT

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

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

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

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

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

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

“The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated

using earlier steps in the Procedure, but for which the intake would not exceed 1.5 microgram per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 microgram per day?") (JECFA, 1999b).

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA status

The JECFA has evaluated a group of 20 flavouring substances consisting of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters. One substance [(E)-3-(Z)-6-nonadien-1-ol acetate] is not in the Register and will therefore not be evaluated. This consideration will therefore deal with 19 JECFA evaluated substances.

1.1.2. EFSA Considerations

The Panel concluded that the 19 substances in the JECFA flavouring group of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters are all structurally related to a group of esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and to branched- and straight-chain unsaturated carboxylic

acids evaluated by EFSA in the Flavouring Group Evaluation 05 (FGE.05) or related to straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters evaluated by EFSA in the Flavouring Group Evaluation 06 (FGE.06).

1.2. Isomers

1.2.1. JECFA status

Fifteen substances in the group of JECFA evaluated linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters can exist as geometrical isomers [FL-no: 02.189, 02.243, 02.249, 05.192, 08.075, 09.559, 09.563, 09.564, 09.566, 09.568, 09.571, 09.846, 09.918, 09.922 and 09.932].

1.2.2. EFSA Considerations

Information is lacking about the stereoisomerism for six of the 15 substances [05.192, 08.075, 09.566, 09.568, 09.571 and 09.846].

1.3. Specifications

1.3.1. JECFA status

JECFA specifications are available for all 19 substances (JECFA, 2004b). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate except that information on isomerism is lacking for six substances [05.192, 08.075, 09.566, 09.568, 09.571 and 09.846], see Section 1.2. For three substances further information on the composition is requested [FL-no: 05.192, 09.568 and 09.922]. See Table 1.

2. Intake Estimations

2.1 JECFA Status

For 17 substances evaluated through the JECFA Procedure intake data are available for the EU, see Table 3.1. For the remaining two substances, production figures are only available for the USA.

2.2 EFSA Considerations

As production figures are only available for the USA for two substances, MSDI values for the EU cannot be calculated for these [FL-no: 02.189 and 02.243].

3. Genotoxicity Data

No monograph has been prepared for this group of JECFA evaluated substances as they were considered in an addendum to 42 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated at the 51st meeting. Three representative linear and branched-chain aliphatic unsaturated primary alcohols and unconjugated aldehydes, carboxylic acids, and related esters in this group have been tested for genotoxicity.

3.1. Genotoxicity Studies – Text Taken From the JECFA (JECFA, 1999a)

In vitro

No evidence of mutagenicity was reported for oleic acid, methyl linoleate, methyl linolenate, or 2,6-dimethyl-5-heptenal in standard and preincubation assays in *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537, or TA1538 with or without the addition of metabolic activation (Wild et al., 1983; Shimizu et al., 1985; Mortelmans et al., 1986; Heck et al., 1989). The maximum concentrations used in these studies ranged from 333 to 50 000 µg/plate. In further bacterial assays, such as the *rec* assay in *Bacillus subtilis* incubated with oleic acid (Osawa & Namiki, 1982), the *his*$^+$ reversion assay in *S. typhimurium* incubated with methyl linoleate or methyl linolenate (MacGregor et al., 1985), and a modified Ames test in *Escherichia coli* WP2 *uvr*A incubated with oleic acid (Shimizu et al., 1985), aliphatic unsaturated unconjugated acids and esters were also shown to be non-mutagenic.

No unscheduled DNA synthesis was seen after exposure of rat hepatocytes to 2,6-dimethyl-5-heptenal at concentrations up to 1 mg/ml (Heck et al., 1989).

In *S. typhimurium* strain TA98, a concentration of 0.1 mmol/L oleic acid was reported to inhibit (by approximately 50%) the mutagenicity of known mutagens, including 3-amino-1,4-dimethyl-5 *H*-pyrido[4,3- *b*]indole, 2-amino-9 *H*-pyridol[2,3- *b*]indole, 2-amino-3-methylimidazo[4,5-*d*]quinoline, benzo[*a*]-pyrene, and aflatoxin B_1, when tested in the presence or absence of metabolic activation (Hayatsu et al., 1981). 2,6-Dimethyl-5-heptenal at a concentration of 25 mmol/L did not cause *Basc* reversion in *Drosophila melanogaster* (Wild et al., 1983).

In vivo

In mice given a maximum single dose of 1540 mg/kg bw 2,6-dimethyl-5-heptenal, all of which survived treatment, the incidence of polychromatic erythrocytes was not statistically significantly increased (Wild et al., 1983).

Oleic acid did not induce oxidative damage in isolated DNA (de Kok et al, 1994). In a three-week study in volunteers, ingestion of oleic acid did not alter the frequency of micronucleated lymphocytes in peripheral blood (Record et al., 1992).

These negative results indicate that the substances in this group of linear and branched-chain aliphatic unsaturated and unconjugated alcohols, aldehydes, acids, and related esters that are used as flavouring substances are neither mutagenic nor genotoxic.

3.2. Genotoxicity Studies - Text Taken from EFSA (FGE.05 (EFSA, 2004a) and FGE.06 (EFSA, 2004h)

In vitro /in vivo

FGE.05

There are *in vitro* genotoxicity data for four candidate substances [FL-no: 09.375, 09.586, 09.647, and 09.652] and for four supporting substances [FL-no: 08.013, 05.074, and a mixture of 09.646 and methyl linolenate]. *In vivo* data are available for two candidate substances [FL-no: 09.586 and 09.647] and for one supporting substance [FL-no: 05.074]. See Tables 2.2 and 2.3.

Studies on candidate substances

***In vitro* studies**

Methyl oleate, methyl methacrylate, ethyl methacrylate and isobutyl 2-methylprop-2-enoate were reported to be nonmutagenic in standard, pre-incubation or liquid suspension protocol Ames assays including *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, and/or TA1538 with or without metabolic activation. In three instances, the results of Ames assays with methyl methacrylate were weakly positive; however, these results were accompanied by cytotoxicity.

Methyl methacrylate and ethyl methacrylate have been tested in several mammalian cell assays. Positive results seen in chromosome aberrations, mouse lymphoma, SCE, HPRT, and/or micronucleus assays in most instances were obtained at high exposure concentrations (i.e. > 10 mM or > 1000 microgram/ml) and (when reported) high levels of cytotoxicity. However, when methyl methacrylate was tested in a mouse lymphoma assay at concentrations between 5 and 10 mM in the presence of S9-mix, it revealed a positive result which was accompanied by only low cytotoxicity (about 80% survival at 5 mM and approximately 40% at 10 mM) (Dearfield et al., 1991).

***In vivo* studies**

Methyl methacrylate was evaluated in a mouse micronucleus study conducted by oral gavage. The result was negative, however, it is not clear whether the substance had reached the bone marrow. Two sex-linked recessive lethal mutation studies (one by inhalation and the other by injection) in *Drosophila melanogaster* were negative, as was a dominant lethal assay in mice conducted *via* inhalation exposure. Rats exposed to high inhalation concentrations of methyl methacrylate did have weak, but statistically significant, increases in chromosome aberrations in bone marrow cells at some exposure levels in comparison to the negative control values both after single and multiple exposures. However, a clear conclusion cannot be drawn from these studies. SCE and chromosome aberration studies with peripheral lymphocytes from male workers occupationally exposed to methyl methacrylate by inhalation for eight hours/day were negative.

Isobutyl 2-methylprop-2-enoate was evaluated in a mouse micronucleus study with oral doses as high as 5000 mg/kg. Results were reported to be negative.

For methyl methacrylate, genotoxicity data were summarized the EU Risk Assessment Report (CEC, 2002) as follows:

"Methyl methacrylate was negative in bacterial gene mutation tests. From mammalian cell culture assays it may be concluded that methyl methacrylate is a high toxicity clastogen (i.e. induction of chromosomal aberrations is bound to highly toxic doses). The effect is not dependent on presence of S9-mix. These findings are in line with results from mouse lymphoma assays where positive findings seem to be due to the induction of small colonies. Marginal increases in SCE frequencies are of low significance."

"*In vivo* an oral mouse bone marrow micronucleus test was negative for doses up to 4520 mg/kg. No clear conclusion could be drawn from bone marrow chromosomal aberration assays with rats. A dominant lethal assay with male mice led to a negative result."

"*In vitro* methyl methacrylate has the potential for induction of mutagenic effects, esp. clastogenicity; however, this potential seems to be limited to high doses with strong toxic effects. Furthermore, the negative *in vivo* micronucleus test and the negative dominant lethal assay indicate that this potential is probably not expressed *in viv*o."

Studies on supporting substances

Mutagenicity/genotoxicity testing has been performed on four supporting substances. The results of these studies are described below and summarized in Tables 2.2 and 2.3.

***In vitro* studies**

No evidence of mutagenicity was reported for oleic acid, methyl linoleate and methyl linolenate, or 2,6-dimethyl-5-heptenal in the standard or pre-incubation protocol Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 with or without the addition of metabolic activation (Shimizu et al., 1985; Mortelmans et al., 1986; Wild et al., 1983; Heck et al., 1989). The maximum doses reported for these studies ranged from 333 to 50000 microgram/plate. In further bacterial assays, such as the rec-assay utilizing *Bacillus subtilis*, incubated with oleic acid (Osawa & Namiki, 1982), the His + reversion assay utilizing *Salmonella typhimurium* incubated with methyl linoleate or methyl linolenate (MacGregor et al., 1985), and a modified Ames test utilizing *Escherichia coli WP2uvrA* incubated with oleic acid (Shimizu et al., 1985), these aliphatic unsaturated non-conjugated acids and esters were non-mutagenic.

With respect to mammalian cell assays, rat hepatocytes were tested for unscheduled DNA synthesis (UDS) after exposure to concentrations of up to 1.0 mg 2,6-dimethyl-5-heptenal/ml. The results from this study showed no genotoxic effects (Heck et al., 1989).

***In vivo* studies**

A bone marrow micronucleus test was conducted *in vivo* in mice with a maximum single dose of 1540 mg/kg 2,6-dimethyl-5-heptenal. All mice survived the treatment. There were no statistically significant increases in the incidence of micronucleated polychromatic erythrocytes (PCEs)

observed (Wild et al., 1983). However, the quality of the study is limited since only a single sampling time was used and the PCE/NCE ratio was not reported. Therefore, it is not clear whether the substance had reached the bone marrow.

In the *Basc* test using *Drosophila melanogaster*, 2,6-dimethyl-5-heptenal was negative when tested at a concentration of 25 mM (Wild et al., 1983).

In summary, genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available as well as the chemical structures of the candidate substances do not raise concerns about genotoxicity for the flavouring substances in this group.

FGE.06

There are experimental data available for one candidate substance, methyl-3-but-3-en-1-ol [FL-no: 02.176], which was not mutagenic in the Ames test.

There are data from *in vitro* genotoxicity tests for six supporting substances [FL-no: 05.074, 05.139, 08.013, 09.011, 09.076, and 09.646]. The most extensively tested substances were oleic acid (six studies) and geranyl acetate (12 studies).

Oleic acid [FL-no: 08.013] gave negative results when tested in *in vitro* tests for point mutations with both bacterial and mammalian cells as well as in a Rec assay. In the absence of exogenous metabolic activation, oleic acid induced chromosomal numerical abnormalities in Chinese hamster V79 cells, but no increase in sister-chromatid exchanges (SCE). The increase in chromosomal numerical abnormalities, although not dose-dependent, was observed at all concentration levels.

Geranyl acetate [FL-no: 09.011] was not mutagenic when tested in the Ames test. Negative results were also obtained in a Rec assay; moreover, it did not induce UDS in rat hepatocytes and chromosomal aberration in CHO cells, where it was also not able to inhibit DNA synthesis. Geranyl acetate gave weakly positive results in the SCE assay in CHO cells, although only at cytotoxic concentrations. In two poorly reported studies, it appeared weakly mutagenic at the TK locus in the mouse lymphoma assay in the presence of exogenous metabolic activation. In contrast, negative results were obtained in a valid, well-reported study on gene mutation at a TK6 locus in human lymphoblasts.

All the remaining *in vitro* genotoxicity studies, performed with different supporting substances, gave negative results.

The genotoxic potential of geranyl acetate [FL-no: 09.011] was assessed also *in vivo*: negative results were obtained in a micronucleous test in mice and in UDS induction in rats. Negative data on *in vivo* genotoxicity were also available for another supporting substance 2,6-dimethyl-5-heptanal [FL-no: 05.074].

In summary, the validity of the weak positive results from the gene mutation assay performed with geranyl acetate is questionable, taking into account the negative results from other *in vitro* and *in*

vivo assays. The reported induction of aneuploidy by oleic acid can be considered as a threshold event. All the remaining genotoxicity tests on supporting substances gave negative results. Only for one candidate substance, methyl-3-but-3-en-1-ol, which was not mutagenic in the Ames test, data are available. On this basis and on the results on supporting substances it can be concluded that genotoxicity is not of concern for the candidate substances in this FGE.

Conclusion on genotoxicity.

FGE.05: In summary, genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available as well as the chemical structures of the candidate substances do not raise concerns about genotoxicity for the flavouring substances in this group.

FGE.06: In summary, the validity of the weak positive results from the gene mutation assay performed with geranyl acetate is questionable, taking into account the negative results from other *in vitro* and *in vivo* assays. The reported induction of aneuploidy by oleic acid can be considered as a threshold event. All the remaining genotoxicity tests on supporting substances gave negative results. Only for one candidate substance, methyl-3-but-3-en-1-ol, which was not mutagenic in the Ames test, data is available. On this basis and on the results on supporting substances it can be concluded that genotoxicity is not of concern for the candidate substances in this FGE.

For a summary of *in vitro* / *in vivo* genotoxicity data see Tables 2.2, 2.3, 2.4 and 2.5.

3.3. EFSA Considerations

The Panel concluded that the data available do not preclude evaluation of the 19 JECFA evaluated linear and branched chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 19 Linear and Branched-Chain Aliphatic Unsaturated, Unconjugated Alcohols, Aldehydes, Acids, and Related Esters by JECFA (JECFA, 2003b):

According to the JECFA all 19 substances belong to structural class I using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded all 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related 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 their structural class I (step A3).

In conclusion the JECFA evaluated all 19 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 19 substances are summarised in Table 3.1: Summary of Safety Evaluation of 19 Linear and Branched-chain Aliphatic Unsaturated, Unconjugated Alcohols, Aldehydes, Acids, and Related Esters (JECFA, 2003b).

4.2. Application of the Procedure to Esters of Branched- and Straight-Chain Aliphatic Saturated Primary Alcohols and of One Secondary Alcohol, and Branched- and Straight-Chain Unsaturated Carboxylic Acids Evaluated by EFSA (EFSA, 2004a) and to Straight- and Branched-Chain Aliphatic Unsaturated Primary Alcohols, Aldehydes, Carboxylic Acids, and Esters Evaluated by EFSA (EFSA, 2004h):

In FGE.05

Twentyfour candidate substances were evaluated in FGE.05 of which 21 are classified into structural class I and three into structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

Twentyone 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 thresholds for the structural classses I and II (step A3).

The remaining three substances, ethyl methacrylate, methyl methacrylate and isobutyl 2-methylprop-2-enoate [FL-no: 09.375, 09.647 and 09.586] were concluded at step B4. Ethyl methacrylate induced neurotoxicity in a 60-day drinking water study in rats even at the lowest dose tested (0.1 % in drinking water, equivalent to approximately 50 mg/kg body weight/day) (Abou-Donia et al., 2000). Accordingly, a NOAEL could not be established. Methyl methacrylate has a neurotoxic potential, as shown in an EU Risk Assessment Report (CEC, 2002). However, an adequate NOAEL from an oral study comparable to that of Abou-Donia et al. (2000) is not available for methyl methacrylate. Therefore, additional toxicity data are required for ethyl methacrylate [FL-no: 09.375], methyl methacrylate [FL-no: 09.647] and isobutyl 2-methylprop-2-enoate [FL-no: 09.586].

In conclusion the Panel evaluated 21 substances as to be of no safety concern at the estimated levels of intake based on the MSDI approach. For the remaining three substances additional toxicity data are required: ethyl methacrylate [FL-no: 09.375], methyl methacrylate [FL-no: 09.647] and isobutyl 2-methylprop-2-enoate [FL-no: 09.586].

The stepwise evaluations of the 24 substances are summarised in Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.05).

In FGE.06

Thirtyfive candidate substances were evaluated in FGE.06 of which 33 substances are classified into structural class I and two into structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

Thirtyfour 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 thresholds for the structural classses I and II (step A3).

The remaining substance, hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] was concluded at step B4. The teratogenic activity of 2-ethylbutyric acid, a hydrolysis product of hex-3-enyl 2-ethylbutyrate, has been described in a single-dose study after subcutaneous administration of 600 mg/kg body weight of 2-ethylbutyric acid to pregnant mice. Further, it should be taken into account that 2-ethylbutyric acid is structurally related to valproic acid, which is a well-known teratogen.

In a study in which 2-ethylbutyric acid was administered by gavage to pregnant rats once daily on gestation days 6 to 15, at dose levels of 0, 150, or 200 mg/kg bw/day, a NOAEL of 200 mg/kg bw/day for the teratogenic activity of 2-ethylbutyric acid could be derived.

The estimated daily *per capita* intake (MSDI) of the candidate substance is 0.58 microgram corresponding to approximately 0.005 microgram 2-ethylbutyric acid/kg bw/day at a body weight of 60 kg. This intake is more than 4×10^7 lower than the NOAEL for teratogenicity.

Based on the results of the safety evaluation sequence this candidate substance [FL-no: 09.884] does not pose a safety concern including for teratogenicity at the estimated level of intake, based on the MSDI approach.

In conclusion the Panel evaluated all 35 substances as to be of no safety concern based on the MSDI approach.

The stepwise evaluations of the 35 substances are summarised in Table 3.3: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.06).

4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances in the group of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters.

5. Conclusion

The Panel concluded that the 19 substances in the JECFA flavouring group of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters are structurally related to the group of esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in the Flavouring Group Evaluation 05 (FGE.05) and related to straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters evaluated by EFSA in the Flavouring Group Evaluation 06 (FGE.06).

One additional substance ((E)-3-(Z)-6-nonadien-1-ol acetate) considered by the JECFA is not in the Register and was therefore not evaluated in this FGE.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances considered in this FGE.

For two substances [FL-no: 02.189 and 02.243] 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 19 substances evaluated through the Procedure use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 19 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications:

Adequate specifications are available for 12 of the 19 JECFA substances. For six substances [FL-no: 05.192, 08.075, 09.566, 09.568, 09.571 and 09.846] information of the isomeric composition is lacking and for three substances additional information on the composition is requested [FL-no: 05.192, 09.568 and 09.922].

Thus, for nine substances [FL-no: 02.189, 02.243, 05.192, 08.075, 09.566, 09.568, 09.571, 09.846 and 09.922] the Panel has reservations (only USA production volumes available and/or missing data on specifications and/or isomerism/composition). For the remaining ten substances [FL-no: 02.249, 05.139, 09.559, 09.563, 09.564, 09.655, 09.917, 09.918, 09.921 and 09.932] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

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

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 2003b)

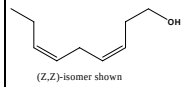
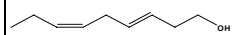
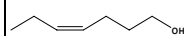
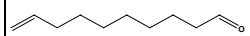
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.189 1283	Nona-3,6-dien-1-ol	 (Z,Z)-isomer shown	3885 10289 76649-25-7	Liquid $C_9H_{16}O$ 140.23	Slightly soluble Soluble	70 (3 hPa) IR NMR 97 %	1.462-1.469 0.863-0.871	CASrn does not specify stereoisomer. According to JECFA: Min. assay value is "97 %" and "1% E,Z isomer; 1% Z,E isomer; 0.5% E,E isomer". Name to be changed to: (Z,Z)-Nona-3,6-dien-1-ol.
02.243 1284	(E,Z)-3,6-Nonadien-1-ol		3884 56805-23-3	Liquid $C_9H_{16}O$ 140.23	Slightly soluble Soluble	73 (20 hPa) IR NMR 92 %	1.462-1.469 0.863-0.871	According to JECFA: Min. assay value is "92%" and secondary components "(E,E)-3,6-nonadien-1-ol".
02.249 1280	(4Z)-Hepten-1-ol		3841 6191-71-5	Liquid $C_7H_{14}O$ 114.19	Insoluble Soluble	77-78 (30 hPa) IR NMR MS 98 %	1.440-1.448 0.845-0.853	
05.139 1286	Dec-9-enal		3912 39770-05-3	Liquid $C_{10}H_{18}O$ 154.25	Insoluble Soluble	213 (961 hPa) IR NMR MS 98 %	1.438-1.442 0.843-0.849	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 2003b)

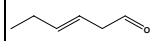
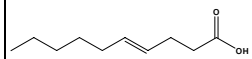
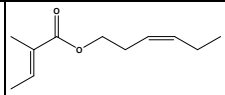
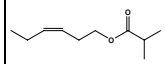
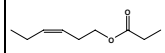
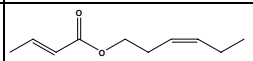
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
05.192 1271	3-Hexenal 6)	 (E)-isomer shown	3923 4440-65-7	Liquid $C_6H_{10}O$ 98.14	Insoluble Soluble	19-20 (26 hPa) IR NMR 80 %	1.425-1.435 0.970-0.980	CASrn does not specify stereoisomers. According to JECFA: Min. assay value is "80 (total of cis & trans isomers)" and secondary compounds "trans-2-hexenal".
08.075 1287	Dec-4-enoic acid 6)	 (E)-isomer shown	3914 10089 26303-90-2	Liquid $C_{10}H_{18}O_2$ 170.25	Insoluble Soluble	97-98 (0.4 hPa) IR NMR MS 97 %	0.915-0.925 1.140-1.160 (20°)	CASrn does not specify stereoisomers.
09.559 1277	Hex-3(cis)-enyl 2-methylcrotonate		3931 67883-79-8	Liquid $C_{11}H_{18}O_2$ 182.26	Insoluble Soluble	105 (7 hPa) IR MS 98 %	1.458-1.462 0.915-0.921	
09.563 1275	Hex-3(cis)-enyl isobutyrate		3929 11783 41519-23-7	Liquid $C_{10}H_{18}O_2$ 170.25	Insoluble Soluble	181-182 IR MS 98 %	1.424-1.432 0.882-0.885	
09.564 1274	Hex-3(cis)-enyl propionate		3933 10683 33467-74-2	Liquid $C_9H_{16}O_2$ 156.23	Insoluble Soluble	83 (22 hPa) IR NMR 97 %	1.428-1.431 0.888-0.892	
09.566 1276	Hex-3-enyl but-2-enoate 6)	 (Z)-isomer in alcohol moiety and (E)-isomer in carboxylic acid moiety shown	3982 65405-80-3	Liquid $C_{10}H_{16}O_2$ 168.23	Insoluble Soluble	218-219(954hPa) IR NMR MS 97 %	1.427-1.437 0.894-0.904	CASrn in Register refers to (Z)-isomer in alcohol moiety & (E)-isomer in acid moiety.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 2003b)

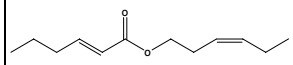
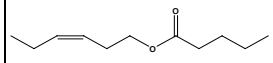
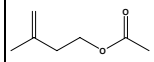
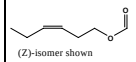
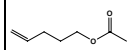
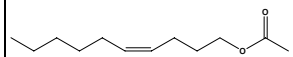
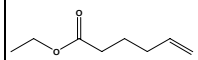
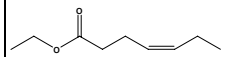
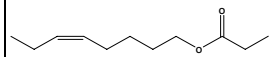
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.568 1279	Hex-3-enyl hex-2-enoate 6)	 (Z)-isomer in alcohol moiety and (E)-isomer in carboxylic acid moiety shown	3928 53398-87-1	Liquid $C_{12}H_{20}O_2$ 196.29	Insoluble Soluble	114-115 (20hPa) IR NMR MS 86 %	1.453-1.461 0.897-0.905	CASrn in Register refers to (Z)-isomer in alcohol moiety & (E)-isomer in acid moiety. According to JECFA: Min. assay value is "86%" and secondary components "3-hexenyl 3-hexenoate, hexenyl hexanoate".
09.571 1278	Hex-3-enyl valerate 6)	 (Z)-isomer shown	3936 10686 35852-46-1	Liquid $C_{11}H_{20}O_2$ 184.28	Insoluble Soluble	108 (26 hPa) IR NMR 97 %	1.432-1.438 0.879-0.885	CASrn in Register refers to (Z)-isomer.
09.655 1269	3-Methylbut-3-enyl acetate		3991 5205-07-2	Liquid $C_7H_{12}O_2$ 128.17	Insoluble Soluble	151-152 IR NMR MS 98 %	1.418-1.426 0.904-0.914	
09.846 1272	3-Hexenyl formate 6)	 (Z)-isomer shown	3353 2153 2315-09-5	Liquid $C_7H_{12}O_2$ 128.17	Insoluble Soluble	155-156 NMR 98 %	1.421-1.431 0.907-0.914	CASrn does not specify stereoisomers. According to JECFA: Min. assay value is "98% (total cis and trans isomers)".
09.917 1270	4-Pentenyl acetate		4011 1576-85-8	Liquid $C_7H_{12}O_2$ 128.17	Insoluble Soluble	144-146 IR NMR MS 98 %	1.415-1.421 0.906-0.916	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of 19 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (JECFA, 2003b)

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
09.918 1288	cis-4-Decenyl acetate		3967 67452-27-1	Liquid $C_{12}H_{22}O_2$ 198.3	Insoluble Soluble	60 (0.07 hPa) IR NMR MS 98 %	1.438-1.440 0.878-0.888	
09.921 1273	Ethyl 5-hexenoate		3976 54653-25-7	Liquid $C_8H_{14}O_2$ 142.2	Insoluble Soluble	181-182 IR NMR MS 95 %	1.430-1.439 0.902-0.912	
09.922 1281	Ethyl cis-4-heptenoate		3975 39924-27-1	Liquid $C_9H_{16}O_2$ 156.23	Insoluble Soluble	52 (4 hPa) IR NMR MS 98 %	1.428-1.431 0.887-0.897	According to JECFA: Min. assay value is "98% (total isomers)".
09.932 1282	(5Z)-Octenylpropionate		3890 196109-18-9	Liquid $C_{11}H_{20}O_2$ 184.28	Insoluble Soluble	68-70 (1 hPa) IR NMR MS 93 %	1.431-1.440 0.880-0.889	According to JECFA: Min. assay value is "93%" and secondary components "(E)-5-octenyl propionate, (Z)-5-octenol".

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.

Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (*in vitro / in vivo*) for 19 Linear and Branched-Chain Aliphatic Unsaturated, Unconjugated Alcohols, Aldehydes, Acids, and Related Esters

No monograph has been prepared for this group of JECFA evaluated substances as they were considered in an addendum to 42 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated at the 51st meeting (1998). The genotoxicity data shown in the table below are for these 42 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA at the 51st meeting (JECFA, 1999a).

Table 2.1: Summary of genotoxicity data of 42 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluted by JECFA at the 51st meeting.

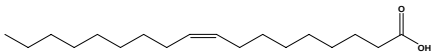
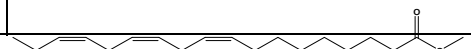
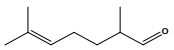
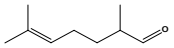
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Maximum Concentration	Results	Reference
In vitro							
08.013 333	Oleic acid		Reverse mutation	*S. typhimurium* TA1535, TA1537, TA98, TA100, TA1538	5000 mg/plate	Negative[1,2]	(Shimizu et al., 1985)
			Reverse mutation	*S. typhimurium* TA1535, TA1537, TA98, TA100	333 mg/plate	Negative[1,2]	(Mortelmans et al., 1986)
			Reverse mutation	*E. coli*	5000 mg/plate	Negative[1,2]	(Shimizu et al., 1985)
			Rec assay	*B. subtilis*	1 mg/plate	Negative[1]	(Osawa & Namiki, 1982)
09.646 346	Methyl linolenate		*His*$^{+}$	*S. typhimurium* TA97, TA102, TA98, TA100, TA1537	1 mg/plate	Negative[1]	(MacGregor et al., 1985)

Table 2.1: Summary of genotoxicity data of 42 linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluted by JECFA at the 51st meeting.

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Maximum Concentration	Results	Reference
			His^{+}	*S. typhimurium* TA97, TA102, TA98, TA100, TA1537	1 mg/plate	Negative[1]	(MacGregor et al., 1985)
05.074 349	2,6-Dimethylhept-5-enal		Reverse mutation	*S. typhimurium* TA1535, TA100, TA1537, TA1538, TA98	3.6 mg/plate	Negative[1]	(Wild et al., 1983)
			Reverse mutation	*S. typhimurium* TA1535, TA100, TA1537, TA1538, TA98	50 mg/plate	Negative[1]	(Heck et al., 1989)
			Unscheduled DNA synthesis	Rat hepatocytes	1 mg/ml	Negative[1]	(Heck et al., 1989)
In vivo							
05.074 349	2,6-Dimethylhept-5-enal		Micronucleus formation	Mouse	1540 mg/ kg bw	Negative	(Wild et al., 1983)
			Basc test	*Drosophila melanogaster*	25 mmol/l	Negative	(Wild et al., 1983)

1 With and without metabolic activation.

2 Modified Ames assay, with preincubation.

Table 2.2: Genotoxicity (*in vitro*) EFSA / FGE.05

Substances in brackets are JECFA evaluated substances in FGE.05

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
(Oleic acid [08.013])	Ames	S. typh. TA1535, TA1537, TA98, TA100, TA1538. E. coli	5000 µg/plate	Neg.[1]	(Shimizu et al., 1985)	Modified Ames, reincubation.
	Ames	S. typh. TA1535, TA98, TA100, TA1537	333 µg/plate	Neg.[1]	(Mortelmans et al., 1986)	Modified Ames, reincubation.
	Rec assay	B. subtilis	1.0 mg/plate	Neg.[1]	(Osawa & Namiki, 1982)	
	SCE	CH V79	2.5 - 10 µg/ml	Neg.	(Kinsella, 1982)	
	Chromosome aberrations	CH V79	2.5 - 10 µg/ml	Pos.	(Kinsella, 1982)	Only numerical abnormalities. No data on cytotoxicity reported.
	6-TG resistance	CH V79	1.0 µg/ml	Neg.	(Kinsella, 1982)	
Methyl oleate [09.652]	Ames	S. typh. TA97, TA98, TA100, TA1535, TA1537	0.100, 0.333, 3.333 and 10 mg/plate	Neg.[1]	(Mortelmans et al., 1986)	
(Methyl linoleate [09.646] & Methyl linolenate (mixture)	Ames (His reversion)	S. typh. TA100, TA98, TA102, TA97, TA1537	1.0 mg/plate	Neg.[1]	(MacGregor et al., 1985)	Tests were conducted with methyl linoleate and methyl linolenate separately, with the same result.
(2,6-Dimethyl-5-heptenal [05.074])	Ames	S. typh. TA1535, TA100, TA1537, TA1538, TA98	3.6 mg/plate	Neg.[1]	(Wild et al., 1983)	
	Ames	S. typh. TA1535, TA100, TA1537, TA1538, TA98	50 mg/plate	Neg.[1]	(Heck et al., 1989)	
(2,6-Dimethyl-5-heptenal [05.074])	UDS	Rat hepatocytes	1.0 mg/ml	Neg.[1]	(Heck et al., 1989)	
Methyl methacrylate [09.647]]	Ames	S. typh. TA98, TA100, TA1535, TA1537	As part of a bonecement extract	Neg.[1]	(Jensen et al., 1991)	
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	150 - 4700 µg/plate	Neg.[1]	(Hachitani et al., 1982)	Text is in Japanese. From the tables reported the result seems to be valid.
	Ames	S. typh. TA98, TA100, TA1535, TA1538	100, 1000 and 9000 ppm (tested as a gas)	Neg.[1]	(Anderson et al., 1979; Rohm & Haas Co., 1976a)	
	Ames	S. typh. TA97, TA98, TA100, TA1535, TA1537	10-10000 µg/plate	Neg.[1]	(Zeiger, 1990)	
	Ames	S. typh. TA98, TA100, TA1535, TA1538	4-2500 µg/plate	Neg.[1]	(ICI, 1976b)	
	Ames	S. typh. TA1535, TA1537, TA1538	10 mg/plate	Neg.[1]	(DuPont, 1975)	
	Ames	S. typh. TA98, TA100, TA1535, TA1537	1000, 2500, 5000, 7500 and 10000 µg/plate	Neg [1]	(DuPont, 1979b)	
	Ames	S. typh. TA100	10, 25 and 50 mM (liquid suspension assay)	Weak pos.[1]	(DuPont, 1979b)	Cytotoxicity at all dose levels ranging from 21 - 58% survival at low-dose level and 18 - 36% survival at high-dose level

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1000 µg/plate	Neg [1]	(Lijinsky & Andrews, 1980)	
	Ames	S. typh. TA97, TA98, TA100, TA1535	33 – 10000 µg/plate	Neg [1]	(NTP, 1986b)	
	Ames	S. typh. TA98, TA1535, TA1537, TA1538	40 - 10000 µg/plate	Neg [1]	(Waegemaekers & Bensink, 1984)	
	Ames	S. typh. TA100	100 - 10000 µg/2 ml	Neg [1]	(Waegemaekers & Bensink, 1984)	
	Ames	S. typh. TA97a, TA98, TA100, TA102, TA104	0.005 – 25 mg/plate (tested eluates in DMSO and saline; 100 µl of eluate is expressed as 5 mg/plate)	Neg.	(Schweikl et al., 1994)	
	Ames	S. typh. TA98, TA100, TA1537	0.08 - 2.5%	Neg.[1]	(DuPont, 1979a)	
	Ames	S. typh. TA1535	0.08 - 2.5%	Neg.[2] Weak pos.[3]	(DuPont, 1979a)	Weak pos.: The dose levels selected for the test were nontoxic or only slightly toxic.
	Ames	S. typh. TA100	25 mM (suspension assay)	Neg. [2] Weak pos.[3]	(DuPont, 1979a)	Survival at 25 mM was 28 - 29%.
	Forward mutation	S. typh. TM677	10 - 100 mM	Weak pos. [2] Neg. [3]	(Poss et al., 1979)	Relative survival was 0.50 at 10 mM and 0.10 at 100 mM.
	Forward Mutation	S. typh. TM677	25 – 50 mM	Weak pos. [2]	(Haskell Laboratory, 1989)	Slight increase in mutagenicity, but percent survival was only 20 - 22% at low-dose level and 12 - 17% at high-dose level.
	Chromosome aberrations	CHO	5000 µg/ml (50 mM)	Weak pos. [2]	(Anderson et al., 1990; NTP, 1986b)	Increase in percentage of aberrant cells was only at concentrations above 10mM; no cytotoxicity data reported.
	Chromosome aberrations	CHO	1600 µg/ml (16 mM)	Pos.	(Anderson et al., 1990; NTP, 1986b)	Increase in percentage of aberrant cells was only at concentrations above 10mM; no cytotoxicity data reported.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
	Chromosome aberrations	L5178Y TK+/- cells	2200 – 3000 µg/ml	Weak pos. [3]	(Doerr et al., 1989)	Survival was 26% at 2200 microgram/ml and 12% at 3000 microgram/ml.
	Mouse lymphoma	L5178Y TK+/- cells	500 µg/ml (5 mM)	Pos. [2]	(Amtower et al., 1986)	No data on cytotoxicity available.
	Mouse lymphoma	L5178Y TK+/- cells	1000 - 3000 µg/ml (10 – 30 mM)	Pos. [3]	(Moore et al., 1988)	Mutagenic responses and increases of small colonies were small, not clearly dose-related and observed only at concentrations above 10 mM. Dose-dependent effects on survival, with 60% survival at 1000 microgram/ml; approximately 15% survival at 3000 microgram/ml.
	Mouse lymphoma	L5178Y TK+/- cells	2200 – 3000 µg/ml (22 – 30 mM)	Pos. [3]	(Doerr et al., 1989)	Increases of mutation frequencies were small and occurred only at concentrations above 10 mM. There was a higher than normal level of small colonies in the control cultures. Dose-dependent effects on survival, with 53 % survival at 1000 microgram/ml and 12 % at 3000 microgram/ml.
	Mouse lymphoma	L5178Y TK+/- cells	500 – 1000 µg/ml (5 – 10 mM)	Pos. [2]	(Dearfield et al., 1991)	Percent survival was approximately 80% at 500 microgram/ml and approximately 40% at 1000 microgram/ml.
	Mouse lymphoma	L5178Y TK+/- cells	1500 – 3000 µg/ml (15 – 30 mM)	Pos. [3]	(Dearfield et al., 1991)	Percent survival was approximately 50% at 1500 microgram/ml and approximately 15% at 3000 microgram/ml.

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
	Mouse lymphoma	L5178Y TK+/- cells	300 nl/ml (cytotoxic concentration) 100 nl/ml	Pos. [2] Neg. [3]	(Rohm & Haas Co., 1985)	
	Mouse lymphoma	L5178Y TK+/- cells	0.125 µl/ml - 1 µl/ml	Pos. [2] Ambiguous[3]	(NTP, 1986b)	Ambiguous: Small but dose-related increases in mutant frequencies and numbers, but dose-related cytotoxicity was observed.
	Mouse lymphoma	L5178Y TK+/- cells	≥ 200 nl/ml 500 – 1500 nl/ml	Pos.[1]	(Myhr et al., 1990)	Treatments of 1500 nl/ml (without activation) and 2000 nl/ml (with activation) considered extremely toxic and/or lethal. No other cytotoxicity data available.
	SCE	Human lymphocytes	0.1 µg/ml	Neg. [3]	(Cannas et al., 1987; Bigatti et al., 1989)	
	SCE	CHO	16 – 5000 µg/ml	Ambiguous[1]	(Anderson et al., 1990)	Small increases in SCE frequency were reported.
	HRPT	CH V79 B cells	10 - 20 µg/ml	Very weak pos. [3]	(Schweikl et al., 1998)	Survival was 71 and 49% at 10 and 20 microgram/ml, respectively.
	Cell transformation	BHK21/C13 cells	0.01 - 0.000001 M	Neg.	(Anderson et al., 1979)	
	Micronucleus	Bi-nucleated L5178Y cells	2200 – 3000 µg/ml (22 - 30 mM)	Ambiguous	(Doerr et al., 1989)	Small but dose-related increases in mutant frequencies and numbers, but dose-related cytotoxicity was observed Increases in frequencies of micro-nucleated cells were small and not clearly dose-related. No cytotoxicity data reported.
Ethyl methacrylate [09.375]	Ames	S. typh. TA98, TA100, TA1535, TA1537	33-10000 µg/plate	Neg.[1]	(Zeiger et al., 1987)	
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	40 – 2500 µg/plate	Neg.[1]	(Waegemaekers & Bensink, 1984)	

Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.05)

Chemical Name [Fl.No.]	Test System	Test Object	Concentration	Result	Reference	Comments
	Mouse lymphoma	L5178Y TK+/- cells	>1400 µg/ml	Weak Pos. [3]	(Moore et al., 1988)	Negative at 1400 microgram/ml and below; survival at 1400 microgram/ml and above ranged from 2 to 33%, with cytotoxicity appearing to reach a plateau at concentrations above 1500 microgram/ml.
	SCE	CHO	NR	Pos.	(NTP, 1987b)	Abstract in table format only, study report not available for re-evaluation.
Isobutyl 2-methylprop-2-enoate [09.586]	Ames	S. typh. TA98, TA100, TA1535, TA1537	100, 333, 1000 and 10000 µg/plate	Neg.[1]	(Zeiger et al., 1987)	

1 With and without metabolic activation.

2 With metabolic activation.

3 Without metabolic activation.

Table 2.3: Genotoxicity (in vitro) EFSA /FGE.06

Substances in brackets are JECFA evaluated substances in FGE.06

Table 2.3: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.06)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
(9-Decenal[1] [05.139])	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537, TA1538	0.001-1 nl/plate (0.001-1 µg/plate)	Negative[2]	(Richold & Jones, 1980)	In the absence of metabolic activation, the highest concentrations were cytotoxic. The study is considered valid.
(Oleic acid [08.013])	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537, TA1538, *E. coli WP2uvrA*	1 - 5000 µg/plate	Negative[2]	(Shimizu et al., 1985)	Modified Ames, preincubation assay. The study is considered valid.

Table 2.3: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.06)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537	1 - 0, 333 µg/plate	Negative[2]	(Mortelmans et al., 1986)	Modified Ames, preincubation assay. Concentrations were selected based on a preliminary experiment. The study is considered valid.
	Rec assay	*B. subtilis*	100 - 1000 µg/plate	Negative[2]	(Osawa & Namiki, 1982)	The validity of this study is unclear.
	SCE test	CH V79	2.5 - 10 µg/ml	Negative	(Kinsella, 1982)	Not cytotoxic. The assay was only performed without metabolic activation. Doses were selected based on a preliminary assay. The study is considered valid.
	Chrom. abs.	CH V79	2.5 - 10 µg/ml	Positive	(Kinsella, 1982)	There was an increase in numerical abnormalities, but not in breaks, not concentration dependent. No cytotoxicity was observed. The assay was only performed without metabolic activation. Doses were selected based on preliminary assay. The study is considered valid.
	6-TG resistance	CH V79	1.0 µg/ml	Negative	(Kinsella, 1982)	Not cytotoxic. Only one concentration level. The assay was only performed without metabolic activation. The validity of the study cannot be evaluated.
(Methyl linoleate & Methyl linolenate (mixture) [09.646])	Ames (His^+ reversion) assay	*S. typh.* TA100, TA98, TA102, TA97, TA1537	125 - 1000 µg/plate	Negative[2]	(MacGregor et al., 1985)	Tests were conducted with methyl linoleate and methyl linolenate separately. Both were negative. Doses were selected based on prelimary assay. The study is considered valid.
Methyl-3-but-3-en-1-ol [02.176]	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537	20 - 5000 µg/plate	Negative[2, 5]	(BASF, 1989c)	The complete report for this study was not provided. The validity of this study cannot be evaluated.
(2,6-Dimethyl-5-heptenal [05.074])	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537, TA1538	Up to 3600 µg/plate	Negative[2]	(Wild et al., 1983)	Five concentrations tested. The study is considered valid.

Table 2.3: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.06)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537, TA1538	Up to 50000 µg/plate	Negative[2]	(Heck et al., 1989)	No information concerning a possible cytotoxic effect nor on the number of concentrations tested. The test guidelines do not require more than 5 mg/plate. The validity of the study cannot be evaluated.
	UDS test	Rat hepatocytes	Up to 1000 µg/ml	Negative[2]	(Heck et al., 1989)	No information concerning the number of concentrations tested. The validity of the study cannot be evaluated.
(Geranyl formate [09.076])	Rec assay	*B. subtilis*	18 µg/disk	Negative	(Oda et al., 1979)	From english abstract. Only one dose level is mentioned in a table. The validity of the study is unclear.
(Geranyl acetate [09.011])	Ames assay	*S. typh.*, TA98, TA100, TA1535	Up to 2000 µg/plate	Negative	(Heck et al., 1989)	No information concerning a possible cytotoxic effect nor on the number of concentrations tested. The validity of the study cannot be evaluated.
	Ames assay	*S. typh.*, TA98, TA100, TA1535, TA1537	1 - 3333 µg/plate	Negative	(Mortelmans et al., 1986)	Modified Ames, preincubation assay. Doses were selected based on preliminary assay. The study is considered valid.
	Rec assay	*B. subtilis*	17 µg/disk	Negative	(Oda et al., 1979)	From english abstract. Only one dose level is mentioned in a table. The validity of this study is unclear.
	Rec assay	*B. subtilis*	Up to 20 µl/disk	Negative	(Yoo, 1986)	From english abstract. No information concerning the number of doses tested. The validity of this study cannot be evaluated.
	Gene mutation	Mouse; L5178Y TK+/-	Up to 100 µg/ml Up to 78 µg/ml	Negative[3]; Positive[4] (weak)	(Heck et al., 1989)	The validity of this study cannot be evaluated.

Table 2.3: Summary of Genotoxicity Data (*in vitro*) EFSA (FGE.06)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
	Gene mutation	Mouse; L5178Y TK+/-	18.3 µg/ml	Negative[3]; Positive[4]	(Tennant et al., 1987)	Detailed information on this study was not provided. The article includes a table presenting the results of different genotoxicity and carcinogenicity tests performed with several compounds.
	SCE test	CHO cells	45 - 80 µg/ml; 50 - 299 µg/ml	Positive (weak)[3]; Positive (weak) or negative [4]	(Galloway et al., 1987)	Weakly positive results, without metabolic activation, were observed at cytotoxic concentrations. Doses were selected based on preliminary assay. The study is considered valid.
	Chromosomal aberrations	CHO cells	60 - 100 µg/ml; 50 - 150 µg/ml	Negative[3];	(Galloway et al., 1987)	Doses were selected based on preliminary assay. The study is considered valid.
	UDS test	Hepatocytes of F344 male rats	NR	Negative	(Mirsalis et al., 1983)	Only an abstract is available. The validity of this study cannot be evaluated.
	Inhibition of DNA synthesis	CHO cells	113 µmole	Negative	(Meigs et al., 1995)	Only one concentration level is mentioned. The validity of this study is unclear.
	UDS test	Hepatocytes of F344 male rats	Up to 100 nl/ml	Negative	(Heck et al., 1989)	No information concerning the number of concentrations tested. The validity of this study cannot be evaluated.
	Gene mutation	Human lymphoblast TK6	Up to 320 µg/ml; Up to 500 µg/ml	Negative[3];	(Caspary et al., 1988)	Compound precipitation was the limiting factor for the maximum concentration. The study is considered valid.

NR = Not Reported.

[1] A substance evaluated at the 61st JECFA meeting structurally related to candidate substances in FGE.06.

[2]With and without metabolic activation.

[3]Without rat liver S-9 activation.

[4]With rat liver S-9 activation.

[5] *Methyl-3-but-3-en-1-ol [FL-no: 02.176] (purity not reported) was tested in a bacterial reversion assay (Ames test) with Salmonella typhimurium strain TA1535, TA100, TA1537 and TA98 with and without exogenous metabolic activation (origin not reported), following the standard plate test and pre-incubation test. It is not reported whether a dose range-finding experiment was performed. The main experiments were conducted at a not reported number of doses from 20 to 5000 microgram/plate. It is not reported whether the doses were tested in duplicate or triplicate. It is not reported the identity of the solvent.*

Result: negative. Eventual bacteriotoxicity or precipitation is not reported.

Remarks: the available report mentions that the study was performed in accordance with the OECD Guideline 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay". The available report does not contain sufficient details nor is it published in a peer-reviewed journal. The validity of this study cannot be evaluated.

Table 2.4: Genotoxicity (*in vivo*) EFSA / FGE.05

Substances in brackets are JECFA evaluated substances in FGE.05

Table 2.4: Summary of Genotoxicity Data (*in vivo*) EFSA (FGE.05)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Reference	Comments
(2,6-Dimethyl-5-heptenal [05.074])	Micronucleus	Mouse (bone marrow)	I.p.	Single dose of 0, 420, 980, and 1540 mg/kg	Neg.	(Wild et al., 1983)	Limited quality since only a single sampling time (30 h after treatment) was used and PCE/NCE ratio was not reported. Therefore it is not clear whether the substance had reached the bone marrow.
	Basc test (Sex-linked recessive lethal mutation)	Drosophila melanogaster	Diet	25 mM	Neg.	(Wild et al., 1983)	A single dose was tested in two experiments. Method not described in detail.

Table 2.4: Summary of Genotoxicity Data (*in vivo*) EFSA (FGE.05)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Reference	Comments
Methyl methacrylate [09.647]	Micronucleus	Mouse (bone marrow)	Gavage	Single dose of 1130 to 4520 mg/kg or 4 doses of 1130 mg/kg	Neg.	(Hachitani et al., 1982)	The study cannot be evaluated as text is in Japanese. Thus, e.g. it is not clear if samples were taken at different sampling times after single treatment and if sampling time was adequate after multiple treatment. Frequency of reticulocytes only slightly changed compared to control. Therefore it is not clear whether the substance had reached the bone marrow.
	Micronucleus	Mouse (bone marrow)	I.p.	Single dose of methacrylate bone cement mixture	Neg.	(Jensen et al., 1991)	Not relevant since an extract of a mixture (containing some additives used as accelerator, stabilizer, colourings etc.) was tested.
	Sex-linked recessive lethal mutation	Drosophila melanogaster	Inh.	1400 ppm	Neg.	(Foureman et al., 1994)	Sufficient experimental details reported. Result is considered as valid.
	Sex-linked recessive lethal mutation	Drosophila melanogaster	Inj.	14000 ppm	Neg.	(Foureman et al., 1994)	Sufficient experimental details reported. Result is considered as valid.
	Dominant lethal	Mouse	Inh., 6h/day for 5 days	100, 1000, and 9000 ppm	Neg.	(ICI, 1976c)	Unpublished non-GLP study. Report contains sufficient details. Result is considered as valid.

Table 2.4: Summary of Genotoxicity Data (*in vivo*) EFSA (FGE.05)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Reference	Comments
	SCE	Human (38 male workers)	Inh.; 8 hrs/day	0.9 - 71.9 ppm	Neg.	(Seiji et al., 1994)	Exposure period was not reported. 11 unexposed subjects were used as controls. A marginal increase was found (6.11 vs. 4.91 SCEs/cell), hoever, this effect was considered to be age-related (and not dependent on MMA exposure). Result is considered as valid.
	Chromosome aberrations	Human (38 male workers)	Inh.; 8 hrs/day	0.9 - 71.9 ppm	Neg.	(Seiji et al., 1994)	Exposure period was not reported. 11 unexposed subjects were used as controls. Result is considered as valid.
	Chromosome aberrations	Rat (bone marrow)	Inh., single 2h exposure or 5h/day for 5 days	100 - 9000 ppm	Weak pos.	(Rohm & Haas Co., 1976b; Rohm & Haas Co., 1979)	"Both studies suffer from inadequate description; esp. the second study demonstrates severe methodological problems, e.g., analysis of 50 metaphases was not possible for 10 out of 27 animals in the acute and 10 out 26 in the subacute test. Altogether, a clear conclusion cannot be drawn from these studies." (CEC 2002)
Isobutyl 2-methyl-prop-2-enoate [09.586]	Micronucleus	Mouse	Gavage	5000 mg/kg	Neg.	(Roehm GmbH., 1989)	Reported to be in accordance with OECD 474, however, the study cannot be re-evaluated as only a summary of the EU-IUCLID database is available. According to this summary, a decrease of

Table 2.4: Summary of Genotoxicity Data (*in vivo*) EFSA (FGE.05)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Reference	Comments
							PCE/NCE ratio was observed. This indicates that the substance had reached the target cells.

Table 2.5: Genotoxicity (*in vivo*) EFSA / FGE.06

Substances in brackets are JECFA evaluated substances in FGE.06

Table 2.5: Summary of Genotoxicity Data (*in vivo*) EFSA (FGE.06)

Chemical Name [FL-no]	Test system	Test Object	Route	Dose	Result	Reference	Comments
(2,6-Dimethyl-5-heptenal [05.074])	Mouse micronucleus assay	NMRI male and female mouse bone marrow	NR	420 - 1540 mg/kg	Negative	(Wild et al., 1983)	Mice received a single dose. Dose levels were not justified. The validity of this study cannot be evaluated.
	Basc test	*D. melanogaster*	NR	25 mM	Negative	(Wild et al., 1983)	Only one dose is mentioned. The validity of this study is unclear.
(Geranyl acetate [09.011])	Mouse micronucleus assay	B6C3F1 mouse bone marrow cells	i.p.	450 - 1800 mg/kg bw/day	Negative	(Shelby et al., 1993)	Selection of maximum dose was justified. The study is considered valid.
	Unscheduled DNA synthesis	F344 male rats hepatocytes	Oral gavage	NR	Negative	(Mirsalis et al., 1983)	Only an abstract is available. The validity of this study cannot be evaluated.

NR = Not Reported.

NA = Not Applicable.

TABLE 3: SUMMARY OF SAFETY EVALUATION TABLES

Table 3.1: Summary of Safety Evaluation of 19 Linear and Branched-chain Aliphatic Unsaturated, Unconjugated Alcohols, Aldehydes, Acids, and Related Esters (JECFA, 2003b)

Table 3.1: Summary of Safety Evaluation of 19 JECFA-Evaluated Substances (JECFA, 2003b)

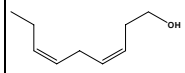
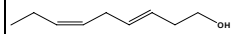
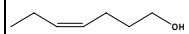
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.189 1283	Nona-3,6-dien-1-ol	 (Z,Z)-isomer shown	ND 0.9	Class I A3: Intake below threshold	4)	MSDI based on USA production figure	CASrn does not specify stereoisomers. JECFA: Min. assay value is "97 % & 1% E,Z isomer; 1% Z,E isomer; 0.5% E,E isomer". Name to be changed to: (Z,Z)-Nona-3,6-dien-1-ol. Stereoisomeric composition to be specified. MSDI based on USA production figure.
02.243 1284	(E,Z)-3,6-Nonadien-1-ol		ND 0.9	Class I A3: Intake below threshold	4)	MSDI based on USA production figure	JECFA: Min. assay value is "92%" and secondary components "(E,E)-3,6-nonadien-1-ol". MSDI based on USA production figure.
02.249 1280	(4Z)-Hepten-1-ol		1.2 2	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of 19 JECFA-Evaluated Substances (JECFA, 2003b)

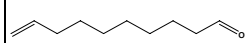
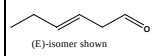
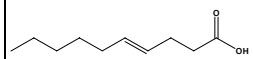
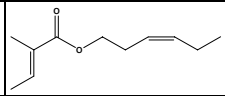
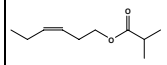
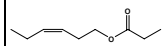
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (μg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
05.139 1286	Dec-9-enal		0.6 18	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
05.192 1271	3-Hexenal	 (E)-isomer shown	24.7 53	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn does not specify stereoisomers. JECFA: Min. assay value is "80 (total of cis & trans isomers)" and secondary compounds "trans-2-hexenal". Stereoisomeric composition and composition of mixture to be specified.
08.075 1287	Dec-4-enoic acid	 (E)-isomer shown	1.7 0.4	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn does not specify stereoisomers. Stereoisomeric composition to be specified.
09.559 1277	Hex-3(cis)-enyl 2-methylcrotonate		0.024 70	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.563 1275	Hex-3(cis)-enyl isobutyrate		12 18	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.564 1274	Hex-3(cis)-enyl propionate		12 18	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of 19 JECFA-Evaluated Substances (JECFA, 2003b)

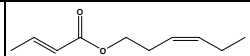
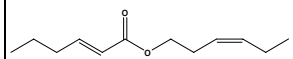
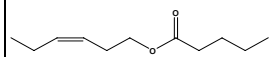
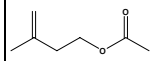
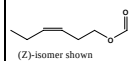
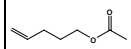
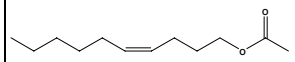
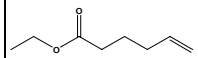
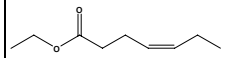
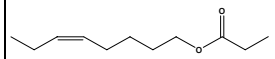
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (μg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [(4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.566 1276	Hex-3-enyl but-2-enoate	 (Z)-isomer in alcohol moiety and (E)-isomer in carboxylic acid moiety shown	0.24 0.2	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn refers to (Z)-isomer in alcohol moiety & (E)-isomer in acid moiety. Stereoisomeric composition to be specified.
09.568 1279	Hex-3-enyl hex-2-enoate	 (Z)-isomer in alcohol moiety and (E)-isomer in carboxylic acid moiety shown	0.12 0.1	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn refers to (Z)-isomer in alcohol moiety & (E)-isomer in acid. JECFA: Min. assay value is "86%" & secondary components "3-hexenyl 3-hexenoate, hexenyl hexanoate". Stereoisomeric composition and composition of mixture to be specified.
09.571 1278	Hex-3-enyl valerate	 (Z)-isomer shown	6.1 9	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn refers to (Z)-isomer. Stereoisomeric composition to be specified.
09.655 1269	3-Methylbut-3-enyl acetate		7.3 11	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.846 1272	3-Hexenyl formate	 (Z)-isomer shown	12 18	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	CASrn does not specify stereoisomer. JECFA: Min. assay value is "98% (total cis and trans isomers)". Stereoisomeric composition to be specified.

Table 3.1: Summary of Safety Evaluation of 19 JECFA-Evaluated Substances (JECFA, 2003b)

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
09.917 1270	4-Pentenyl acetate		3.4 4	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.918 1288	cis-4-Decenyl acetate		1.7 2	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.921 1273	Ethyl 5-hexenoate		3.4 4	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach.
09.922 1281	Ethyl cis-4-heptenoate		3.4 4	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	JECFA: Min. assay value is "98%(total isomers)". Composition of mixture to be specified.
09.932 1282	(5Z)-Octenylpropionate		0.12 4	Class I A3: Intake below threshold	4)	No safety concern at estimated levels of intake as flavouring substances based on the MSDI approach	JECFA: Min. assay value is "93%" and secondary components "(E)-5-octenyl propionate, (Z)-5-octenol".

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

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

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

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

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

ND: not determined

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.05)

Table 3.2: Summary of Safety Evaluation Applying the Procedure (FGE.05) (based on intakes calculated by the MSDI approach)

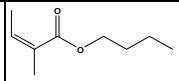
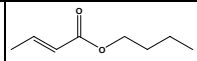
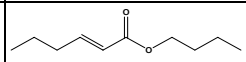
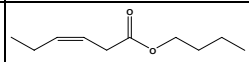
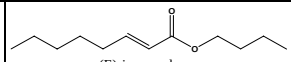
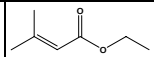
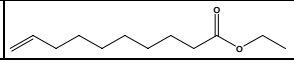
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.321	Butyl 2-methylbut-2(cis)-enoate		1.2	Class I A3: Intake below threshold	4)	6)	
09.324	Butyl but-2-enoate	 (E)-isomer shown	1.7	Class I A3: Intake below threshold	4)	7)	
09.329	Butyl hex-2-enoate	 (E)-isomer shown	1.0	Class I A3: Intake below threshold	4)	7)	
09.330	Butyl hex-3-enoate	 (Z)-isomer shown	0.12	Class I A3: Intake below threshold	4)	7)	
09.335	Butyl oct-2-enoate	 (E)-isomer shown	0.66	Class I A3: Intake below threshold	4)	7)	
09.365	Ethyl 3-methylcrotonate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.370	Ethyl dec-9-enoate		0.012	Class I A3: Intake below threshold	4)	6)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (FGE.05) (based on intakes calculated by the MSDI approach)

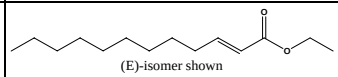
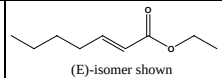
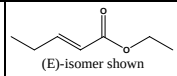
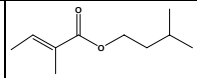
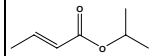
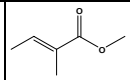
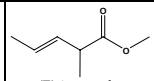
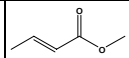
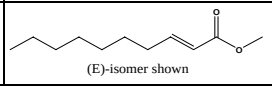
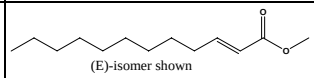
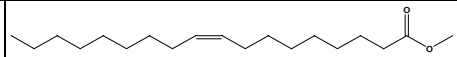
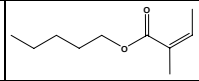
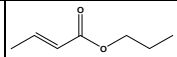
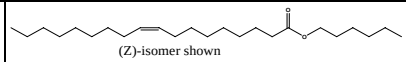
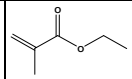
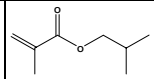
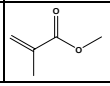
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.372	Ethyl dodec-2-enoate	 (E)-isomer shown	0.34	Class I A3: Intake below threshold	4)	7)	
09.374	Ethyl hept-2-enoate	 (E)-isomer shown	0.61	Class I A3: Intake below threshold	4)	7)	
09.379	Ethyl pent-2-enoate	 (E)-isomer shown	0.037	Class I A3: Intake below threshold	4)	7)	
09.596	Isopentyl 2-methylcrotonate		0.012	Class I A3: Intake below threshold	4)	6)	
09.603	Isopropyl crotonate		0.24	Class I A3: Intake below threshold	4)	6)	
09.624	Methyl 2-methylcrotonate		0.12	Class I A3: Intake below threshold	4)	6)	
09.625	Methyl 2-methylpent-3-enoate	 (E)-isomer shown	0.0012	Class I A3: Intake below threshold	4)	7)	
09.636	Methyl crotonate		0.12	Class I A3: Intake below threshold	4)	6)	
09.637	Methyl dec-2-enoate	 (E)-isomer shown	0.37	Class I A3: Intake below threshold	4)	7)	

Table 3.2: Summary of Safety Evaluation Applying the Procedure (FGE.05) (based on intakes calculated by the MSDI approach)

FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.641	Methyl dodec-2-enoate	 (E)-isomer shown	0.56	Class I A3: Intake below threshold	4)	7)	
09.652	Methyl oleate		1.2	Class I A3: Intake below threshold	4)	6)	
09.680	Pentyl 2-methylisocrotonate		0.74	Class I A3: Intake below threshold	4)	6)	
09.699	Propyl crotonate		0.085	Class I A3: Intake below threshold	4)	6)	
09.865	Hexyl 9-octadecenoate	 (Z)-isomer shown	0.24	Class I A3: Intake below threshold	4)	7)	
09.375	Ethyl methacrylate		0.12	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		a)
09.586	Isobutyl 2-methylprop-2-enoate		0.012	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		a)
09.647	Methyl methacrylate		0.061	Class II B3: Intake below threshold, B4: No adequate NOAEL	Additional data required		a)

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

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

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

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

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

6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).

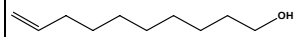
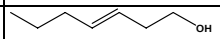
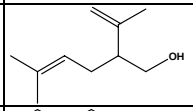
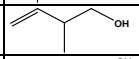
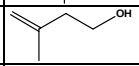
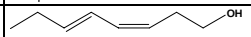
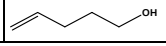
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce.

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

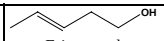
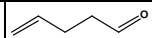
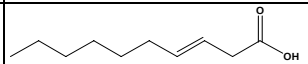
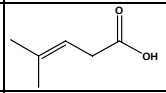
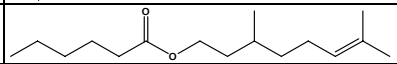
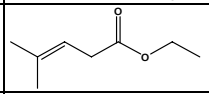
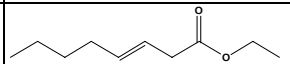
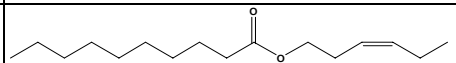
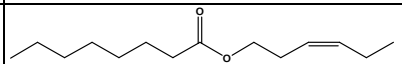
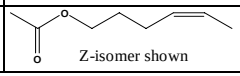
a) See sections 5 and 9.

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.06)

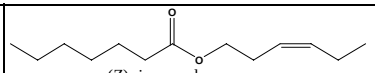
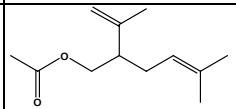
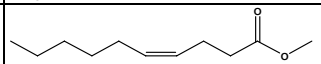
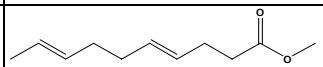
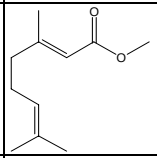
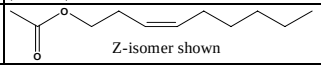
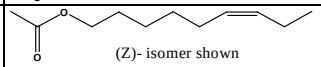
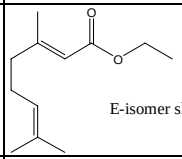
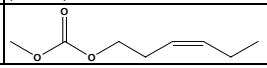
Table 3.3: Summary of Safety Evaluation Applying the Procedure (FGE.06) (based on intakes calculated by the MSDI approach)

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
02.138	Dec-9-en-1-ol		0.15	Class I A3: Intake below threshold	4)	6)	
02.152	Hept-3-en-1-ol	 (E)-isomer shown	0.012	Class I A3: Intake below threshold	4)	7)	
02.170	Lavandulol		0.012	Class I A3: Intake below threshold	4)	7)	
02.175	2-Methylbut-3-en-1-ol		1.4	Class I A3: Intake below threshold	4)	6)	
02.176	3-Methylbut-3-en-1-ol		0.13	Class I A3: Intake below threshold	4)	6)	
02.195	Octa-3,5-dien-1-ol	 (3Z, 5E)- isomer shown	0.061	Class I A3: Intake below threshold	4)	7)	
02.201	Pent-4-en-1-ol		0.012	Class I A3: Intake below threshold	4)	6)	

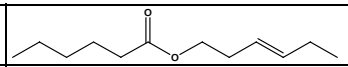
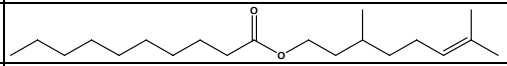
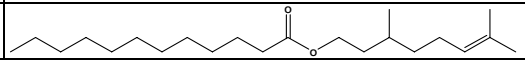
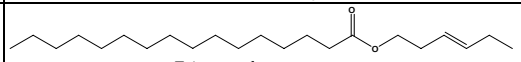
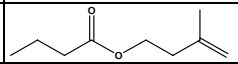
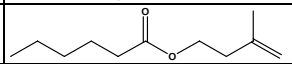
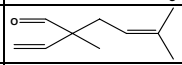
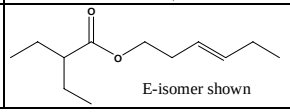
Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

02.222	3-Pentenol-1	 E-isomer shown	0.5	Class I A3: Intake below threshold	4)	7)	
05.061	Oct-6-enal	 (E)- isomer shown	0.0012	Class I A3: Intake below threshold	4)	7)	
05.174	Pent-4-enal		0.11	Class I A3: Intake below threshold	4)	6)	
08.074	Dec-3-enoic acid	 E-isomer shown	0.19	Class I A3: Intake below threshold	4)	7)	
08.100	4-Methylpent-3-enoic acid		1.8	Class I A3: Intake below threshold	4)	6)	
09.341	Citronellyl hexanoate		0.97	Class I A3: Intake below threshold	4)	6)	
09.368	Ethyl 4-methylpent-3-enoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.377	Ethyl oct-3-enoate	 E-isomer shown	0.35	Class I A3: Intake below threshold	4)	7)	
09.567	Hex-3-enyl decanoate	 (Z)- isomer shown	0.0024	Class I A3: Intake below threshold	4)	7)	
09.569	Hex-3-enyl octanoate	 (Z)- isomer shown	0.49	Class I A3: Intake below threshold	4)	7)	
09.572	Hex-4-enyl acetate	 Z-isomer shown	0.0012	Class I A3: Intake below threshold	4)	7)	

Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

09.575	3-Hexenyl heptanoate	 (Z)- isomer shown	0.61	Class I A3: Intake below threshold	4)	7)	
09.612	Lavandulyl acetate		0.012	Class I A3: Intake below threshold	4)	6)	
09.638	Methyl dec-4-enoate	 (Z)- isomer shown	0.0012	Class I A3: Intake below threshold	4)	7)	
09.640	Methyl deca-4,8-dienoate	 (4E, 8E)-isomer shown	0.012	Class I A3: Intake below threshold	4)	7)	
09.643	Methyl geranate		0.95	Class I A3: Intake below threshold	4)	7)	
09.672	Non-3-enyl acetate	 Z-isomer shown	0.012	Class I A3: Intake below threshold	4)	7)	
09.673	Non-6-enyl acetate	 (Z)- isomer shown	0.12	Class I A3: Intake below threshold	4)	7)	
09.831	Ethyl 3,7-dimethyl-2,6-octadienoate	 E-isomer shown	0.61	Class I A3: Intake below threshold	4)	7)	
09.838	3-Hexenyl methyl carbonate		0.012	Class I A3: Intake below threshold	4)	6)	

Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

09.855	trans-3-Hexenyl hexanoate		0.21	Class I A3: Intake below threshold	4)	6)	
09.871	Citronellyl decanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.872	Citronellyl dodecanoate		0.061	Class I A3: Intake below threshold	4)	6)	
09.885	Hex-3-enyl hexadecanoate	 E-isomer shown	0.049	Class I A3: Intake below threshold	4)	7)	
09.897	3-Methylbut-3-en-1-yl butyrate		0.012	Class I A3: Intake below threshold	4)	6)	
09.898	3-Methylbut-3-en-1-yl hexanoate		0.012	Class I A3: Intake below threshold	4)	6)	
05.143	2,5-Dimethyl-2-vinylhex-4-enal		0.12	Class II A3: Intake below threshold	4)	6)	
09.884	Hex-3-enyl-2-ethylbutyrate	 E-isomer shown	0.58	Class II B3: Intake below threshold, B4: Adequate NOEL exists	4)	7)	

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

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

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

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

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

6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).

7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce.

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

REFERENCES:

Abou-Donia, M.B., Abdel-Rahman, A.A., Kishk, A.M., Walker,D., Markwiese, B.J., Acheson, S.K., Reagan, K.E., Swartzwelder, S., Jensen, K. F., 2000. Neurotoxicity of ethyl methacrylate in rats. J. Toxicol. Environ. Health (part A) 59, 97-118.

Amtower, A.L., Brock, K.H., Doerr, C.D., Dearfeld, K.L., Moore, M.M., 1986. Genotoxicity of three acrylate compounds in L5178Y mouse lymphoma cells. Environ. Mutag. 8(suppl. 6), 4.

Anderson, D., Longstaff, E., Ashby, J., 1979. An assessment of the carcinogenic and mutagenic potential of methylmethacrylate. Toxicol. Appl. Pharmacol. 48(1- Part 2), A29.

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L., Loveday, K.S., 1990. Chromosome aberration and sister chromatid exchange test results with 42 chemicals. Environ. Mol. Mutag. 16(Suppl. 18), 55-137.

BASF, 1989c. Abteilung Toxikologie, unveroeffentlichte Untersuchung (88/36). Cited in European Commission - European Chemicals Bureau, 1996. IUCLID Dataset, CAS no. 763-32-6. Section 5.5 Genetic toxicity 'in Vitro'.

Bigatti, M.P., Lamberti, L., Cannas, M., Rossi, E., 1989. Lack of sister-chromatid exchange induction by polymethyl methacrylate bone cement in human lymphocytes cultured in vitro. Mutat. Res. 227, 21-24.

Cannas, M., Bigatti, P., Rossi, E., Rossi, P., 1987. In vitro research on the possibility of chromosomal damage caused by polymethyl methacrylate in orthopaedics. A preliminary report. Ital. J. Orthop. Traumatol. 13(3), 387-391.

Caspary, W.J., Langenbach, R., Penman, B.W., Crespi, C., Myhr, B.C., Mitchell, A.D., 1988. The mutagenic activity of selected compounds at the TK locus rodent vs. human cells. Mutat. Res. 196, 61-81.

CEC, 2002. European Union Risk Assessment Report, methyl methacrylate, vol. 22.

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

de Kok, T.M., ten Vaarwerk, F., Zwingman, I., van Maanen, J.M., Kleinjans, J.C., 1994. Peroxidation of linoleic, arachidonic and oleic acid in relation to the induction of oxidative DNA damage and cytogenetic effects. Carcinogenesis, 15, 1399-1404.

Dearfield, K.L., Harrington-Brock, K., Doerr, C.L., Rabinowitz, J.R., Moore, M.M., 1991. Genotoxicity in mouse lymphoma cells of chemicals capable of Michael addition. Mutagenesis 6(6), 519-525.

Doerr, C., Harrington-Brock, K., Moore, M.M., 1989. Micronucleus, chromosome aberration, and small-colony TK mutant analysis to quantitate chromosomal damage in L5178Y mouse lymphoma cells. Mutat. Res. 222, 191-203.

DuPont, E.I., 1975. In vitro microbiological mutagenicity studies on methyl methacrylate monomer with attachments, cover sheets and letter dated 092484 (sanitized). Barsky, F.C. EPA Doc 86-8900008145, microfiche no. OTS0520931. May 3, 1975. Unpublished report submitted by EFFA to SCF.

DuPont, E.I., 1979a. Mutagenicity evaluation in Salmonella/typhimurium with attachments, cover sheets and letter dated 092484 (sanitized). Russell, J.F. EPA Doc 86-890000804S, microfiche no. OTS0520921. May 9, 1979. Unpublished report submitted by EFFA to SCF.

DuPont, E.I., 1979b. Mutagenic activity in the Salmonella/microsome assay with attachments, cover sheets and letter dated 092484 (sanitized). Sippel, M.E. EPA Doc 86-890000815S, microfiche No, OTS0520932. February 28,1979. Unpublished report submitted by EFFA to SCF.

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

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

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

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

EFSA, 2004h. Opinion of the Scientific Panel AFC related to Flavouring Group Evaluation 6 (FGE.06): Straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters from chemical groups 1 and 4 (Commission Regulation (EC) No 1565/2000 of 18 July 2000). Adopted 7 October 2004. EFSA-Q-2003-149.

EFSA, 2004a. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with food on a request from the Commission related to Flavouring Group Evaluation 5: Esters of 23 branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and 24 branched- and straight-chain unsaturated carboxylic acids from chemical groups 1, 2, and 5 (Commission Regulation (EC) No 1565/2000 of 18 July 2000). EFSA-Q-2003-148. Adopted on 23 february 2005. The EFSA Journal 204, 1-74.

Foureman, P., Mason, J.M., Valencia, R., Zimmering, S., 1994. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environ. Mol. Mutag. 23, 208-227.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutag. 10(Suppl. 10), 1-175.

Hachitani, N., Takeya, A., Takazawa, Y., 1982. [Studies on mutagenicity of life-related environmental agents. III. Ames and mouse bone marrow micronucleus assays of acryl resin monomers and major additives]. Jap. J. Public Health 29(5), 236-239. (In Japanese)

Haskell Laboratory, 1989. Submission sheet from Haskell Laboratory submitting a mutagenicity study in Salmonella and a glove permeation study with methyl methacrylate with attachments. EPA Doc 86-890000816, microfiche no. OTS0544277. June 12, 1989. Unpublished report submitted by EFFA to SCF.

Hayatsu, H., Inoue, K., Ohta, H., Namba, T., Togawa, K., Hayatsu, T., Makita, M., Wataya, Y., 1981. Inhibition of the mutagenicity of cooked-beef basic fraction by its acidic fraction. Mutat. Res. 91, 437-442.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9(1), 257-272.

ICI, 1976b. Methyl methacrylate: Short-term predictive tests for carcinogenicity: Results with methyl methacrylate monomer (MMM) in mammal with cover letter dated 071789 (sanitized). EPA Doc 86-8900013938, microfiche no. OTS0544294. Unpublished data submitted by EFFA to SCF.

ICI, 1976c. Methyl methacrylate monomer dominant lethal study in the mouse with attachments and cover sheet dated 071789 (sanitized). EPA Doc 86-890001375S, microfiche no. OTS0521010. November 16, 1976. Unpublished data submitted by EFFA to SCF.

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

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

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

JECFA, 1999a. Safety evaluation of certain food additives. The fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series: 42. IPCS, WHO, Geneva.

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

JECFA, 2003b. Compendium of food additive specifications. Addendum 11. Joint FAO/WHO Expert Commitee of Food Additives 61st session. Rome, 10-19 June 2003. FAO Food and Nutrition paper 52 Add. 11.

JECFA, 2004a. Evaluation of certain food additives. Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, no. 922. Rome, 10-19 June 2003.

JECFA, 2004b. Safety evaluation of certain food additives and contaminants. Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 52. IPCS, WHO, Geneva.

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

Jensen, J.S., Sylvest, A., Trap, B., Jensen, J.C., 1991. Genotoxicity of acrylic bone cements. Pharmacol. Toxicol. 69, 386-389.

Kinsella, A.R., 1982. Elimination of metabolic co-operation and the induction of sister chromatid exchanges are not properties common to all promoting or co-carcinogenic agents. Carcinogenesis 3(5), 499-503.

Lijinsky, W., Andrews, A.W., 1980. Mutagenicity of vinyl compounds in Salmonella typhimurium. Teratog. Carcinog. Mutag. 1, 259-267.

MacGregor, J.T., Wilson, R.E., Neff, W.E., Frankel, E.N., 1985. Mutagenicity tests of lipid oxidation products in Salmonella typhimurium: Monohydroperoxides and secondary oxidation products of methyl linoleate and methyl linolenate. Food Chem. Toxicol. 23(12), 1041-1047.

Meigs, T.E., Sherwood, S.W., Simoni, R.D., 1995. Farnesyl acetate, a derivative of an isoprenoid of the mevalonate pathway, inhibits DNA replication in hamster and human cells. Exp. Cell Res. 219(2), 461-470.

Mirsalis, J., Tyson, K., Beck, J., Loh, E., Steinmetz, K., Contreras, C., Austere, L., Martin, S., Spalding, J., 1983. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. Environ. Mol. Mutag. 5(3), 482.

Moore, M.M., Amtower, A., Doerr, C.L., Brock, K.H., Dearfield, K.L., 1988. Genotoxicity of acrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate in L5178Y mouse lymphoma cells. Environ. Mol. Mutag. 11, 49-63.

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

Myhr, B., McGregor, D., Bowers, L., Riach, C., Brown, A.G., Edwards, I., McBride, D., Martin, R., Caspary, W.J., 1990. L5178Y mouse lymphoma cell mutation assay results with 41 compounds. Environ. Mol. Mutag. 16 Suppl. 18, 138-167.

NTP, 1986b. NTP technical report on the toxicology and carcinogenesis studies of methyl methacrylate (CAS no. 80-62-6) in F344/N rats and B6C3F1 mice (inhalation studies). October 1986. NTP-TR 314. NIH Publication no. 87-2570.

NTP, 1987b. National Toxicology Program annual plan for fiscal year 1987. May, 1987. NTP-87-001.

Oda, Y., Hamono, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1979. [Mutagenicity of food flavors in bacteria]. Shokuhin. Eisei. Hen. 9, 177-181. (In Japanese)

Osawa, T., Namiki, M., 1982. Mutagen formation in the reaction of nitrite with the food components analogous to sorbic acid. Agric. Biol. Chem. 45, 2299-2304.

Poss, R., Thilly, W.G., Kaden, D.A., 1979. Methylmethacrylate is a mutagen for Salmonella typhimurium. J. Bone Jt. Surg. 61-A(8), 1203-1207.

Record, I.R., Konstantinopoulos, M., Nestel, P.J. ,1992. A comparative study of micronucleus frequency in peripheral blood lymphocytes of human subjects give dietary cis, trans and saturated fat. Food Chem. Toxicol., 30, 585-588.

Richold, M., Jones, E., 1980. Ames metabolic activation test to assess the potential mutagenic effect of 9-decenal. Unpublished data submitted by EFFA to SCF.

Roehm GmbH., 1989. Unpublished Report no. 89-001. Cited in European Commission - European Chemicals Bureau, 2000. IUCLID Dataset, CAS no. 97-86-9. Section 5 Toxicity.

Rohm & Haas Co., 1976a. Methylmethacrylate monomer (MMM): Estimation of mutagenic potential in the Salmonella typhimurium plate incorporation mutagenicity assay with cover letter dated 071789 (sanitized). EPA Doc 86-890001382S, microfiche no. OTS0544286. November 30, 1976. Unpublished data submitted by EFFA to SCF.

Rohm & Haas Co., 1976b. Methylmethacrylate monomer: Cytogenetic study in rats with cover letter dated 071789 (sanitized). EPA Doc 86-890001381S, microfiche no. OTS0544285. November 30, 1976. Unpublished data submitted by EFFA to SCF.

Rohm & Haas Co., 1979. Methyl methacrylate: A second cytogenetic study in rats with cover letter dated 071789 (sanitized). EPA Doc 86-890001380S, microfiche no. OTS0544284. May 22, 1979. Unpublished data submitted by EFFA to SCF.

Rohm & Haas Co., 1985. Mutagenicity evaluation of TD-80-254 in the mouse lymphoma forward mutation assay, Rohm & Haas protocol no. 81 P-259 final report Rohm & Haas report no. 81RC-136. Methyl methacrylate. EPA Doc FYI-OTS-0785-0367 FW, microfiche no. 0367. April 1, 1985. Unpublished ata submitted by EFFA to SCF.

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

Schweikl, H., Schmalz, G., Bey, B., 1994. Mutagenicity of dentin bonding agents. J. Biomed. Mater. Res. 28, 1061-1067.

Schweikl, H., Schmalz, G., Rackebrandt, K., 1998. The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells. Mutat. Res. 415, 119-130.

Seiji, K., Inoue, O., Kawai, T., Mizunuma, K., Yasugi, T., Moon, C.-S., Takeda, S., Ikeda, M., 1994. Absence of mutagenicity in peripheral lymphocytes of workers occupationally exposed to methyl methacrylate. Ind. Health 32, 97-105.

Shelby, M.D., Erexson, G.L., Hook, G.J., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ. Mol. Mutag. 21(2), 160-179.

Shimizu, H., Suzuki, Y., Takemura, N., Goto, S., Matsushita, H., 1985. The results of microbial mutation test for forty-three industrial chemicals. Jap. J. Ind. Health 27, 400-419.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., Minor, R., 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236, 933-941.

Waegemaekers, T.H.J.M., Bensink, M.P.M., 1984. Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test. Mutat. Res. 137, 95-102.

Wild, D., King, M.T., Gocke, E., Eckhard, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, BASC and micronucleus tests. Food Chem. Toxicol. 21(6), 707-719.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka City Med. J. 34(3-4), 267-288. (In Japanese)

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., 1987. Salmonella mutagenicity tests. 3. Results from the testing of 255 chemicals. Environ. Mol. Mutag. 9(Suppl. 9), 1-110.

Zeiger, E., 1990. Mutagenicity of 42 chemicals in Salmonella. Environ. Mol. Mutag. 16(Suppl. 18), 32-54.

Flavouring Group Evaluation 62 (FGE.62) . Consideration of linear and branched-chain aliphatic unsaturated, unconjugated alcohols, aldehydes, acids, and related esters evaluated by JECFA (61st meeting) structurally related to esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids evaluated by EFSA in FGE.05 (2005)

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