EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 06, Revision 2 (FGE.06Rev2): Straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters from chemical groups 1 and 4

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 06, Revision 2 (FGE.06Rev2):

Straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters from chemical groups 1 and 4[1]

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

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to evaluate the 48 flavouring substances in this Flavouring Group Evaluation 06, Revision 2 (FGE.06Rev2), using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These 48 flavouring substances belong to chemical groups 1 and 4, Annex I of the Commission Regulation (EC) No 1565/2000.

The present Flavouring Group Evaluation deals with 48 straight- and branched-chain unsaturated primary alcohols, aldehydes, carboxylic acids and esters.

Eight of the 48 flavouring substances possess a chiral centre [FL-no: 02.170, 02.175, 05.143, 09.341, 09.612, 09.871, 09.872 and 09.938].

Thirty-one of the 48 substances can exist as geometrical isomers [FL-no: 02.152, 02.195, 02.222, 02.234, 05.061, 05.082, 05.203, 05.217, 05.218, 05.220, 08.074, 08.102, 09.377, 09.567, 09.569, 09.572, 09.575, 09.638, 09.640, 09.643, 09.672, 09.673, 09.674, 09.831, 09.838, 09.855, 09.884, 09.885, 09.928, 09.937 and 09.939]. For 13 of these substances [FL-no: 02.152, 02.222, 05.061,

1 On request from the Commission, Question No EFSA-Q-2010-01131, adopted on 30 September 2010.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Groups on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Wilfried Bursch, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Gerard Pascal, Iona Pratt, Gerrit Speijers, Harriet Wallin and EFSA's staff member Kim Rygaard Nielsen for the preparatory work on this scientific Opinion.

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05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884, 09.885] no indication has been given that one of the possible isomers has preponderance in the commercial flavouring material.

Forty-six candidate substances are classified into structural class I. The remaining two substances [FL-no: 05.143 and 09.884] are classified into structural class II.

Thirty-eight of the flavouring substances in the present group have been reported to occur naturally in a wide range of food items.

According to the default MSDI approach, the 48 flavouring substances in this group have intakes in Europe from 0.001 to 120 microgram/*capita*/day, which are below the thresholds of concern value for both structural class I (1800 microgram/person/day) and structural class II (540 microgram/person/day) substances.

On the basis of the reported annual production volumes in Europe (MSDI approach), the combined intake of the 46 candidate substances belonging to structural class I and of the two candidate substances belonging to structural class II would result in a total intake of approximately 255 and 0.7 microgram/*capita*/day, respectively. These values are below the thresholds of concern for structural class I and class II substances of 1800 and 540 microgram/person/day, respectively. The total combined estimated intake of 65 of the 70 supporting substances for which European annual production data are available and of the 46 candidate substances from structural class I is approximately 6700 microgram/*capita*/day, which exceeds the threshold of concern for structural class I (1800 microgram/person/day). However, the substances are expected to be efficiently metabolised and are not expected to saturate the metabolic pathways.

For the substances in this group the limited data available do not give rise to safety concern with respect to genotoxicity and carcinogenicity.

Except for hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] the candidate substances are expected to be metabolised to innocuous substances at the estimated levels of use as flavouring substances. One of the hydrolysis products of [FL-no: 09.884], 2-ethylbutyric acid, showed teratogenic potential in one mouse subcutaneous single-dose study, and is structurally related to valproic acid, which is a known teratogen. However, an additional study in which 2-ethylbutyric acid was given by gavage to pregnant rats showed a NOAEL of 200 mg/kg bw/day of 2-ethylbutyric acid. This dose is more than 4×10^7 times higher than the MSDI for 2-ethylbutyric acid arising from the intake of the candidate substance, [FL-no: 09.884]. Accordingly, the candidate substance [FL-no: 09.884] does not pose a safety concern with respect to teratogenicity when used at the level of intake as flavouring substance estimated on the basis of the MSDI approach.

It was noted that where toxicity data were available they were consistent with the conclusions in the present flavouring group evaluation using the Procedure.

It is considered that on the basis of the default MSDI approach these 48 candidate substances would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

When the estimated intakes were based on the mTAMDI approach they ranged from 36 to 40000 microgram/person/day for the 45 flavouring substances from structural class I for which data have been provided. Thus, the intakes were all above the threshold of concern for structural class I of 1800 microgram/person/day, except for nine flavouring substances [FL-no: 05.061, 05.174, 05.082, 05.203, 05.217, 05.218, 05.220, 09.937 and 09.939]. The estimated intakes of the two flavouring substances assigned to structural class II, based on the mTAMDI are 1600 and 3900 microgram/person/day, which is above the threshold of concern for structural class II of 540 microgram/person/day. The nine substances [FL-no: 05.061, 05.174, 05.082, 05.203, 05.217, 05.218, 05.220, 09.937 and 09.939],

which have mTAMDI intake estimates below the threshold of concern for structural class I, are also expected to be metabolised to innocuous products.

Thus, for 38 of the 48 flavouring substances considered in this Opinion, the intakes, estimated on the basis of the mTAMDI, exceed the relevant threshold for their structural class, to which the flavouring substance has been assigned. For one substance [FL-no: 09.647] no use levels were provided. Therefore, for these 39 substances more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be reconsidered along the steps of the Procedure. Subsequently, additional data might become necessary.

In order to determine whether the conclusion for the 48 candidate substances can be applied to the material of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity for the materials of commerce have been provided for 46 of the 48 flavouring candidate substances. An ID test is missing for [FL-no: 09.938] and a boiling point is lacking for [FL-no: 09.674]. Otherwise the specifications are adequate for all 48 candidate substances, except that information on composition of stereoisomeric mixture has not been specified sufficiently for 13 of the substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884 and 09.885].

Thus, the final evaluation of the materials of commerce cannot be performed for 14 substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884, 09.885 and 09.938], pending further information. The remaining 34 substances [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176, 02.195, 02.201, 02.234, 05.082, 05.143, 05.174, 05.217, 05.220, 08.100, 09.341, 09.368, 09.567, 09.569, 09.572, 09.575, 09.612, 09.638, 09.643, 09.672, 09.673, 09.838, 09.855, 09.871, 09.872, 09.897, 09.898, 09.928, 09.937 and 09.939] would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

KEYWORDS

Straight-chain, branched-chain, unsaturated, primary alcohols, aldehydes, carboxylic acids, esters, flavourings, safety.

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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996a) 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 2008/163/EC (EC, 2009a). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

The FGE is revised to include substances for which data were submitted after the deadline as laid down in Commission Regulation (EC) No 622/2002 and to take into account additional information that has been made available since the previous Opinion on this FGE.

The Revision also includes newly notified substances belonging to the same chemical groups evaluated in this FGE.

After the completion of the evaluation programme the Union List of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96) (EC, 1996a).

HISTORY OF THE EVALUATION

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.06	7 October 2004	http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620762005.htm	35
FGE.06Rev1	7 February 2007	http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178710471245.htm	47
FGE.06Rev2	29 September 2010		48

The present revision of FGE.06, FGE.06Rev2, includes the assessment of one additional candidate substance [FL-no: 09.674].

No toxicity or metabolism data were provided for this substance. A search in open literature did not provide any further data on toxicity or metabolism for this substance.

Furthermore, information from Industry on missing specifications received after publication of the last revision is included in the present revision. (EFFA, 2010a).

TERMS OF REFERENCE

The European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances in the Register prior to their authorisation and inclusion in a Union List according to Commission Regulation (EC) No 1565/2000 (EC, 2000a). In addition, the Commission requested EFSA to evaluate newly notified flavouring substances, where possible, before finalising the evaluation programme.

ASSESSMENT

1. Presentation of the Substances in Flavouring Group Evaluation 06, Revision 2

1.1. Description

The present Flavouring Group Evaluation 6 Revision 2, FGE.06Rev2, using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000 (the Procedure – shown in schematic form in Annex I of this FGE), deals with 48 straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids and esters. These 48 flavouring substances (candidate substances) belong to chemical groups 1 and 4 of Annex I of Regulation (EC) No 1565/2000 (EC, 2000a).

The 48 flavouring substances under consideration, with their chemical Register name, FLAVIS (FL-), Chemical Abstract Service (CAS-), Council of Europe (CoE-), and Flavor and Extract Manufacturers' Association (FEMA-) numbers, structure and specifications, are listed in Table 1. This group of candidate flavouring substances includes 27 straight or branched-chain esters [FL-no: 09.341, 09.368, 09.377, 09.567, 09.569, 09.572, 09.575, 09.612, 09.638, 09.640, 09.643, 09.672, 09.673, 09.674, 09.831, 09.838, 09.855, 09.871, 09.872, 09.884, 09.885, 09.897, 09.898, 09.928, 09.937, 09.938 and 09.939], ten straight or branched-chain alcohols [FL-no: 02.125, 02.138, 02.152, 02.170, 02.175, 02.176, 02.195, 02.201, 02.222 and 02.234], eight straight or branched-chain aldehydes [FL-no: 05.061, 05.082, 05.143, 05.174, 05.203, 05.217, 05.218 and 05.220], and three straight or branched-chain carboxylic acids [FL-no: 08.074, 08.100 and 08.102].

The outcome of the safety evaluation is summarised in Table 2a.

The hydrolysis products of the candidate esters are listed in Table 2b.

The 48 candidate substances are structurally related to flavouring substances (supporting substances) evaluated at the 49th, 51st or 61st meetings of the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) (JECFA, 1999b; JECFA, 2000a; JECFA, 2004a). That is, they are structurally related to 26 esters derived from branched-chain terpenoid alcohols and aliphatic acyclic linear and branched-chain carboxylic acids (JECFA, 1998a) or to 44 linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, carboxylic acids and related esters (JECFA, 1999a; JECFA, 2004a), previously evaluated by the JECFA. The names and structures of the 70 supporting substances are listed in Table 3, together with their evaluation status (CoE, 1992; JECFA, 1999b; JECFA, 2000a; JECFA, 2004a; SCF, 1995).

Additional substances evaluated by the JECFA and structurally related to the 70 supporting substances are also taken into consideration in FGE.06Rev2 regarding toxicity and metabolism studies.

1.2. Stereoisomers

It is recognised that geometrical and optical isomers of substances may have different properties. Their flavour may be different, they may have different chemical properties resulting in possible variability in their absorption, distribution, metabolism, elimination and toxicity. Thus information must be provided on the configuration of the flavouring substance, i.e. whether it is one of the geometrical/optical isomers, or a defined mixture of stereoisomers. The available specifications of purity will be considered in order to determine whether the safety evaluation carried out for candidate substances for which stereoisomers may exist can be applied to the material of commerce. Flavouring substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number etc.).

Eight of the 48 flavouring substances possess a chiral centre [FL-no: 02.170, 02.175, 05.143, 09.341, 09.612, 09.871, 09.872 and 09.938].

Due to the presence and the position of double bonds, 31 of the 48 substances can exist as geometrical isomers [FL-no: 02.152, 02.195, 02.222, 02.234, 05.061, 05.082, 05.203, 05.217, 05.218, 05.220, 08.074, 08.102, 09.377, 09.567, 09.569, 09.572, 09.575, 09.638, 09.640, 09.643, 09.672, 09.673, 09.674, 09.831, 09.838, 09.855, 09.884, 09.885, 09.928, 09.937 and 09.939]. The geometrical isomeric form is clear for only 18 substances: [FL-no: 02.195, 02.234, 05.082, 05.217, 05.220, 09.567, 09.569, 09.572, 09.575, 09.638, 09.643, 09.672, 09.673, 09.838, 09.855, 09.928, 09.937 and 09.939]. In the remaining 13 cases [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884 and 09.885], no indication has been given that one of the possible isomers has preponderance in the commercial flavouring material (see Table 1). For 12 of these 13 flavouring substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.831, 09.884 and 09.885] Industry has informed that they exist as a “mixture of isomers” 2010a) (see Table 1). However, the Panel does not consider this information sufficient and requests data on the actual ratios. For [FL-no: 09.674] the stereoisomeric composition has to be specified.

1.3. Natural Occurrence in Food

Thirty-eight of the 48 candidate substances have been reported to occur naturally in fruits, essential oils, tea, herbs, mushrooms, beer, wine, beverage, meat, pork fat, cheese and/or butter (TNO, 2000).

Quantitative data on the natural occurrence in food have been reported for 21 of the 38 substances.

These reports include among other:

- 2-Methylbut-3-en-1-ol [FL-no: 02.175]: up to 1.1 mg/kg in guava fruit
- Hex-4-enyl acetate [FL-no: 09.572]: 1.56 mg/kg (Z-isomer) and < 0.05 mg/kg (E-isomer) in banana
- 3-Methylbut-3-en-1-ol [FL-no: 02.176]: 0.001 mg/kg in roasted chicken and up to 0.12 mg/kg in wine
- 4-Methylpent-3-enoic acid [FL-no: 08.100]: 0.32 mg/kg in beer
- 9-Octadecenal [FL-no: 05.203]: 2 mg/kg in roasted chicken
- trans-3-Hexenyl acetate [FL-no: 09.928]: up to 0.05 mg/kg in banana, up to 0.01 mg/kg in guava fruit, up to 0.005 mg/kg in mango and up to 0.01 mg/kg in passiflora
- Methyl (3Z)-hexenoate [FL-no: 09.937]: up to 0.25 mg/kg in guava fruit
- Ethyl (3Z)-hexenoate [FL-no: 09.939]: up to 0.15 mg/kg in passiflora juice.

Twenty-six of the 38 candidate substances which have been reported to occur naturally in food can exist as geometrical isomers. For six of these 26 flavourings [FL-no: 08.074, 09.567, 09.575, 09.672, 09.673 and 09.885] natural occurrence in food has only been reported for the Z-isomer (TNO, 2000).

According to the Flavour Industry three of the candidate substances [FL-no: 05.061, 05.217, 05.218 and 09.674] in the present group are of artificial origin and have not been reported to occur naturally in foods (EFFA, 2002d; EFFA, 2004u; Flavour Industry, 2008f).

2. Specifications

Purity criteria for the 48 candidate substances have been provided by the Flavour Industry (EFFA, 2001c; EFFA, 2002b; EFFA, 2004u; Flavour Industry, 2004a; EFFA, 2006c; Flavour Industry, 2008f).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000a), the purity criteria for two of the candidate substances [FL-no: 09.674 and 09.938] is insufficient. An ID test is missing for [FL-no: 09.938] and a boiling point is lacking for [FL-no: 09.674]. Otherwise the specifications are adequate for all 48 candidate substances, except that information on composition of stereoisomeric mixture has not been specified sufficiently for 13 substances (see Section 1.2 and Table 1).

3. Intake Data

Annual production volumes of the flavouring substances as surveyed by the Industry can be used to calculate the "Maximised Survey-derived Daily Intake" (MSDI) by assuming that the production figure only represents 60 % of the use in food due to underreporting and that 10 % of the total EU population are consumers (SCF, 1999a).

However, the Panel noted that due to year-to-year variability in production volumes, to uncertainties in the underreporting correction factor and to uncertainties in the percentage of consumers, the reliability of intake estimates on the basis of the MSDI approach is difficult to assess.

The Panel also noted that in contrast to the generally low *per capita* intake figures estimated on the basis of this MSDI approach, in some cases the regular consumption of products flavoured at use levels reported by the Flavour Industry in the submissions would result in much higher intakes. In such cases, the human exposure thresholds below which exposures are not considered to present a safety concern might be exceeded.

Considering that the MSDI model may underestimate the intake of flavouring substances by certain groups of consumers, the SCF recommended also taking into account the results of other intake assessments (SCF, 1999a).

One of the alternatives is the "Theoretical Added Maximum Daily Intake" (TAMDI) approach, which is calculated on the basis of standard portions and upper use levels (SCF, 1995) for flavourable beverages and foods in general, with exceptional levels for particular foods. This method is regarded as a conservative estimate of the actual intake by most consumers because it is based on the assumption that the consumer regularly eats and drinks several food products containing the same flavouring substance at the upper use level.

One option to modify the TAMDI approach is to base the calculation on normal rather than upper use levels of the flavouring substances. This modified approach is less conservative (e.g., it may underestimate the intake of consumers being loyal to products flavoured at the maximum use levels reported) (EC, 2000a). However, it is considered as a suitable tool to screen and prioritise the flavouring substances according to the need for refined intake data (EFSA, 2004a).

3.1. Estimated Daily *per Capita* Intake (MSDI Approach)

The intake estimation is based on the Maximised Survey-derived Daily Intake (MSDI) approach, which involves the acquisition of data on the amounts used in food as flavourings (SCF, 1999a). These data are derived from surveys on annual production volumes in Europe. These surveys were conducted in 1995 by the International Organization of the Flavour Industry, in which flavour manufacturers reported the total amount of each flavouring substance incorporated into food sold in the EU during the previous year (IOFI, 1995). The intake approach does not consider the possible natural occurrence in food.

Average *per capita* intake (MSDI) is estimated on the assumption that the amount added to food is consumed by 10 % of the population[4] (Eurostat, 1998). This is derived for candidate substances from estimates of annual volume of production provided by Industry and incorporates a correction factor of 0.6 to allow for incomplete reporting (60 %) in the Industry surveys (SCF, 1999a).

In the present Flavouring Group Evaluation (FGE.06Rev2) the total annual volume of production of the 48 candidate substances from use as flavouring substances in Europe has been reported to be approximately 2200 kg (EFFA, 2001c; EFFA, 2002c; EFFA, 2004v; EFFA, 2006d; EFFA, 2008b; Flavour Industry, 2004a). For 65 of the 70 supporting substances the total annual volume of production is approximately 52000 kg (JECFA, 1999b; JECFA, 2000a; EFFA, 2002c). The annual volumes of production in Europe for five of the substances [FL-no: 02.110, 08.059, 09.141, 09.646 and 09.927] were not reported.

On the basis of the annual volume of production reported for the 48 candidate substances, MSDI values for each of these flavourings have been estimated (Table 2a).

About 94 % of the total annual volume of production for the candidate substances is accounted for by two flavourings methyl (3Z)-hexenoate [FL-no: 09.937] and ethyl (3Z)-hexenoate [FL-no: 09.939]. The estimated MSDI values of methyl (3Z)-hexenoate and of ethyl (3Z)-hexenoate from use as flavouring substances are 120 microgram/*capita*/day. For all the remaining candidate substances the estimated daily *per capita* intakes are below 2 microgram (Table 2a).

3.2. Intake Estimated on the Basis of the Modified TAMDI (mTAMDI)

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995).

The assumption is that a person may consume a certain amount of flavourable foods and beverages per day.

For the present evaluation of the 48 candidate substances, information on food categories and normal and maximum use levels[5,6,7] were submitted by the Flavour Industry for 47 of the 48 candidate substances (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a). For these 47 substances the use in flavoured food products divided into the food categories, outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000a), is shown in Table 3.1. For the present calculation of mTAMDI, the reported normal use levels were used. In the case where different normal use levels were reported for different food categories the highest reported normal use level was used.

[4] EU figure 375 millions. This figure relates to EU population at the time for which production data are available, and is consistent (comparable) with evaluations conducted prior to the enlargement of the EU. No production data are available for the enlarged EU.

[5] ”Normal use” is defined as the average of reported usages and ”maximum use” is defined as the 95th percentile of reported usages (EFFA, 2002i).

[6] The normal and maximum use levels in different food categories (EC, 2000) have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

[7] The use levels from food category 5 “Confectionery” have been inserted as default values for food category 14.2 “Alcoholic beverages” for substances for which no data have been given for food category 14.2 (EFFA, 2007a).

Table 3.1 Use of Candidate Substances

Food category	Description	Flavourings used *
01.0	Dairy products, excluding products of category 2	47 except [FL-no: 02.125]
02.0	Fats and oils, and fat emulsions (type water-in-oil)	47 except [FL-no: 02.125, 05.220]
03.0	Edible ices, including sherbet and sorbet	47
04.1	Processed fruits	47 except [FL-no: 02.125]
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Only [FL-no: 09.928, 09.937, 09.938, 09.939]
05.0	Confectionery	47
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	47 except [FL-no: 02.125, 02.234]
07.0	Bakery wares	47 except [FL-no: 02.125]
08.0	Meat and meat products, including poultry and game	47 except [FL-no: 02.125, 05.220]
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	47 except [FL-no: 02.125, 05.220]
10.0	Eggs and egg products	None
11.0	Sweeteners, including honey	None
12.0	Salts, spices, soups, sauces, salads, protein products etc.	47 except [FL-no: 02.125, 05.143, 05.220]
13.0	Foodstuffs intended for particular nutritional uses	47 except [FL-no: 02.125, 05.143, 05.220, 09.937, 09.938, 09.939]
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	47
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	47
15.0	Ready-to-eat savouries	47 except [FL-no: 02.125]
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	47 except [FL-no: 02.125, 05.220]

* No use levels have been submitted for [FL-no: 09.674]

According to the Flavour Industry the normal use levels for the candidate substances are in the range of 0.02 – 100 mg/kg food, and the maximum use levels are in the range of 0.1 to 500 mg/kg (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a). Information on use levels have not been provided for [FL-no: 09.674].

The mTAMDI values for the 45 candidate substances from structural class I for which data have been provided (see Section 6) range from 36 to 40000 microgram/person/day. For the remaining two candidate substances from structural class II the mTAMDI is 1600 and 3900 microgram/person/day.

For detailed information on use levels and intake estimations based on the mTAMDI approach, see Section 6 and Annex II.

4. Absorption, Distribution, Metabolism and Elimination

Specific information regarding absorption, distribution, metabolism and excretion is not available for any of the candidate substances.

The aliphatic alcohols, aldehydes and carboxylic acids in the present flavouring group are all expected to be absorbed from the gastrointestinal tract. Aliphatic esters are expected to be hydrolysed in the gut to yield the corresponding alcohols and carboxylic acids prior to absorption, or in the liver following absorption.

In general, short chain (< C8) linear and branched-chain aliphatic esters, alcohols, aldehydes and carboxylic acids are rapidly absorbed from the gastrointestinal tract. Long-chain carboxylic acids, such

as linoleic acid and oleic acid, are readily absorbed from micelles in the jejunum, re-esterified with glycerol in chylomicrons and transported via the lymphatic system.

In vitro hydrolysis data from studies with esters structurally related to the candidate substances indicate that the esters included in this evaluation are hydrolysed to yield the corresponding alcohols and carboxylic acids in the gut prior to absorption or in the blood and liver following absorption.

Candidate alcohols are oxidized to their corresponding carboxylic acids via aldehydes. Candidate aldehydes are oxidized to their corresponding carboxylic acids. In general, the carboxylic acids included in the present flavouring group or resulting from the hydrolysis of esters or oxidation of alcohols and aldehydes are expected to complete their metabolism in the fatty acid pathway or tricarboxylic acid cycle.

Branched-chain carboxylic acids resulting from ester hydrolysis, alcohol or aldehyde oxidation may be metabolised via omega- and/or beta-oxidation to yield polar metabolites, which are excreted as such or as glucuronic acid conjugates, primarily in the urine. The two terpene alcohols resulting from the hydrolysis of four of the candidate esters included in the present flavouring group are expected to undergo omega-oxidation and excretion as such or after conjugation with glucuronic acid.

The hydrolysis of the candidate substance hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] generates 2-ethylbutyric acid [FL-no: 08.045], which is resistant to beta-oxidation and has shown teratogenic potential (see Section 8.3). Although 2-ethylbutyric acid can be further conjugated with glucuronic acid or undergo omega-oxidation (see Annex III) the candidate substance [FL-no: 09.884] cannot be anticipated to be metabolised to innocuous products.

Terminal double bonds appear in eleven candidate substances [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176, 02.201, 05.143, 05.174, 09.612, 09.897 and 09.898]. Of these, six are alcohols [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176 and 02.201], two are aldehydes [FL-no: 05.143 and 05.174], and three are esters [FL-no: 09.612, 09.897 and 09.898]. Although theoretically, these double bonds may be oxidised to give reactive epoxides, it is expected that for these candidate substances, the metabolism via this pathway is negligible. The terminal double bonds are all present in molecules that have alcohol- or aldehyde functions at the end distal from the double bond. The alcohol- and aldehyde functions are expected to be readily attacked by oxidation processes, ultimately yielding unsaturated carboxylic acids, and also hydrolysis of the esters would yield the unsaturated alcohols. Biochemical attack of these carboxylic acids via e.g. beta-oxidation or conjugation with glucuronic acid is expected to be much more efficient and rapid than microsomal oxidation.

In summary, it is generally anticipated that the candidate esters will undergo hydrolysis in the gastrointestinal tract, blood and liver to yield their corresponding aliphatic alcohols and carboxylic acids. Alcohols and aldehydes are oxidised to the corresponding carboxylic acids. The carboxylic acids will proceed their metabolism in the fatty acid pathway, tricarboxylic acid cycle, or undergo further oxidation and excretion as such or after glucuronic acid conjugation. Except for one candidate substance, hex-3-enyl 2-ethylbutyrate [FL-no: 09.884], all the candidate substances can be anticipated to be metabolised to innocuous products.

A more detailed discussion follows in the Annex III on hydrolysis of linear and branched-chain esters, metabolism of linear saturated/unsaturated primary alcohols, aldehydes and carboxylic acids, and branched-chain unsaturated primary alcohols, aldehydes and carboxylic acids.

For more detailed information, see Annex III.

5. Application of the Procedure for the Safety Evaluation of Flavouring Substances

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach. Where the mTAMDI approach indicates that the intake of a flavouring substance might exceed its

corresponding threshold of concern, a formal safety assessment is not carried out using the Procedure. In these cases the Panel requires more precise data on use and use levels. For comparison of the intake estimations based on the MSDI approach and the mTAMDI approach, see Section 6.

For the safety evaluation of the 48 candidate substances from chemical groups 1 and 4 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the substances are summarised in Table 2a.

Step 1

All candidate substances are classified according to the decision tree approach by Cramer et al. (Cramer et al., 1978) into structural class I, except two ([FL-no: 05.143 and 09.884]), which are classified into structural class II.

Step 2

Step 2 requires consideration of the metabolism of the candidate substances.

All candidate substances but one are expected to be metabolised into innocuous products. The one remaining substance, hex-3-enyl 2-ethylbutyrate [FL-no: 09.884], will be hydrolysed to give 2-ethylbutyric acid [FL-no: 08.045], which showed teratogenic potential in one mouse subcutaneous single-dose study, and is structurally related to valproic acid, which is a known teratogen (see Section 8.3).

Accordingly, except for [FL-no: 09.884], all other flavouring substances (i.e. 47 substances) in the present flavouring group proceed via the A-side of the Procedure scheme (Annex I).

The candidate substance [FL-no: 09.884] can, after hydrolysis, generate a potential teratogenic metabolite (2-ethylbutyric acid). Although this hydrolysis product is expected to be metabolised e.g. via conjugation with glucuronic acid or omega oxidation, it cannot be excluded that adverse effects might be elicited, and therefore [FL-no: 09.884] proceeds via the B-side of the Procedure scheme (Annex I).

Step A3

Forty-six of the 47 candidate substances proceeding via the A-side have been assigned to structural class I and have estimated European daily *per capita* intakes (MSDI) ranging from 0.001 to 120 microgram (Table 2a). These intakes are below the threshold of concern of 1800 microgram/person/day for structural class I.

One of these 47 candidate substances proceeding via the A-side, [FL-no: 05.143], has been assigned to structural class II and has an estimated European daily *per capita* intake (MSDI) of 0.1 microgram (Table 2a). This intake is below the threshold of concern of 540 microgram/person/day for structural class II.

For these 47 candidate substances the conditions of use do not result in an intake greater than the threshold of concern for the respective structural classes.

Based on results of the safety evaluation sequence these 47 candidate substances proceeding via the A-side of the Procedure do not pose a safety concern when used as flavouring substances at estimated levels of intake, based on the MSDI approach.

Step B3

This step is only relevant for [FL-no: 09.884] for which the estimated European daily *per capita* Intake (MSDI) is 0.58 microgram, which is far less than the threshold of concern for its structural class

(i.e. 540 microgram/person/day for class II). Accordingly, this candidate substance proceed to step B4 of the Procedure.

Step B4

The teratogenic activity of 2-ethylbutyric acid, a hydrolysis product of hex-3-enyl 2-ethylbutyrate [FL-no: 09.884], has been described in a single-dose study after subcutaneous administration of 600 mg/kg body weight (bw) 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 x 10^7 lower than the NOAEL for teratogenicity.

Based on the results of the safety evaluation sequence (Annex I) 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.

6. Comparison of the Intake Estimations Based on the MSDI Approach and the mTAMDI Approach

The estimated intakes for 45 of the candidate substances in structural class I based on the mTAMDI range from 36 to 40000 microgram/person/day. For nine of the substances [FL-no: 05.061, 05.082, 05.174, 05.203, 05.217, 05.218, 05.220, 09.937 and 09.939] the mTAMDI is below the threshold of concern of 1800 microgram/person/day. For 36 of the candidate substances from class I, the mTAMDI is above the threshold of concern For one substance [FL-no: 09.674] no information on use levels have been provided. For comparison of the intake estimates based on the MSDI approach and the mTAMDI approach see Table 6.1.

The estimated intakes of the two substances [FL-no: 05.143 and 09.884] assigned to structural class II, based on the mTAMDI are 1600 and 3900 microgram/person/day, respectively, which is above the threshold of concern for structural class II substances of 540 microgram/person/day. For comparison of the MSDI- and mTAMDI-values see Table 6.1.

Thus, for 39 of the 48 candidate substances further information is required. This would include more reliable intake data and where required additional toxicity data

For comparison of the MSDI and mTAMDI values, see Table 6.1

Table 6.1 Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.125	Undec-10-en-1-ol	0.37	3900	Class I	1800
02.138	Dec-9-en-1-ol	0.15	3900	Class I	1800
02.152	Hept-3-en-1-ol	0.012	3900	Class I	1800
02.170	Lavandulol	0.012	3900	Class I	1800
02.175	2-Methylbut-3-en-1-ol	1.4	3900	Class I	1800
02.176	3-Methylbut-3-en-1-ol	0.13	3900	Class I	1800
02.195	Octa-3,5-dien-1-ol	0.061	3900	Class I	1800
02.201	Pent-4-en-1-ol	0.012	3900	Class I	1800
02.222	3-Pentenol-1	0.5	3900	Class I	1800

02.234	3-Nonen-1-ol	0.011	3900	Class I	1800
05.061	Oct-6-enal	0.0012	1600	Class I	1800
05.082	Dodeca-3,6-dienal	0.011	1600	Class I	1800
05.174	Pent-4-enal	0.11	1600	Class I	1800
05.203	9-Octadecenal	0.0097	1600	Class I	1800
05.217	5-Decenal	0.11	1600	Class I	1800
05.218	16-Octadecenal	0.011	1600	Class I	1800
05.220	4Z-Dodecenal	1.2	36	Class I	1800
08.074	Dec-3-enoic acid	0.19	3200	Class I	1800
08.100	4-Methylpent-3-enoic acid	1.8	3200	Class I	1800
08.102	Non-3-enoic acid	0.011	3200	Class I	1800
09.341	Citronellyl hexanoate	0.97	3900	Class I	1800
09.368	Ethyl 4-methylpent-3-enoate	0.12	3900	Class I	1800
09.377	Ethyl oct-3-enoate	0.35	3900	Class I	1800
09.567	Hex-3-enyl decanoate	0.0024	3900	Class I	1800
09.569	Hex-3-enyl octanoate	0.49	3900	Class I	1800
09.572	Hex-4-enyl acetate	0.0012	3900	Class I	1800
09.575	3-Hexenyl heptanoate	0.61	3900	Class I	1800
09.612	Lavandulyl acetate	0.012	3900	Class I	1800
09.638	Methyl dec-4-enoate	0.0012	3900	Class I	1800
09.640	Methyl deca-4,8-dienoate	0.012	3900	Class I	1800
09.643	Methyl geranate	0.95	3900	Class I	1800
09.672	Non-3-enyl acetate	0.012	3900	Class I	1800
09.673	Non-6-enyl acetate	0.12	3900	Class I	1800
09.674	Nona-3,6-dienyl acetate	0.0024		Class I	1800
09.831	Ethyl 3,7-dimethyl-2,6-octadienoate	0.61	3900	Class I	1800
09.838	3-Hexenyl methyl carbonate	0.012	3900	Class I	1800
09.855	trans-3-Hexenyl hexanoate	0.21	3900	Class I	1800
09.871	Citronellyl decanoate	0.12	3900	Class I	1800
09.872	Citronellyl dodecanoate	0.061	3900	Class I	1800
09.885	Hex-3-enyl hexadecanoate	0.049	3900	Class I	1800
09.897	3-Methylbut-3-en-1-yl butyrate	0.012	3900	Class I	1800
09.898	3-Methylbut-3-en-1-yl hexanoate	0.012	3900	Class I	1800
09.928	trans-3-Hexenyl acetate	1.8	3900	Class I	1800
09.937	Methyl (3Z)-hexenoate	120	800	Class I	1800
09.938	6-Methyl-5-hepten-2-yl acetate	1.2	40000	Class I	1800
09.939	Ethyl (3Z)-hexenoate	120	800	Class I	1800
05.143	2,5-Dimethyl-2-vinylhex-4-enal	0.12	1600	Class II	540
09.884	Hex-3-enyl-2-ethylbutyrate	0.58	3900	Class II	540

7. Considerations of Combined Intakes from Use as Flavouring Substances

Because of structural similarities of candidate and supporting substances, it can be anticipated that many of the flavourings are metabolised through the same metabolic pathways and that the metabolites may affect the same target organs. Further, in case of combined exposure to structurally related flavourings, the pathways could be overloaded. Therefore, combined intake should be considered. As flavourings not included in this FGE may also be metabolised through the same pathways, the combined intake estimates presented here are only preliminary. Currently, the combined intake estimates are only based on MSDI exposure estimates, although it is recognised that this may lead to underestimation of exposure. After completion of all FGEs, this issue should be readdressed.

The total estimated combined daily *per capita* intake of structurally related flavourings is estimated by summing the MSDI for individual substances.

On the basis of the reported annual volume of production in Europe (EFFA, 2001e; EFFA, 2002c; EFFA, 2006c; EFFA, 2004u; Flavour Industry, 2004a), the combined estimated daily *per capita* intake as flavouring of the 46 candidate substances assigned to structural class I is approximately 255 microgram, which does not exceed the threshold of concern for the structural class of 1800 microgram/person/day.

For the two candidate substances assigned to structural class II the combined estimated daily *per capita* intake is 0.7 microgram, which does not exceed the threshold of concern for structural class II of 540 microgram/person/day.

The candidate substance hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] can be hydrolysed to the potential teratogenic substance 2-ethylbutyric acid (and hex-3-en-1-ol). No other candidate substances

but one supporting substance, geranyl 2-ethylbutyrate [FL-no: 09.515], can be hydrolysed to 2-ethylbutyric acid (and geraniol). The estimated combined intake of these two substances corresponds to 0.5 microgram 2-ethylbutyric acid/*capita*/day. This combined intake corresponds to 0.01 microgram 2-ethylbutyric acid/kg bw/day which is more than 2 x 10^7 lower than the NOAEL of 200 mg/kg bw/day for teratogenicity of 2-ethylbutyric acid in the rat (Narotsky et al., 1994). Therefore, it can be concluded that the combined intake of hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] and geranyl 2-ethylbutyrate [FL-no: 09.515] does not pose a safety concern with respect to teratogenicity when used as flavouring substances at their estimated level of intakes, based on the MSDI approach.

The 48 candidate substances are structurally related to 70 supporting substances evaluated by the JEFCA at its 49th, 51st and 61st meeting (JECFA, 1998a; JECFA, 1999a; JECFA, 2004a). The production volumes of some of the 70 supporting substances were much higher than for the candidate substances. It was noted that the estimated combined intake (in Europe) is approximately 6400 microgram/*capita*/day for 65 of the substances, all belonging to structural class I. The estimated levels of intake in Europe were not reported for five of the supporting substances [FL-no: 02.110, 08.059, 09.141, 09.646 and 09.927]. The total combined intake of the candidate and supporting substances is 6700 microgram/*capita*/day which exceeds the threshold of concern for a compound belonging to structural class I. However, at the level of exposure resulting from the use as flavourings, all the candidate and supporting substances are expected to be efficiently metabolised and would not be expected to saturate the metabolic pathways. For these reasons and in the light of toxicological data on supporting substances (Annex IV), the total combined intake of these substances would not be expected to be of safety concern.

8. Toxicity

8.1. Acute Toxicity

Data are available for four of the candidate substances and 42 supporting and structurally related substances. A few of these flavouring substances have oral LD_{50} values in mice and rats between 600 and 3000 mg/kg body weight (bw) but most have LD_{50} values higher than 5000 mg/kg bw, indicating low oral acute toxicity of the candidate substances in the present group.

The acute toxicity data are summarised in Annex IV, Table IV.1.

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

No subacute, subchronic, chronic nor carcinogenicity studies are available on the candidate substances.

Twelve supporting substances were tested for subacute/subchronic toxicity and/or chronic toxicity, see Annex IV, Table IV.2.

Three mouse carcinogenicity studies were performed with oleic acid [FL-no: 08.013] or oleic acid/linoleic acid mixture [FL-no: 08.013/08.041] (El-Khatib & Cora, 1981; Szepsenwol & Boschetti, 1975; Szepsenwol, 1978) and two carcinogenicity studies were performed with citronellyl acetate/geranyl acetate mixture [FL-no: 09.012 / 09.011] in mice and rats (NTP, 1987a).

The Panel noted the data provided on oleic acid [FL-no: 08.013] as a supporting substance. The former EU Scientific Committee on Food allocated in 1991 an ADI “not specified” to fatty acids, including oleic acid (CEC, 1991). High intakes of fatty acids may stimulate tumour development in the gastro-intestinal tract due to promoter activity, which can be considered as a threshold event (Zhang et al., 1996; Reddy, 1995; Liu et al., 2001; Reddy, 1992). In addition, apart from aneuploidy (threshold genotoxic event), no other genotoxic effects with oleic acid were observed. The Panel concludes, that

the carcinogenicity of the oleic acid or linoleic acid/oleic acid mixture, if any, is not relevant with respect to assessment of the candidate substances in this group.

A mixture of 29 % citronellyl acetate and 71 % geranyl acetate [FL-no: 09.012/09.011] was tested in rats and mice at dose levels of 0, 1000, and 2000 mg/kg bw/day (rats) or 0, 500 and 1000 mg/kg bw/day (mice) via gavage (NTP, 1987a). These studies showed an increase of kidney tubular cell adenomas in low dose male rats, 2/50 (4 %), but 0/50 in controls and highest dose male rats. For skin squamous cell papillomas there was an increase 4/50 (8 %) in low dose male rats, but 0/50 in controls and 1/50 in highest dose male rats. The increased tumor incidence was observed in low dose male rats and not in mice and in female rats. The authors concluded that "under the conditions of these studies, geranyl acetate was not carcinogenic for F344/N rats or $B6C3F_1$ mice of either sex; however, the reduced survival observed in high dose male rats, high dose male mice, and high and low dose female mice lowered the sensitivities of these studies for detecting neoplastic responsers in these groups. In male rats the marginal increases of squamous cell papillomas of the skin and tubular cell adenomas of the kidney may have been related to administration of geranyl acetate" (NTP, 1987a). Further, geranyl acetate, the main component of the mixture tested, was not genotoxic in a set of *in vitro* and *in vivo* tests (see Section 8.4). There were no genotoxicity studies available on citronellyl acetate. The Panel concurs the conclusions of the peer reviewed NTP study that geranyl acetate was not carcinogenic.
Repeated dose toxicity data are summarised in Annex IV, Table IV.2.

8.3. Developmental / Reproductive Toxicity Studies

No adequate developmental and reproductive toxicity studies are available for any candidate substances for the present flavouring group evaluation (see Table IV.3).

Two studies on developmental toxicity are available on a hydrolysis product, 2-ethylbutyric acid, of the candidate substance hex-3-enyl 2-ethylbutyrate [FL-no: 09.884]. Nau and Loescher (1986) studied valproic acid, and a number of metabolites of valproic acid, as well as other related substances including 2-ethylbutyric acid [FL-no: 08.045]. The substances were tested with regard to their teratogenicity in mouse following single subcutaneous injections of 600 mg/kg on day 8 of gestation. Valproic acid as well as 4-en-valproic acid and a number of substances structurally related to valproic acid induced neural tube defects with an incidence from 0 % in controls, up to 61 % of live fetuses from mice treated with valproic acid (2 % of live fetuses for 2-ethylbutyric acid) (Nau & Löscher, 1986). The study demonstrates that teratogenicity varies significantly within the group of valproic acid metabolites and structurally related substances.

Narotsky and co-workers (1994) studied the developmental effects of 2-ethylbutyric acid (and other aliphatic acids), administered by gavage to pregnant rats (Narotsky et al., 1994). Groups of pregnant Sprague-Dawley rats were given 0, 150 or 200 mg/kg bw/day of 2-ethylbutyric acid, on gestation days 6 to 15. No developmental effects could be demonstrated.

Developmental/reproductive toxicity data are summarised in Annex IV, Table IV.3.

8.4. Genotoxicity Studies

Experimental data are 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 unscheduled DNA synthesis (UDS) in rat hepatocytes or chromosomal aberration in Chinese hamster ovary (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 micronucleus 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. Data are available for one candidate substance, methyl-3-but-3-en-1-ol, which was not mutagenic in the Ames test. 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.

Genotoxicity data are summaries in Annex IV, Table IV.4 and Table IV.5.

9. Conclusions

The 48 candidate substances are straight- and branched-chain unsaturated primary alcohols, aldehydes, carboxylic acids or esters and belong to chemical groups 1 or 4.

Eight of the 48 flavouring substances possess a chiral centre [FL-no: 02.170, 02.175, 05.143, 09.341, 09.612, 09.871, 09.872 and 09.938].

Thirty-one of the 48 substances can exist as geometrical isomers [FL-no: 02.152, 02.195, 02.222, 02.234, 05.061, 05.082, 05.203, 05.217, 05.218, 05.220, 08.074, 08.102, 09.377, 09.567, 09.569, 09.572, 09.575, 09.638, 09.640, 09.643, 09.672, 09.673, 09.674, 09.831, 09.838, 09.855, 09.884, 09.885, 09.928, 09.937 and 09.939]. For 13 of these substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884, 09.885] no indication has been given that one of the possible isomers has preponderance in the commercial flavouring material.

Forty-six candidate substances are classified into structural class I. The remaining two substances [FL-no: 05.143 and 09.884] are classified into structural class II.

Thirty-eight of the flavouring substances in the present group have been reported to occur naturally in a wide range of food items.

According to the default MSDI approach, the 48 flavouring substances in this group have intakes in Europe from 0.001 to 120 microgram/*capita*/day, which are below the thresholds of concern value for

both structural class I (1800 microgram/person/day) and structural class II (540 microgram/person/day) substances.

On the basis of the reported annual production volumes in Europe (MSDI approach), the combined intake of the 46 candidate substances belonging to structural class I and of the two candidate substances belonging to structural class II would result in a total intake of approximately 255 and 0.7 microgram/*capita*/day, respectively. These values are below the thresholds of concern for structural class I and class II substances of 1800 and 540 microgram/person/day, respectively. The total combined estimated intake of 65 of the 70 supporting substances for which European annual production data are available and of the 46 candidate substances from structural class I is approximately 6700 microgram/*capita*/day, which exceeds the threshold of concern for structural class I (1800 microgram/person/day). However, the substances are expected to be efficiently metabolised and are not expected to saturate the metabolic pathways.

For the substances in this group the limited data available do not give rise to safety concern with respect to genotoxicity and carcinogenicity.

Except for hex-3-enyl 2-ethylbutyrate [FL-no: 09.884] the candidate substances are expected to be metabolised to innocuous substances at the estimated levels of use as flavouring substances. One of the hydrolysis products of [FL-no: 09.884], 2-ethylbutyric acid, showed teratogenic potential in one mouse subcutaneous single-dose study, and is structurally related to valproic acid, which is a known teratogen. However, an additional study in which 2-ethylbutyric acid was given by gavage to pregnant rats showed a NOAEL of 200 mg/kg bw/day of 2-ethylbutyric acid. This dose is more than 4×10^7 times higher than the MSDI for 2-ethylbutyric acid arising from the intake of the candidate substance, [FL-no: 09.884]. Accordingly, the candidate substance [FL-no: 09.884] does not pose a safety concern with respect to teratogenicity when used at the level of intake as flavouring substance estimated on the basis of the MSDI approach.

It was noted that where toxicity data were available they were consistent with the conclusions in the present flavouring group evaluation using the Procedure.

It is considered that on the basis of the default MSDI approach these 48 candidate substances would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

When the estimated intakes were based on the mTAMDI approach they ranged from 36 to 40000 microgram/person/day for the 45 flavouring substances from structural class I for which data have been provided. Thus, the intakes were all above the threshold of concern for structural class I of 1800 microgram/person/day, except for nine flavouring substances [FL-no: 05.061, 05.082, 05.174, 05.203, 05.217, 05.218, 05.220, 09.937 and 09.939]. The estimated intakes of the two flavouring substances assigned to structural class II, based on the mTAMDI are 1600 and 3900 microgram/person/day, which is above the threshold of concern for structural class II of 540 microgram/person/day. The nine substances [FL-no: 05.061, 05.082, 05.174, 05.203, 05.217, 05.218, 05.220, 09.937 and 09.939], which have mTAMDI intake estimates below the threshold of concern for structural class I, are also expected to be metabolised to innocuous products.

Thus, for 38 of the 48 flavouring substances considered in this Opinion, the intakes, estimated on the basis of the mTAMDI, exceed the relevant threshold for their structural class, to which the flavouring substance has been assigned. For one substance [FL-no: 09.647] no use levels were provided. Therefore, for these 39 substances more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be reconsidered along the steps of the Procedure. Subsequently, additional data might become necessary.

In order to determine whether the conclusion for the 48 candidate substances can be applied to the material of commerce, it is necessary to consider the available specifications. Adequate specifications

including complete purity criteria and identity for the materials of commerce have been provided for 46 of the 48 flavouring candidate substances. An ID test is missing for [FL-no: 09.938] and a boiling point is lacking for [FL-no: 09.674]. Otherwise the specifications are adequate for all 48 candidate substances, except that information on composition of stereoisomeric mixture has not been specified sufficiently for 13 of the substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884 and 09.885].

Thus, the final evaluation of the materials of commerce cannot be performed for 14 substances [FL-no: 02.152, 02.222, 05.061, 05.203, 05.218, 08.074, 08.102, 09.377, 09.640, 09.674, 09.831, 09.884, 09.885 and 09.938], pending further information. The remaining 34 substances [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176, 02.195, 02.201, 02.234, 05.082, 05.143, 05.174, 05.217, 05.220, 08.100, 09.341, 09.368, 09.567, 09.569, 09.572, 09.575, 09.612, 09.638, 09.643, 09.672, 09.673, 09.838, 09.855, 09.871, 09.872, 09.897, 09.898, 09.928, 09.937 and 09.939] would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 06 REVISION 2

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

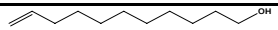
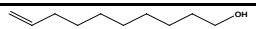
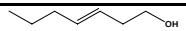
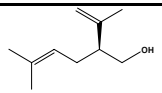
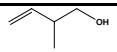
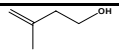
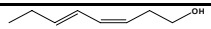
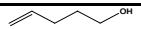
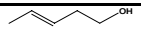
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
02.125	Undec-10-en-1-ol		10319 112-43-6	Liquid $C_{11}H_{22}O$ 170.29	Practically insoluble or insoluble 1 ml in 1 ml	245-248 MS 95 %	1.445-1.451 0.845-0.851	
02.138	Dec-9-en-1-ol		13019-22-2	Liquid $C_{10}H_{20}O$ 156.27	Practically insoluble or insoluble 1 ml in 1 ml	86 (3 hPa) MS 95 %	1.445-1.451 0.842-0.848	
02.152	Hept-3-en-1-ol	 (E)-isomer shown	10219 10606-47-0	Liquid $C_7H_{14}O$ 114.19	Practically insoluble or insoluble 1 ml in 1 ml	80 (27 hPa) MS 95 %	1.439-1.445 0.848-0.854	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
02.170	Lavandulol		498-16-8	Liquid $C_{10}H_{18}O$ 154.25	Practically insoluble or insoluble 1 ml in 1 ml	78 (7 hPa) MS 95 %	1.467-1.473 0.877-0.883	Register name to be changed to (R)-(-)-Lavandulol.
02.175	2-Methylbut-3-en-1-ol		10259 4516-90-9	Liquid $C_5H_{10}O$ 86.13	Sparingly soluble 1 ml in 1 ml	122 MS 95 %	1.421-1.427 0.841-0.847	Racemate.
02.176	3-Methylbut-3-en-1-ol		10260 763-32-6	Liquid $C_5H_{10}O$ 86.13	Sparingly soluble 1 ml in 1 ml	130 MS 95 %	1.431-1.437 0.850-0.856	
02.195	Octa-3,5-dien-1-ol		70664-96-9	Liquid $C_8H_{14}O$ 126.20	Practically insoluble or insoluble 1 ml in 1 ml	90 (24 hPa) NMR 95 %	1.457-1.463 0.865-0.871	Register name to be changed to Octa-(3Z,5E)-dien-1-ol.
02.201	Pent-4-en-1-ol		821-09-0	Liquid $C_5H_{10}O$ 86.13	Sparingly soluble 1 ml in 1 ml	137 MS 95 %	1.427-1.433 0.843-0.849	
02.222	3-Pentenol-1	 E-isomer shown	10298 39161-19-8	Liquid $C_5H_{10}O$ 86.13	Sparingly soluble 1 ml in 1 ml	134 MS 95 %	1.432-1.438 0.846-0.852	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

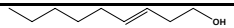
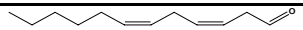
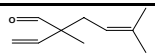
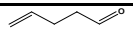
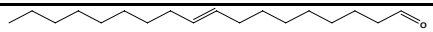
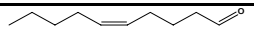
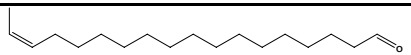
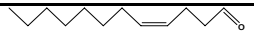
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
02.234	3-Nonen-1-ol		4412 10293 10340-23-5	Liquid $C_9H_{18}O$ 142.24	Practically insoluble or insoluble 1 ml in 1 ml	115 (33 hPa) MS 95 %	1.452-1.458 0.862-0.868	Register name to be changed to (3Z)-Nonen-1-ol (EFFA, 2010a).
05.061	Oct-6-enal	 (E)- isomer shown	664 63826-25-5	Liquid $C_8H_{14}O$ 126.20	Practically insoluble or insoluble 1 ml in 1 ml	87 (67 hPa) NMR 95 %	1.433-1.439 0.842-0.848	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
05.082	Dodeca-3,6-dienal		2121 13553-09-8	Liquid $C_{12}H_{20}O$ 180.24	Practically insoluble or insoluble 1 ml in 1 ml	226 MS 95 %	1.440-1.446 0.844-0.850	Register name to be changed to Dodeca-(3Z,6Z)-dienal (EFFA, 2010a).
05.143	2,5-Dimethyl-2-vinylhex-4-enal		56134-05-5	Liquid $C_{10}H_{16}O$ 152.24	Sparingly soluble 1 ml in 1 ml	72 (16 hPa) MS 95 %	1.452-1.458 0.845-0.851	Racemate (EFFA, 2010a).
05.174 1619	Pent-4-enal		2100-17-6	Liquid C_5H_8O 84.12	Slightly soluble 1 ml in 1 ml	103 MS 95 %	1.413-1.420 0.849-0.855	
05.203 1641	9-Octadecenal		5090-41-5	Liquid $C_{18}H_{34}O$ 266.47	Practically insoluble or insoluble 1 ml in 1 ml	168 (5 hPa) MS 95 %	1.455-1.461 0.848-0.854	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
05.217	5-Decenal		21662-08-8	Liquid $C_{10}H_{18}O$ 154.25	Practically insoluble or insoluble 1 ml in 1 ml	92 (3 hPa) MS 95 %	1.441-1.447 0.842-0.848	Register name to be changed to (5Z)-Decenal (EFFA, 2010a).
05.218	16-Octadecenal		56554-87-1	Solid $C_{18}H_{34}O$ 266.46	Practically insoluble or insoluble 1 ml in 1 ml	391 56 MS 95 %	n.a. n.a.	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
05.220 1636	4Z-Dodecenal		4036 21944-98-9	Liquid $C_{12}H_{22}O$ 182.30	Slightly soluble Very soluble	254 n.a. IR NMR MS	1.443-1.449 0.843-0.849	Known imputities: 1.06 % 4E-dodecenal, 3.66 %

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

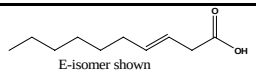
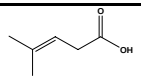
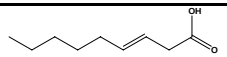
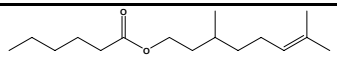
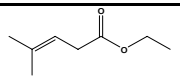
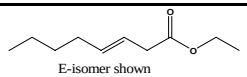
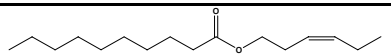
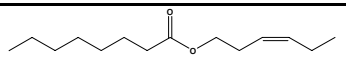
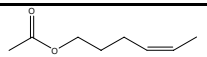
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
						94 %		dodecanal (FL-no: 05.011), 1.29 % tetradecane (FL-no: 01.057).
08.074	Dec-3-enoic acid	 E-isomer shown	10088 15469-77-9	Liquid $C_{10}H_{18}O_2$ 170.25	Practically insoluble or insoluble 1 ml in 1 ml	158 MS 95 %	1.437-1.457 0.933-0.939	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
08.100	4-Methylpent-3-enoic acid		504-85-8	Liquid $C_6H_{10}O_2$ 114.14	Sparingly soluble 1 ml in 1 ml	99 (13 hPa) MS 95 %	1.443-1.449 0.973-0.979	
08.102	Non-3-enoic acid		10154 4124-88-3	Liquid 156.22	Very slightly soluble 1 ml in 1 ml	158 (24 hPa) MS 95 %	1.445-1.451 0.925-.0931	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
09.341	Citronellyl hexanoate		10580-25-3	Liquid $C_{16}H_{30}O_2$ 254.41	Practically insoluble or insoluble 1 ml in 1 ml	240 MS 95 %	1.446-1.450 0.871-0.876	Racemate (EFFA, 2010a).
09.368	Ethyl 4-methylpent-3-enoate		10615 6849-18-9	Liquid $C_8H_{14}O_2$ 142.20	Practically insoluble or insoluble 1 ml in 1 ml	66 (23 hPa) MS 95 %	1.427-1.433 0.910-0.916	
09.377 1632	Ethyl oct-3-enoate	 E-isomer shown	4361 10618 1117-65-3	Liquid $C_{10}H_{18}O_2$ 170.25	Practically insoluble or insoluble 1 ml in 1 ml	94 (13 hPa) MS 95 %	1.431-1.439 0.903-0.910	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
09.567	Hex-3-enyl decanoate		85554-69-4	Liquid $C_{16}H_{30}O_2$ 254.41	Practically insoluble or insoluble 1 ml in 1 ml	315 MS 95 %	1.439-1.445 0.875-0.881	Register name to be changed to Hex-(3Z)-enyl decanoate.
09.569	Hex-3-enyl octanoate		61444-41-5	Liquid $C_{14}H_{26}O_2$ 226.36	Practically insoluble or insoluble 1 ml in 1 ml	286 MS 95 %	1.431-1.451 0.878-0.884	Register name to be changed to Hex-(3Z)-enyl octanoate.
09.572	Hex-4-enyl acetate		42125-17-7	Liquid $C_8H_{14}O_2$ 142.20	Practically insoluble or insoluble 1 ml in 1 ml	73 (27 hPa) MS	1.426-1.432 0.900-0.906	Register name to be changed to Hex-(4Z)-enyl acetate.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

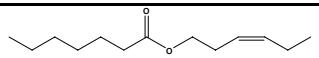
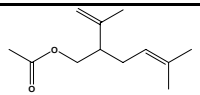
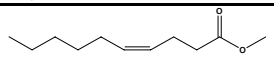
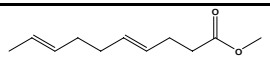
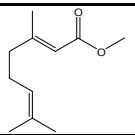
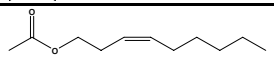
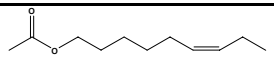
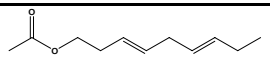
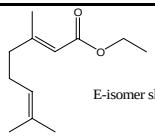
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
						95 %		
09.575	3-Hexenyl heptanoate		61444-39-1	Liquid $C_{13}H_{24}O_2$ 212.33	Practically insoluble or insoluble 1 ml in 1 ml	270 MS 95 %	1.433-1.439 0.880-0.886	Register name to be changed to (3Z)-Hexenyl heptanoate.
09.612	Lavandulyl acetate		25905-14-0	Liquid $C_{12}H_{20}O_2$ 196.29	Practically insoluble or insoluble 1 ml in 1 ml	100 (15 hPa) MS 95 %	1.453-1.459 0.909-0.915	Racemate (EFFA, 2010a).
09.638	Methyl dec-4-enoate		10784 7367-83-1	Liquid $C_{11}H_{20}O_2$ 184.28	Practically insoluble or insoluble 1 ml in 1 ml	112 (20 hPa) MS 95 %	1.438-1.444 0.891-0.897	Register name to be changed to Methyl dec-(4Z)-enoate.
09.640	Methyl deca-4,8-dienoate	 (4E, 8E)-isomer shown	10782 1191-03-3	Liquid $C_{11}H_{18}O_2$ 182.26	Practically insoluble or insoluble 1 ml in 1 ml	241 NMR 95 %	1.443-1.449 0.904-0.910	Mixture of (E,E)/(E,Z)/(Z,E)/(Z,Z) (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
09.643	Methyl geranate		10797 1189-09-9	Liquid $C_{11}H_{18}O_2$ 182.26	Insoluble 1 ml in 1 ml	97 (13 hPa) MS 95 %	1.465-1.471 0.916-0.925	
09.672	Non-3-enyl acetate		13049-88-2	Liquid $C_{11}H_{20}O_2$ 184.28	Practically insoluble or insoluble 1 ml in 1 ml	61 (0.1 hPa) MS 95 %	1.429-1.435 0.886-0.892	Register name to be changed to Non-(3Z)-enyl acetate.
09.673	Non-6-enyl acetate		76238-22-7	Liquid $C_{11}H_{20}O_2$ 184.28	Practically insoluble or insoluble 1 ml in 1 ml	90 (4 hPa) MS 95 %	1.432-1.438 0.886-0.892	Register name to be changed to Non-(6Z)-enyl acetate.
09.674	Nona-3,6-dienyl acetate 6)		76649-26-8	Liquid $C_{11}H_{18}O_2$ 182.26	Insoluble Soluble	 MS 98%	1.4410-1.4610 0.890-0.910	BP 7). (Z)- or (E)-isomer not specified by CASrn in Register.
09.831	Ethyl 3,7-dimethyl-2,6-octadienoate	 E-isomer shown	13058-12-3	Liquid $C_{12}H_{20}O_2$ 196.29	Practically insoluble or insoluble 1 ml in 1 ml	114 (13 hPa) MS 95 %	1.463-1.469 0.911-0.917	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

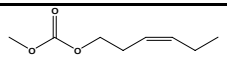
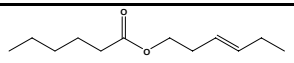
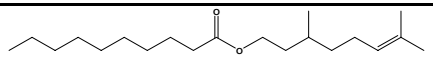
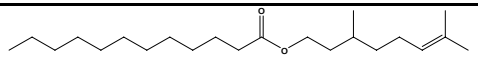
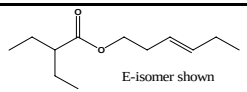
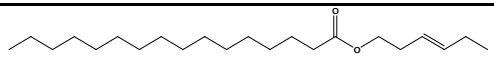
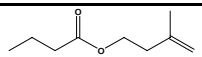
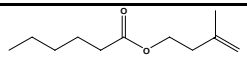
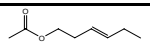
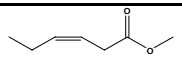
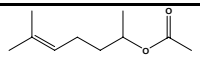
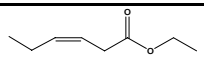
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.838	3-Hexenyl methyl carbonate		67633-96-9	Liquid $C_8H_{14}O_3$ 158.19	Slightly soluble 1 ml in 1 ml	78 (4 hPa) MS 98 %	1.426-1.430 0.966-0.971	Register name to be changed (3Z)-Hexenyl methyl carbonate.
09.855	trans-3-Hexenyl hexanoate		56922-82-8	Liquid $C_{12}H_{22}O_2$ 198.30	Practically insoluble or insoluble 1 ml in 1 ml	253 MS 95 %	1.428-1.434 0.883-0.889	
09.871	Citronellyl decanoate		72934-06-6	Liquid $C_{20}H_{38}O_2$ 310.52	Practically insoluble or insoluble 1 ml in 1 ml	202 (13 hPa) NMR 95 %	1.448-1.454 0.869-0.875	Racemate (EFFA, 2010a).
09.872	Citronellyl dodecanoate		72934-07-7	Liquid $C_{22}H_{42}O_2$ 338.57	Practically insoluble or insoluble 1 ml in 1 ml	217 (13 hPa) NMR 95 %	1.450-1.456 0.867-0.873	Racemate (EFFA, 2010a).
09.884	Hex-3-enyl-2-ethylbutyrate	 E-isomer shown	233666-04-1	Liquid $C_{12}H_{22}O_2$ 198.30	Practically insoluble or insoluble 1 ml in 1 ml	243 NMR 95 %	1.426-1.432 0.881-0.887	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
09.885	Hex-3-enyl hexadecanoate	 E-isomer shown	233666-03-0	Liquid $C_{22}H_{42}O_2$ 338.57	Practically insoluble or insoluble 1 ml in 1 ml	387 NMR 95 %	1.454-1.460 0.867-0.873	Mixture of (Z)- and (E)-isomers (EFFA, 2010a). Composition of stereoisomeric mixture to be specified.
09.897	3-Methylbut-3-en-1-yl butyrate		54702-13-5	Liquid $C_9H_{16}O_2$ 156.22	Practically insoluble or insoluble 1 ml in 1 ml	184 MS 95 %	1.439-1.445 0.886-0.892	
09.898	3-Methylbut-3-en-1-yl hexanoate		53655-22-4	Liquid $C_{11}H_{20}O_2$ 184.28	Practically insoluble or insoluble 1 ml in 1 ml	223 MS 95 %	1.453-1.458 0.877-0.883	
09.928	trans-3-Hexenyl acetate		4413 3681-82-1	Liquid $C_8H_{14}O_2$ 142.20	Practically insoluble or insoluble 1 ml in 1 ml	201 MS 97 %	1.420-1.426 0.893-0.899	
09.937 1624	Methyl (3Z)-hexenoate		13894-62-7	Liquid $C_7H_{12}O_2$ 128.17	Sparingly soluble Soluble	85 (107 hPa) MS > 95 %	1.422-1.430 0.914-0.924	

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 06 Revision 2

FL-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)	Specification comments
09.938 1838	6-Methyl-5-hepten-2-yl acetate		4177 19162-00-6	Liquid $C_{10}H_{18}O_2$ 170.25	Insoluble Soluble	184 > 97 %	1.420-1.429 0.893-0.903	ID 8). Racemate (EFFA, 2010a).
09.939 1626	Ethyl (3Z)-hexenoate		 64187-83-3	Liquid $C_8H_{14}O_2$ 142.20	Sparingly soluble Soluble	90 (67 hPa) MS > 96 %	1.420-1.429 0.893-0.903	

1) *Solubility in water, if not otherwise stated.*
2) *Solubility in 95 % ethanol, if not otherwise stated.*
3) *At 1013.25 hPa, if not otherwise stated.*
4) *At 20°C, if not otherwise stated.*
5) *At 25°C, if not otherwise stated.*
6) *Stereoisomeric composition not specified.*
7) *BP: Missing boiling point.*
8) *ID: Missing identification test.*

TABLE 2A: SUMMARY OF SAFETY EVALUATION APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH)

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

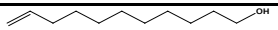
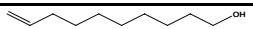
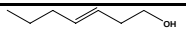
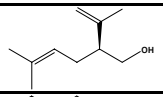
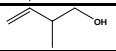
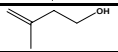
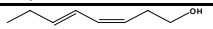
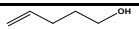
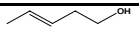
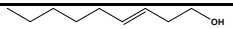
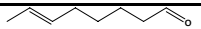
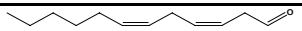
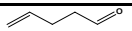
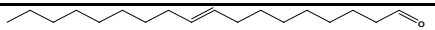
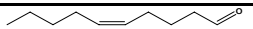
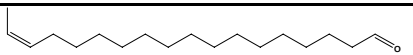
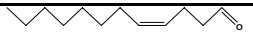
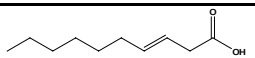
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.125	Undec-10-en-1-ol		0.37	Class I A3: Intake below threshold	4)	6)	
02.138	Dec-9-en-1-ol		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)	6)	
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		0.061	Class I A3: Intake below threshold	4)	6)	
02.201	Pent-4-en-1-ol		0.012	Class I A3: Intake below threshold	4)	6)	
02.222	3-Pentenol-1	 E-isomer shown	0.5	Class I A3: Intake below threshold	4)	7)	
02.234	3-Nonen-1-ol		0.011	Class I A3: Intake below threshold	4)	6)	
05.061	Oct-6-enal	 (E)- isomer shown	0.0012	Class I A3: Intake below threshold	4)	7)	
05.082	Dodeca-3,6-dienal		0.011	Class I A3: Intake below threshold	4)	6)	
05.174 1619	Pent-4-enal		0.11	Class I A3: Intake below threshold	4)	6)	
05.203 1641	9-Octadecenal		0.0097	Class I A3: Intake below threshold	4)	7)	
05.217	5-Decenal		0.11	Class I A3: Intake below threshold	4)	6)	
05.218	16-Octadecenal		0.011	Class I A3: Intake below threshold	4)	7)	
05.220 1636	4Z-Dodecenal		1.2	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)	

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

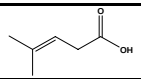
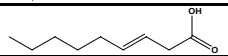
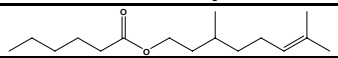
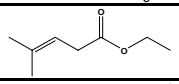
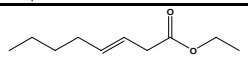
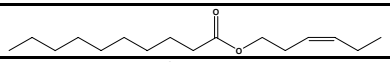
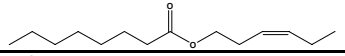
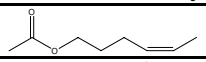
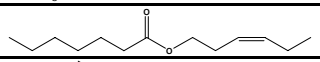
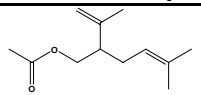
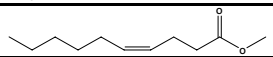
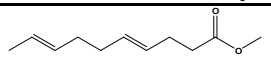
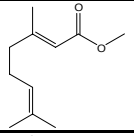
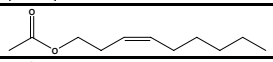
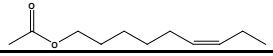
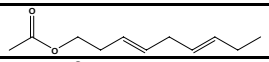
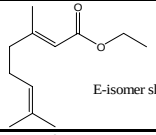
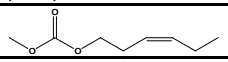
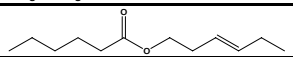
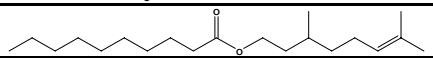
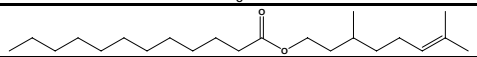
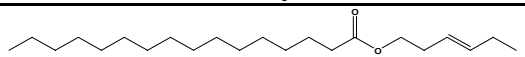
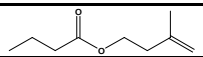
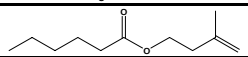
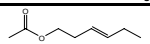
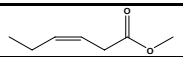
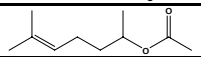
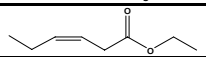
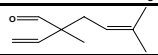
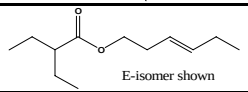
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
08.100	4-Methylpent-3-enoic acid		1.8	Class I A3: Intake below threshold	4)	6)	
08.102	Non-3-enoic acid		0.011	Class I A3: Intake below threshold	4)	7)	
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 1632	Ethyl oct-3-enoate	 E-isomer shown	0.35	Class I A3: Intake below threshold	4)	7)	
09.567	Hex-3-enyl decanoate		0.0024	Class I A3: Intake below threshold	4)	6)	
09.569	Hex-3-enyl octanoate		0.49	Class I A3: Intake below threshold	4)	6)	
09.572	Hex-4-enyl acetate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.575	3-Hexenyl heptanoate		0.61	Class I A3: Intake below threshold	4)	6)	
09.612	Lavandulyl acetate		0.012	Class I A3: Intake below threshold	4)	6)	
09.638	Methyl dec-4-enoate		0.0012	Class I A3: Intake below threshold	4)	6)	
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)	6)	
09.672	Non-3-enyl acetate		0.012	Class I A3: Intake below threshold	4)	6)	
09.673	Non-6-enyl acetate		0.12	Class I A3: Intake below threshold	4)	6)	

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

FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.674	Nona-3,6-dienyl acetate		0.0024	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)	
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)	
09.928	trans-3-Hexenyl acetate		1.8	Class I A3: Intake below threshold	4)	6)	
09.937 1624	Methyl (3Z)-hexenoate		120	Class I A3: Intake below threshold	4)	6)	
09.938 1838	6-Methyl-5-hepten-2-yl acetate		1.2	Class I A3: Intake below threshold	4)	7)	
09.939 1626	Ethyl (3Z)-hexenoate		120	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 NOAEL exists	4)	7)	

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 µg/person/day , Class II = 540 µg/person/day , Class III = 90 µg/person/day.

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

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

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

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

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

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

TABLE 2B: EVALUATION STATUS OF HYDROLYSIS PRODUCTS OF CANDIDATE ESTERS

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

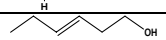
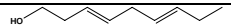
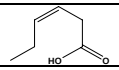
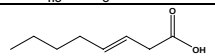
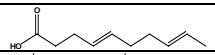
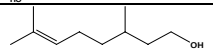
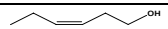
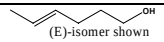
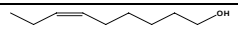
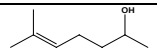
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
	Methanol CH_4O 32.04		Not evaluated as flavouring substance		Not in EU-Register
	Hex-3(trans)-en-1-ol		Not evaluated as flavouring substance		Not in EU-Register (former [FL-no: 02.158]
	3,6 Nonadienol		Not evaluated as flavouring substance		Not in EU-Register
	Hex-(3Z)-enoic acid		Not evaluated as flavouring substance		Not in EU-Register
	Oct-3-enoic acid		Not evaluated as flavouring substance		Not in EU-Register (former [FL-no: 08.105]
	Deca-4,8-dienoic acid		Not evaluated as flavouring substance		Not in EU-Register
02.011	Citronellol 1219		No safety concern a) Category A b)	Class I A3: Intake below threshold	
02.056	Hex-3(cis)-en-1-ol 315		Category 1 c) No safety concern d) Category A b)	Class I A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	
02.074	Hex-4-en-1-ol 318	 (E)-isomer shown	Category 2 c) No safety concern d) Category B b)	Class I A3: Intake below threshold	
02.078	Ethanol 41		Category 1 c) No safety concern e)	No evaluation	At the forty-sixth JECFA meeting (JECFA, 1997a), the Committee concluded that ethanol posed no safety concern at its current level of intake when ethyl esters are used as flavouring agents.
02.093	Non-6-en-1-ol 324		No safety concern d)	Class I A3: Intake below threshold	
02.124	6-Methylhept-5-en-2-ol		Category 2 c)	Class I A3: Intake below threshold	

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

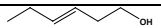
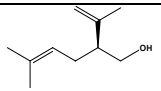
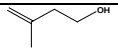
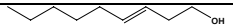
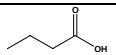
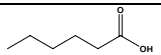
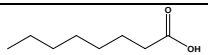
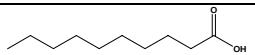
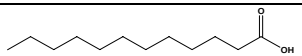
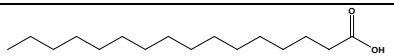
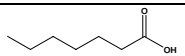
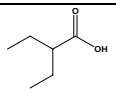
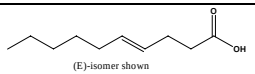
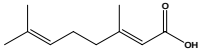
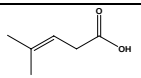
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
			FGE.07		
02.159	Hex-3-en-1-ol 315		Category A b)	No evaluation	
02.170	Lavandulol		FGE.06	Class I A3: Intake below threshold	
02.176	3-Methylbut-3-en-1-ol		FGE.06	Class I A3: Intake below threshold	
02.234	3-Nonen-1-ol		FGE.06	Class I A3: Intake below threshold	
08.002	Acetic acid 81		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake above threshold, A4: Endogenous	
08.005	Butyric acid 87		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake above threshold, A4: Endogenous	
08.009	Hexanoic acid 93		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake above threshold, A4: Endogenous	
08.010	Octanoic acid 99		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake above threshold, A4: Endogenous	
08.011	Decanoic acid 105		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake below threshold	
08.012	Dodecanoic acid 111		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake below threshold	
08.014	Hexadecanoic acid 115		Category 1 c) No safety concern f) Deleted b)	Class I A3: Intake below threshold	

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
08.028	Heptanoic acid 96		Category 1 c) No safety concern f) Category A b)	Class I A3: Intake below threshold	
08.045	2-Ethylbutyric acid 257		Category 1 c) No safety concern f) Category B b)	Class II A3: Intake below threshold	
08.075	Dec-4-enoic acid 1287	 (E)-isomer shown	No safety concern a)	Class I A3: Intake below threshold	
08.081	Geranic acid 1825			Class I A3: Intake below threshold	
08.100	4-Methylpent-3-enoic acid		FGE.06	Class I A3: Intake below threshold	

1) Category 1: Considered safe in use Category 2: Temporarily considered safe in use Category 3: Insufficient data to provide assurance of safety in use Category 4): Not acceptable due to evidence of toxicity.

2) No safety concern at estimated levels of intake.

3) Category A: Flavouring substance, which may be used in foodstuffs Category B: Flavouring substance which can be used provisionally in foodstuffs.

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

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

a) (JECFA, 2004a).

b) (CoE, 1992).

c) (SCF, 1995).

d) (JECFA, 2000a).

e) (JECFA, 1997a).

f) (JECFA, 1999b).

TABLE 3: SUPPORTING SUBSTANCES SUMMARY

Table 3: Supporting Substances Summary

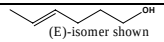
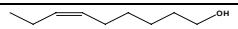
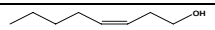
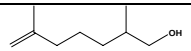
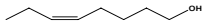
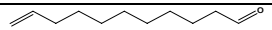
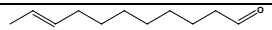
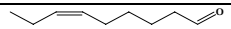
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
02.056	Hex-3(cis)-en-1-ol		2563 750c 928-96-1	315 JECFA specification (JECFA, 1998b)	3700	Category 1 a) No safety concern b) Category A c)	
02.074	Hex-4-en-1-ol	 (E)-isomer shown	3430 2295 6126-50-7	318 JECFA specification (JECFA, 1998b)	2.4	Category 2 a) No safety concern b) Category B c)	JECFA evaluated 4-hexen-1-ol (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
02.093	Non-6-en-1-ol		3465 10294 35854-86-5	324 JECFA specification (JECFA, 2000d)	2.2	No safety concern b)	JECFA evaluated cis-6-nonen-1-ol (CASrn as in Register). CASrn in Register refers to (Z)-isomer. Register name to be changed to Non-6Z-en-1-ol.
02.094	Oct-3-en-1-ol		3467 10296 20125-84-2	321 JECFA specification (JECFA, 1998b)	4.7	Category 2 a) No safety concern b)	JECFA evaluated cis-3-octen-1-ol (CASrn as in Register). CASrn in Register refers to the (Z)-isomer. Register name to be changed to Oct-3Z-en-1-ol.
02.110	2,6-Dimethylhept-6-en-1-ol		3663 36806-46-9	348 JECFA specification (JECFA, 2003b)	ND	Category 3 a) No safety concern b)	JECFA evaluated 2,6-dimethyl-6-hepten-1-ol (CASrn as in Register). (R)- or (S)-enantiomer not specified by CASrn in Register.
02.113	Oct-5(cis)-en-1-ol		3722 64275-73-6	322 JECFA specification (JECFA, 2003b)	0.4	Category 2 a) No safety concern b)	
05.035	Undec-10-enal		3095 122 112-45-8	330 JECFA specification (JECFA, 2001c)	0.32	No safety concern b) Category B c)	
05.036	Undec-9-enal	 (E)-isomer shown	3094 123 143-14-6	329 JECFA specification (JECFA, 2003b)	0.97	No safety concern b) Category A c)	JECFA evaluated 9-undecenal (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
05.059	Non-6(cis)-enal		3580 661 2277-19-2	325 JECFA specification (JECFA, 2003b)	1.7	No safety concern b) Category B c)	

Table 3: Supporting Substances Summary

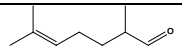
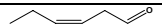
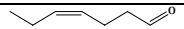
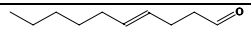
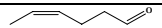
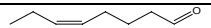
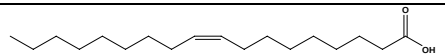
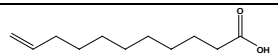
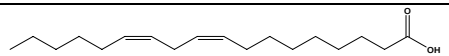
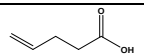
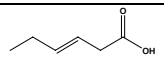
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
05.074	2,6-Dimethylhept-5-enal		2389 2006 106-72-9	349 JECFA specification (JECFA, 2003b)	27	Category 1 a) No safety concern b) Category B c)	JECFA evaluated 2,6-dimethyl-5-heptenal (CASrn as in Register). (R)- or (S)-enantiomer not specified by CASrn in Register.
05.075	Hex-3(cis)-enal		2561 2008 6789-80-6	316 JECFA specification (JECFA, 2000d)	4.1	No safety concern b) Category B c)	
05.085	Hept-4-enal	 (Z)-isomer shown	3289 2124 6728-31-0	320 JECFA specification (JECFA, 2000d)	1.6	No safety concern b) Category B c)	JECFA evaluated 4-heptenal (CASrn as in Register). CASrn in Register refers to the (Z)-isomer.
05.096	4-Decenal	 (E)-isomer shown	3264 2297 30390-50-2	326 JECFA specification (JECFA, 2001c)	0.97	No safety concern b) Category B c)	JECFA evaluated 4-decenal (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
05.113	Hex-4-enal		3496 10337 4634-89-3	319 JECFA specification (JECFA, 2000d)	0.024	No safety concern b)	JECFA evaluated cis-4-hexenal (CASrn as in Register). CASrn in Register refers to the (Z)-isomer. Register name to be changed to Hex-4Z-enal.
05.128	Oct-5(cis)-enal		3749 41547-22-2	323 JECFA specification (JECFA, 2003b)	0.0012	No safety concern b)	
08.013	Oleic acid		2815 13 112-80-1	333 JECFA specification (JECFA, 2000d)	830	Category 1 a) No safety concern b) Deleted c)	
08.039	Undec-10-enoic acid		3247 689 112-38-9	331 JECFA specification (JECFA, 1998b)	26	Category 1 a) No safety concern b) Category A c)	
08.041	Octadeca-9,12-dienoic acid		3380 694 60-33-3	332 JECFA specification (JECFA, 2003b)	110	Category 1 a) No safety concern b) Deleted c)	Register name to be changed to Linoleic acid.
08.048	Pent-4-enoic acid		2843 2004 591-80-0	314 JECFA specification (JECFA, 1998b)	3.9	No safety concern b) Category B c)	
08.050	Hex-3-enoic acid	 (E)-isomer shown	3170 2256 4219-24-3	317 JECFA specification (JECFA, 2000d)	9.4	Category 1 a) No safety concern b) Category B c)	JECFA evaluated 3-hexenoic acid (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.

Table 3: Supporting Substances Summary

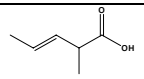
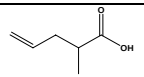
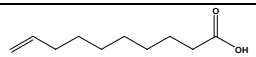
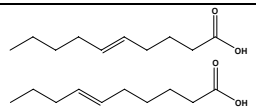
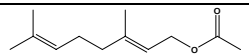
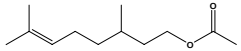
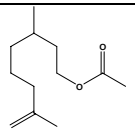
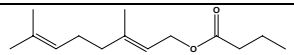
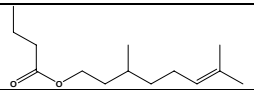
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
08.058	2-Methylpent-3-enoic acid	 (E)-isomer shown	3464 10147 37674-63-8	347 JECFA specification (JECFA, 2001c)	1.2	Category 1 a) No safety concern b)	JECFA evaluated 2-methyl-3-pentenoic-acid (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
08.059	2-Methylpent-4-enoic acid		3511 10148 1575-74-2	355 JECFA specification (JECFA, 1998b)	ND	Category N a) No safety concern b)	JECFA evaluated 2-methyl-4-pentenoic-acid (CASrn as in Register). (R)- or (S)-enantiomer not specified by CASrn in Register.
08.065	Dec-9-enoic acid		3660 10090 14436-32-9	328 JECFA specification (JECFA, 2001c)	0.097	Category 1 a) No safety concern b)	
08.068	Dec-(5- and 6)-enoic acid	 (E)-isomers shown	3742 72881-27-7	327 JECFA specification (JECFA, 2000d)	3.4	Category N a) No safety concern b)	JECFA evaluated 5 & 6-decenoic acid (mixture) (CASrn as in Register). CASrn in Register refers to incompletely defined substance.
09.011	Geranyl acetate		2509 201 105-87-3	58 JECFA specification (JECFA, 2001c)	470	No safety concern d) Category A c)	GrADI: 0-0.5 (JECFA, 1980a).
09.012	Citronellyl acetate		2311 202 150-84-5	57 JECFA specification (JECFA, 2003b). (R) or (S) enatiomer not specified by CASrn in Register	190	No safety concern d) Category A c)	GrADI: 0-0.5 (JECFA, 1980a). R- or S-enantiomer not specified by CASrn in Register.
09.033	Rhodinyl acetate		2981 223 141-11-7	60 JECFA specification (JECFA, 2003b)	0.97	No safety concern d) Deleted c)	CASrn in Register refers to 3,7-dimethyl-7-octen-1-ol-1-acetate; (R)- or (S)-enantiomer not specified by CASrn in Register. Register name corresponds to CASrn 9448-73-9; which is the (S)-enantiomer.
09.048	Geranyl butyrate		2512 274 106-29-6	66 JECFA specification (JECFA, 2003b)	52	No safety concern d) Category A c)	
09.049	Citronellyl butyrate		2312 275 141-16-2	65 JECFA specification (JECFA, 2003b)	27	No safety concern d) Category A c)	R- or S-enantiomer not specified by CASrn in Register.

Table 3: Supporting Substances Summary

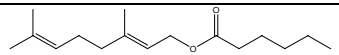
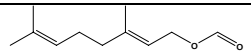
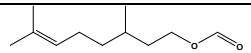
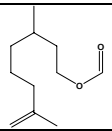
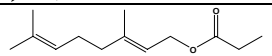
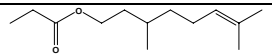
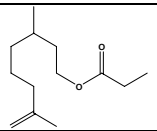
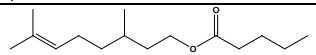
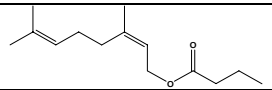
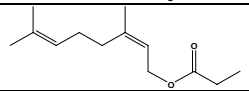
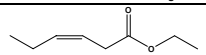
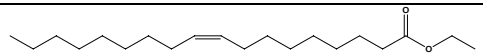
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (μg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.067	Geranyl hexanoate		2515 317 10032-02-7	70 JECFA specification (JECFA, 2001c)	0.061	No safety concern d) Category A c)	
09.076	Geranyl formate		2514 343 105-86-2	54 JECFA specification (JECFA, 2003b)	280	No safety concern d) Category A c)	
09.078	Citronellyl formate		2314 345 105-85-1	53 JECFA specification (JECFA, 2005b)	87	No safety concern d) Category A c)	GrADI: 0-0.5 (JECFA, 1980a). R- or S-enantiomer not specified by CASrn in Register.
09.079	Rhodinyl formate		2984 346 141-09-3	56 JECFA specification (JECFA, 2003b)	0.061	No safety concern d) Deleted c)	R- or S-enantiomer not specified by CASrn in Register.
09.128	Geranyl propionate		2517 409 105-90-8	62 JECFA specification (JECFA, 2003b)	69	No safety concern d) Category A c)	
09.129	Citronellyl propionate		2316 410 141-14-0	61 JECFA specification (JECFA, 2003b)	35	No safety concern d) Category A c)	R- or S-enantiomer not specified by CASrn in Register.
09.141	Rhodinyl propionate		2986 422 105-89-5	64 JECFA specification (JECFA, 2001c)	ND	No safety concern d) Deleted c)	R- or S-enantiomer not specified by CASrn in Register.
09.151	Citronellyl valerate		2317 469 7540-53-6	69 JECFA specification (JECFA, 2000d)	0.61	No safety concern d) Category A c)	R- or S-enantiomer not specified by CASrn in Register.
09.167	Neryl butyrate		2774 505 999-40-6	67 JECFA specification (JECFA, 1997b)	0.35	No safety concern d) Category B c)	
09.169	Neryl propionate		2777 509 105-91-9	63 JECFA specification (JECFA, 1997b)	3.7	No safety concern d) Category B c)	
09.191	Ethyl hex-3-enoate	 (Z)-isomer shown	3342 2396-83-0	335 JECFA specification (JECFA, 1998b)	3.2	No safety concern b)	JECFA evaluated ethyl-3-hexenoate (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
09.192	Ethyl oleate		2450 633 111-62-6	345 JECFA specification (JECFA, 1998b)	60	No safety concern b) Category A c)	

Table 3: Supporting Substances Summary

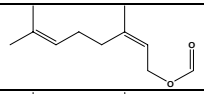
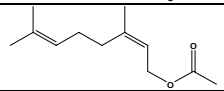
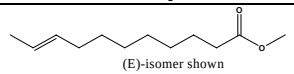
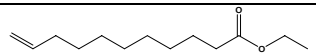
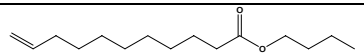
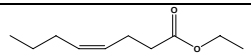
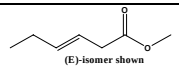
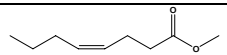
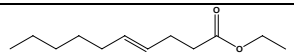
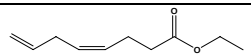
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.212	Neryl formate		2776 2060 2142-94-1	55 JECFA specification (JECFA, 2005b)	0.0061	No safety concern d) Category B c)	
09.213	Neryl acetate		2773 2061 141-12-8	59 JECFA specification (JECFA, 1997b)	150	No safety concern d) Category B c)	
09.236	Methyl undec-9-enoate	 (E)-isomer shown	2750 2101 5760-50-9	342 JECFA specification (JECFA, 2000d)	34	No safety concern b) Deleted c)	JECFA evaluated methyl 9-undecanoate (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
09.237	Ethyl undec-10-enoate		2461 10634 692-86-4	343 JECFA specification (JECFA, 1998b)	1.5	No safety concern b) Deleted c)	
09.238	Butyl undec-10-enoate		2216 2103 109-42-2	344 JECFA specification (JECFA, 2001c)	0.037	No safety concern b) Category B c)	
09.265	Ethyl oct-4-enoate		3344 10619 34495-71-1	338 JECFA specification (JECFA, 2003b)	1.2	No safety concern b)	JECFA evaluated ethyl cis-4-octenoate (CASrn as in Register). CASrn in Register refers to (Z)-isomer. Register name to be changed to Ethyl oct-4Z-enoate.
09.267	Methyl hex-3-enoate	 (E)-isomer shown	3364 10801 2396-78-3	334 JECFA specification (JECFA, 2001c)	0.56	No safety concern b)	Z- or E-isomer not specified by name and CASrn in Register.
09.268	Methyl oct-4(cis)-enoate		3367 10834 21063-71-8	337 JECFA specification (JECFA, 2003b)	0.37	No safety concern b)	
09.284	Ethyl dec-4-enoate		3642 10578 76649-16-6	341 JECFA specification (JECFA, 2000d)	1.8	No safety concern b)	JECFA evaluated ethyl trans-4-decenoate (CASrn as in Register). CASrn refers to (E)-isomer. Register name to be changed to E-Ethyl dec-4-enoate.
09.290	Ethyl octa-4,7-dienoate		3682 69925-33-3	339 JECFA specification (JECFA, 2000d)	1.8	No safety concern b)	JECFA evaluated ethyl cis-4,7-octadienoate (CASrn as in Register). CASrn in Register refers to the (Z)-isomer. Register name to be changed to Ethyl octa-

Table 3: Supporting Substances Summary

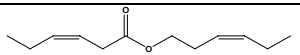
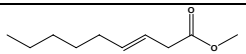
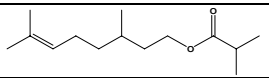
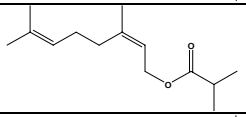
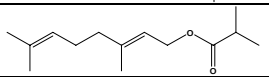
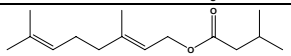
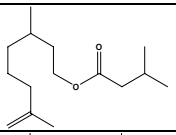
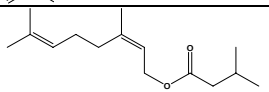
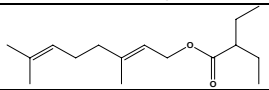
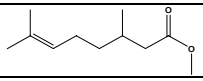
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
							4Z,7-dienoate.
09.291	Hex-3-enyl hex-3-enoate		3689 61444-38-0	336 JECFA specification (JECFA, 1998b)	3.2	No safety concern b)	JECFA evaluated cis-3-hexenyl cis-3-hexenoate (CASrn as in Register). CASrn in Register refers to the (Z)/(Z)-isomer. Register name to be changed to Hex-3Z-enyl hex-3Z-enoate.
09.298	Methyl non-3-enoate	 (E)-isomer shown	3710 13481-87-3	340 JECFA specification (JECFA, 2000d)	1.6	No safety concern b)	JECFA evaluated methyl 3-nonenoate (CASrn as in Register). (Z)- or (E)-isomer not specified by CASrn in Register.
09.421	Citronellyl isobutyrate		2313 296 97-89-2	71 JECFA specification (JECFA, 2003b)	11	No safety concern d) Category A c)	R- or S-enantiomer not specified by CASrn in Register.
09.424	Neryl isobutyrate		2775 299 2345-24-6	73 JECFA specification (JECFA, 2003b)	1.7	No safety concern d) Category B c)	
09.431	Geranyl isobutyrate		2513 306 2345-26-8	72 JECFA specification (JECFA, 2001c)	110	No safety concern d) Category B c)	
09.453	Geranyl isovalerate		2518 448 109-20-6	75 JECFA specification (JECFA, 2000d)	41	No safety concern d) Category B c)	
09.465	Rhodinyl isovalerate		2987 460 7778-96-3	77 JECFA specification (JECFA, 2001c)	0.012	No safety concern d) Deleted c)	CASrn in Register refers to 3S-enantiomer.
09.471	Neryl isovalerate		2778 508 3915-83-1	76 JECFA specification (JECFA, 1997b)	0.024	No safety concern d) Category B c)	
09.515	Geranyl 2-ethylbutyrate		3339 11667 73019-14-4	78 JECFA specification (JECFA, 2001c)	0.49	No safety concern d)	
09.517	Methyl citronellate		3361 10781 2270-60-2	354 JECFA specification (JECFA, 2000d)	0.13	No safety concern b)	R- or S-enantiomer not specified by CASrn in Register.

Table 3: Supporting Substances Summary

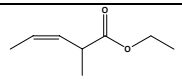
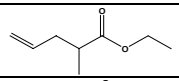
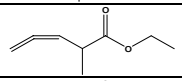
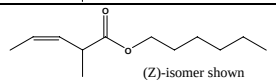
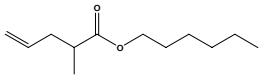
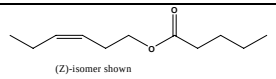
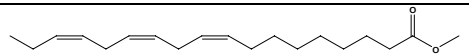
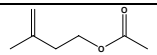
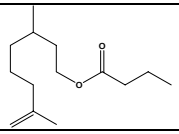
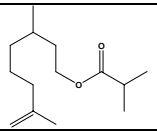
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.524	Ethyl 2-methylpent-3-enoate	 (Z)-isomer shown	3456 10612 1617-23-8	350 JECFA specification (JECFA, 2001c)	4.9	No safety concern b)	JECFA evaluated ethyl 2-methyl-3-pentenoate (CASrn as in Register). (Z)- or (E)-isomer nor (R) or (S) enantiomer not specified by Register CASrn.
09.527	Ethyl 2-methylpent-4-enoate		3489 10613 53399-81-8	351 JECFA specification (JECFA, 1998b)	0.024	No safety concern b)	(R) or (S) enantiomer not specified by Register CASrn.
09.540	Ethyl 2-methylpenta-3,4-dienoate		3678 60523-21-9	353 JECFA specification (JECFA, 2000d)	0.012	No safety concern e)	(R) or (S) enantiomer not specified by Register CASrn.
09.546	Hexyl-2-methylpent-(3 and 4)-enoate	 (Z)-isomer shown 	3693 58625-95-9	352 JECFA specification (JECFA, 2001c)	0.024	No safety concern b)	JECFA evaluated hexyl 2-methyl-3&4-pentenoate (mixture) (CASrn as in Register). Register CASrn refers to the (E)-isomer. (R) or (S) enantiomer not specified by Register CASrn.
09.571	Hex-3-enyl valerate	 (Z)-isomer shown	3936 10686 35852-46-1	1278 JECFA specification (JECFA, 2003b)	6.1	No safety concern f)	JECFA evaluated cis-3-hexenyl valerate (CASrn as in Register). Register CASrn refers to the (Z)-isomer.
09.646	Methyl linolenate		3411 714 301-00-8	346 JECFA specification (JECFA, 2003b)	ND	No safety concern b) Category A c)	JECFA evaluated a mixture of methyl linoleate and methyl linolenate (CASrn as in Register). Register CASrn refers to the (Z)/(Z)/(Z)-isomer (i.e. methyl linolenate).
09.655	3-Methylbut-3-enyl acetate		3991 5205-07-2	1269 JECFA specification (JECFA, 2003b)	7.3	No safety concern f)	
09.927	Rhodinyl butyrate		2982 141-15-1	68 JECFA specification (JECFA, 2005b)	ND	No safety concern d)	

Table 3: Supporting Substances Summary

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/*capita*/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.940	Rhodinyl isobutyrate		2983 138-23-8	74 JECFA specification (JECFA, 2001c)	0.012	No safety concern d)	JECFA CASrn 1338-23-8 not valid.

1) EU 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) Category 1: Considered safe in use, Category 2: Temporarily considered safe in use, Category 3: Insufficient data to provide assurance of safety in use, Category 4: Not acceptable due to evidence of toxicity.

3) No safety concern at estimated levels of intake.

4) Category A: Flavouring substance, which may be used in foodstuffs, Category B: Flavouring substance which can be used provisionally in foodstuffs.

a) (SCF, 1995).

b) (JECFA, 2000a).

c) (CoE, 1992).

d) (JECFA, 1999b).

e) (JECFA, 2007c).

f) (JECFA, 2004a).

ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), named the "Procedure", is shown in schematic form in Figure I.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999a), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b).

The Procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II, III) for which thresholds of concern (human exposure thresholds) have been specified. Exposures below these thresholds are not considered to present a safety concern.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1800, 540 or 90 microgram/person/day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996a).

In Step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- can the flavourings be predicted to be metabolised to innocuous products[8] (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous[9] (Step A4)?
- does a NOAEL exist on the flavourings or on structurally related substances (Step A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure.

The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

[8] *"Innocuous metabolic products": Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent" (JECFA, 1997a).*

[9] *"Endogenous substances": Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997a).*

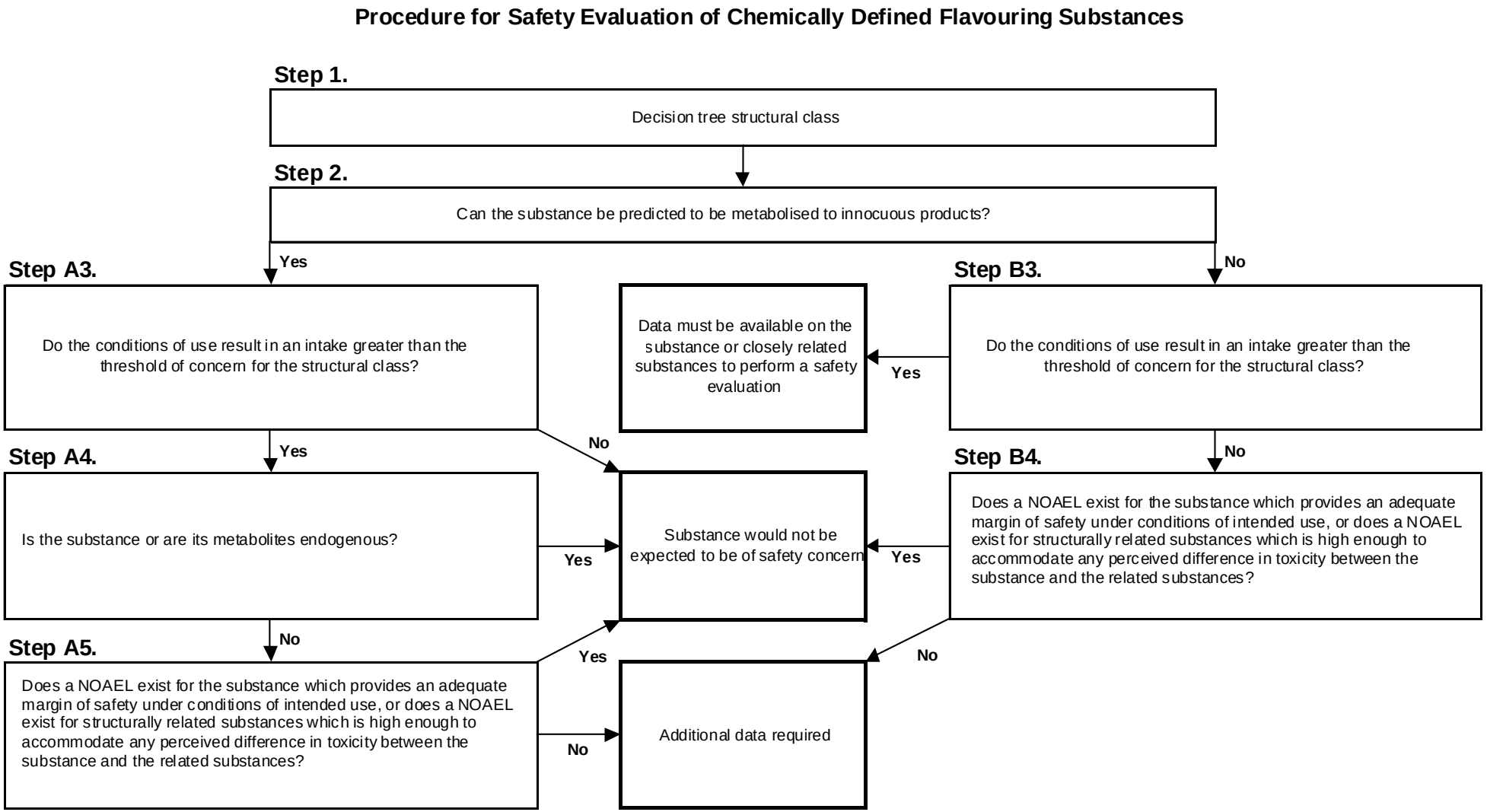


Figure I.1 *Procedure for SafetyE valuation of Chemically Defined Flavouring Substances*

ANNEX II: USE LEVELS / MTAMDI

II.1 Normal and Maximum Use Levels

For each of the 18 Food categories (Table II.1.1) in which the candidate substances are used, Flavour Industry reports a "normal use level" and a "maximum use level" (EC, 2000a). According to the Industry the "normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

Table II.1.1 Food categories according to Commission Regulation (EC) No 1565/2000 (EC, 2000a)

Food category	Description
01.0	Dairy products, excluding products of category 02.0
02.0	Fats and oils, and fat emulsions (type water-in-oil)
03.0	Edible ices, including sherbet and sorbet
04.1	Processed fruit
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds
05.0	Confectionery
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery
07.0	Bakery wares
08.0	Meat and meat products, including poultry and game
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms
10.0	Eggs and egg products
11.0	Sweeteners, including honey
12.0	Salts, spices, soups, sauces, salads, protein products, etc.
13.0	Foodstuffs intended for particular nutritional uses
14.1	Non-alcoholic ("soft") beverages, excl. dairy products
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts
15.0	Ready-to-eat savouries
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0

The "normal and maximum use levels" are provided by Industry for 47 of the 48 candidate substances in the present flavouring group (Table II.1.2).

Table II.1.2 Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.06Rev2 (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a).

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
02.125	-	-	4	-	-	4	-	-	-	-	-	-	-	-	4	4	-	-
	-	-	10	-	-	10	-	-	-	-	-	-	-	-	10	10	-	-
02.138	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.152	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.170	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.175	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.176	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.195	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.201	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
02.222	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25

Table II.1.2 Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.06Rev2 (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a).

FL-no	Food Categories																	
	Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	**02.0**	**03.0**	**04.1**	**04.2**	**05.0**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
02.234	7 35	5 25	10 50	7 35	- -	10 50	- -	5 25	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
05.061	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.082	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.143	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	- -	- -	2 10	4 20	3 15	2 10
05.174	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.203	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.217	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.218	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
05.220	0,05 0,16	- -	0,08 0,16	0,04 0,08	- -	0,1 8	0,1 0,2	0,1 0,2	- -	- -	- -	- -	- -	- -	0,05 0,1	0,08 0,16	0,1 0,2	- -
08.074	3 15	2 10	3 15	2 10	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	3 15	10 50	15 75	5 25
08.100	3 15	2 10	3 15	2 10	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	3 15	10 50	15 75	5 25
08.102	3 15	2 10	3 15	2 10	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	3 15	10 50	15 75	5 25
09.341	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.368	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.377	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.567	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.569	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.572	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.575	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.612	7 35	2 10	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.638	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.640	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.643	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.672	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.673	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.831	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.838	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.855	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.871	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.872	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.884	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.885	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.897	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25

Table II.1.2 Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.06Rev2 (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a).

FL-no	Food Categories																	
	Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	**02.0**	**03.0**	**04.1**	**04.2**	**05.0**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.1**	**14.2**	**15.0**	**16.0**
09.898	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
09.928	7	5	10	7	7	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	35	50	25	50	10	10	-	-	25	50	25	50	100	25
09.937	0,02	0,02	0,2	0,02	0,02	2	0,4	0,2	0,02	0,02	-	-	0,02	-	2	2	0,02	0,02
	0,4	0,4	4	0,4	0,4	40	8	4	0,4	0,4	-	-	0,4	-	40	40	0,4	0,4
09.938	1	1	10	1	1	100	20	10	1	1	-	-	1	-	100	100	1	1
	5	5	50	5	5	500	100	50	5	5	-	-	5	-	500	500	5	5
09.939	0,02	0,2	0,2	0,02	0,02	2	0,4	0,2	0,02	0,02	-	-	0,02	-	2	2	0,02	0,02
	0,4	0,4	4	0,4	0,4	40	8	4	0,4	0,4	-	-	0,4	-	40	40	0,4	0,4

II.2 mTAMDI Calculations

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amount of flavourable foods and beverages listed in Table II.2.1. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

Table II.2.1 Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995)

Class of product category	Intake estimate (g/day)
Beverages (non-alcoholic)	324.0
Foods	133.4
Exception a: Candy, confectionery	27.0
Exception b: Condiments, seasonings	20.0
Exception c: Alcoholic beverages	20.0
Exception d: Soups, savouries	20.0
Exception e: Others, e.g. chewing gum	e.g. 2.0 (chewing gum)

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 (EC, 2000a) and reported by the Flavour Industry in the following way (see Table II.2.2):

- Beverages (SCF, 1995) correspond to food category 14.1 (EC, 2000a)
- Foods (SCF, 1995) correspond to the food categories 1, 2, 3, 4.1, 4.2, 6, 7, 8, 9, 10, 13, and/or 16 (EC, 2000a)
- Exception a (SCF, 1995) corresponds to food category 5 and 11 (EC, 2000a)
- Exception b (SCF, 1995) corresponds to food category 15 (EC, 2000a)
- Exception c (SCF, 1995) corresponds to food category 14.2 (EC, 2000a)
- Exception d (SCF, 1995) corresponds to food category 12 (EC, 2000a)
- Exception e (SCF, 1995) corresponds to others, e.g. chewing gum.

Table II.2.2 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995)

	Food categories according to Commission Regulation 1565/2000	Distribution of the seven SCF food categories		
Key	Food category	Food	Beverages	Exceptions
01.0	Dairy products, excluding products of category 02.0	Food		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03.0	Edible ices, including sherbet and sorbet	Food		
04.1	Processed fruit	Food		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Food		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07.0	Bakery wares	Food		
08.0	Meat and meat products, including poultry and game	Food		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10.0	Eggs and egg products	Food		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Food		
14.1	Non-alcoholic ("soft") beverages, excl. dairy products		Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts			Exception c
15.0	Ready-to-eat savouries			Exception b
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0	Food		

The mTAMDI values (see Table II.2.3) are presented for each of the 47 flavouring substances in the present flavouring group, for which Industry has provided use and use levels (EFFA, 2001c; EFFA, 2002a; EFFA, 2004v; EFFA, 2006d; EFFA, 2007a; Flavour Industry, 2004a). The mTAMDI values are only given for the highest reported normal use levels.

TableII.2.3 Estimated intakes based on the mTAMDI approach

FL-no	EU Register name	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.125	Undec-10-en-1-ol	3900	Class I	1800
02.138	Dec-9-en-1-ol	3900	Class I	1800
02.152	Hept-3-en-1-ol	3900	Class I	1800
02.170	Lavandulol	3900	Class I	1800
02.175	2-Methylbut-3-en-1-ol	3900	Class I	1800
02.176	3-Methylbut-3-en-1-ol	3900	Class I	1800
02.195	Octa-3,5-dien-1-ol	3900	Class I	1800
02.201	Pent-4-en-1-ol	3900	Class I	1800
02.222	3-Pentenol-1	3900	Class I	1800
02.234	3-Nonen-1-ol	3900	Class I	1800
05.061	Oct-6-enal	1600	Class I	1800
05.082	Dodeca-3,6-dienal	1600	Class I	1800
05.174	Pent-4-enal	1600	Class I	1800
05.203	9-Octadecenal	1600	Class I	1800
05.217	5-Decenal	1600	Class I	1800
05.218	16-Octadecenal	1600	Class I	1800
05.220	4Z-Dodecenal	36	Class I	1800
08.074	Dec-3-enoic acid	3200	Class I	1800
08.100	4-Methylpent-3-enoic acid	3200	Class I	1800
08.102	Non-3-enoic acid	3200	Class I	1800
09.341	Citronellyl hexanoate	3900	Class I	1800
09.368	Ethyl 4-methylpent-3-enoate	3900	Class I	1800
09.377	Ethyl oct-3-enoate	3900	Class I	1800
09.567	Hex-3-enyl decanoate	3900	Class I	1800
09.569	Hex-3-enyl octanoate	3900	Class I	1800
09.572	Hex-4-enyl acetate	3900	Class I	1800
09.575	3-Hexenyl heptanoate	3900	Class I	1800
09.612	Lavandulyl acetate	3900	Class I	1800

09.638	Methyl dec-4-enoate	3900	Class I	1800
09.640	Methyl deca-4,8-dienoate	3900	Class I	1800
09.643	Methyl geranate	3900	Class I	1800
09.672	Non-3-enyl acetate	3900	Class I	1800
09.673	Non-6-enyl acetate	3900	Class I	1800
09.674	Nona-3,6-dienyl acetate		Class I	1800
09.831	Ethyl 3,7-dimethyl-2,6-octadienoate	3900	Class I	1800
09.838	3-Hexenyl methyl carbonate	3900	Class I	1800
09.855	trans-3-Hexenyl hexanoate	3900	Class I	1800
09.871	Citronellyl decanoate	3900	Class I	1800
09.872	Citronellyl dodecanoate	3900	Class I	1800
09.885	Hex-3-enyl hexadecanoate	3900	Class I	1800
09.897	3-Methylbut-3-en-1-yl butyrate	3900	Class I	1800
09.898	3-Methylbut-3-en-1-yl hexanoate	3900	Class I	1800
09.928	trans-3-Hexenyl acetate	3900	Class I	1800
09.937	Methyl (3Z)-hexenoate	800	Class I	1800
09.938	6-Methyl-5-hepten-2-yl acetate	40000	Class I	1800
09.939	Ethyl (3Z)-hexenoate	800	Class I	1800
05.143	2,5-Dimethyl-2-vinylhex-4-enal	1600	Class II	540
09.884	Hex-3-enyl-2-ethylbutyrate	3900	Class II	540

ANNEX III: METABOLISM

III.1. Introduction

The present FGE consists of 48 straight- and branched-chain unsaturated primary alcohols, aldehydes, carboxylic acids and esters.

Groups with 70 related supporting substances has been evaluated by the JECFA (JECFA, 1998a; JECFA, 1999a; JECFA, 2004b)

III.2. Absorption, Distribution and Elimination

Specific information regarding absorption, distribution, metabolism and excretion is not available for any of the candidate substances.

However, in general, short chain (< C8) linear and branched-chain saturated/unsaturated aliphatic esters, alcohols, aldehydes and carboxylic acids are absorbed from the gastrointestinal tract (JECFA, 2000a; Dawson et al., 1964b; Gaillard & Derache, 1965). Long-chain carboxylic acids, such as linoleic acid and oleic acid, are readily absorbed from micelles in the jejunum, re-esterified with glycerol in chylomicrons and transported via the lymphatic system (Borgström, 1974). Radiolabeled linoleic and oleic acids have been administered by different routes to a variety of mammals and humans, demonstrating that fatty acid uptake occurs in all tissues, including the brain, by passive/facilitated diffusion and/or active transport (Dhopeshwarkar & Mead, 1973; Harris et al., 1980; Abumrad et al., 1984; Schulthess et al., 2000). Large lipid soluble organic molecules are absorbed by passive diffusion across hydrofobic domains in cell membranes (Klaassen, 1996).

A more detailed discussion follows on metabolism of linear saturated/unsaturated primary alcohols, aldehydes and carboxylic acids, and branched-chain unsaturated primary alcohols, aldehydes, and carboxylic acids.

A relevant discussion of the general aspects of metabolism for these types of substances may be found in FAO/WHO JECFA 42/51 (JECFA, 2000a).

III.3. Metabolism

III.3.1. Hydrolysis of Esters *in vitro*

Aliphatic esters are hydrolysed to the component alcohols and carboxylic acids as shown in Figure III.1. The carboxylesterase or esterase classes of enzymes, the most important of which are the beta-esterases, catalyse ester hydrolysis (Heymann, 1980). In mammals, these enzymes occur throughout the body in most tissues (Heymann, 1980), but predominate in the hepatocytes (Heymann, 1980). The substrate specificity of beta-carboxylesterase isoenzymes has been correlated with the structure of the alcohol and carboxylic acid components (i.e. R and R', see Figure III.1) (Heymann, 1980).

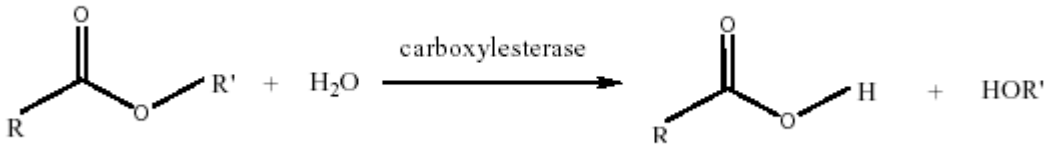


Figure III.1. *Ester hydrolysis.*

In vitro hydrolysis studies of various esters have been performed with specific carboxylesterase isoenzymes isolated from pig and rat livers (Junge & Heymann, 1979; Arndt & Krisch, 1973). Different isoenzymes showed large differences in hydrolysis rates, pending on the chain length of carboxyl and alcohol moiety. The authors concluded that it appears reasonable to assume a coorperative and complementary function of the different carboxylesterase enzymes in the hydrolysis of the various esters (Junge & Heymann, 1979).

In vitro hydrolysis data have been reported for structurally related esters of saturated linear and branched-chain carboxylic acids. Butyl acetate, ethyl butyrate, ethyl heptanoate, ethyl nonanoate and ethyl laurate were 10 to 37 % hydrolysed in artificial gastric juice (pH 1.2 at 37 °C) in two hours, and 72 to 100 % hydrolysed in artificial pancreatic juice (pH 7.5 at 37 °C) in one to two hours (Gangolli & Shilling, 1968). The half-lives of ethyl butyrate, ethyl heptanoate and ethyl laurate are in the range from 490 to 770 minutes in artificial gastric juice and from approximately 5.7 to 9.8 minutes in artificial pancreatic juice (Longland et al., 1977). The half-lives of butyl acetate, isoamyl butyrate, ethyl hexanoate, and ethyl heptanoate were 0.0491 to 0.492 seconds in rat liver tissue preparations and 0.0108 to 0.550 seconds in rat small intestinal mucosa (Longland et al., 1977). A concentration of 15 microlitre citronellyl acetate/l was reported to be completely hydrolysed within two hours by simulated intestinal fluid containing pancreatin (Grundschober, 1977). A concentration of < 18 microlitre citronellyl phenylacetate/l was reported to be 60 % hydrolysed within two hours (Grundschober, 1977).

Generally hydrolysis appears to be faster in homogenates from rat liver and intestinal mucosa than in artificial gastric and pancreatic juices (Longland et al., 1977).

An *in vitro* hydrolysis study on carbonate esters of alpha-, beta-naphtol and p-nitrophenol showed that carbonate esters are also hydrolysed by liver carboxyl esterase from human, rat and mouse (Huang et al., 1993).

In vitro hydrolysis data from studies with esters related to the candidate substances, indicate that the esters included in this evaluation can be hydrolysed in the gut to yield the corresponding alcohols and carboxylic acids of the esters prior to absorption or in the liver following absorption (Grundschober, 1977; Longland et al., 1977; Gangolli & Shilling, 1968; Leegwater & Straten, 1974a).

III.3.2. Metabolism of Linear Saturated/Unsaturated Primary Alcohols, Aldehydes and Carboxylic acids

The alcohols formed via ester or acetal hydrolysis are subsequently oxidized to the corresponding aldehydes (formed by the oxidation of alcohols to their corresponding aldehydes), which are efficiently oxidized to the corresponding saturated/unsaturated carboxylic acids by high capacity enzyme pathways. Isoenzyme mixtures of NAD^+/NADH-dependent alcohol dehydrogenase (ADH) obtained from human liver microsomes have been reported to catalyse oxidation of linear primary aliphatic saturated/unsaturated alcohols (Pietruszko et al., 1973). A comparison of the alcohol structure with enzyme binding affinity of ADH indicates that increased binding (lower K_m) occurs with increasing chain length (i.e. C1 to C6) of the substrate and the presence of unsaturation. However, maximum reaction rates of oxidation are essentially constant regardless of the alcohol structure suggesting that alcohol-enzyme binding is not the rate limiting

step for oxidation; rather, the activity of this enzyme appears to be dependent upon the lipophilic character of the alcohol substrate (Klesov et al., 1977).

Similarly, aldehyde dehydrogenase (ALDH) present predominantly in hepatic cytosol exhibits broad specificity for oxidation of aldehydes (Feldman & Weiner, 1972; Eckfeldt & Yonetani, 1982). ALDH is more active for higher molecular weight aldehydes (Nakayasu et al., 1978). Xanthine oxidase and aldehyde oxidase also catalyse oxidation of a wide range of aldehydes to the corresponding unsaturated carboxylic acids (Beedham, 1988).

At elevated levels of exposure and prior to oxidation to the corresponding carboxylic acid, the aldehyde may conjugate with sulphydryl groups such as glutathione to yield thiohemiacetals. Oxidation of low molecular weight aldehydes requires glutathione which implies that the substrate for ALDH-mediated oxidation may be the thiohemiacetal (Brabec, 1993).

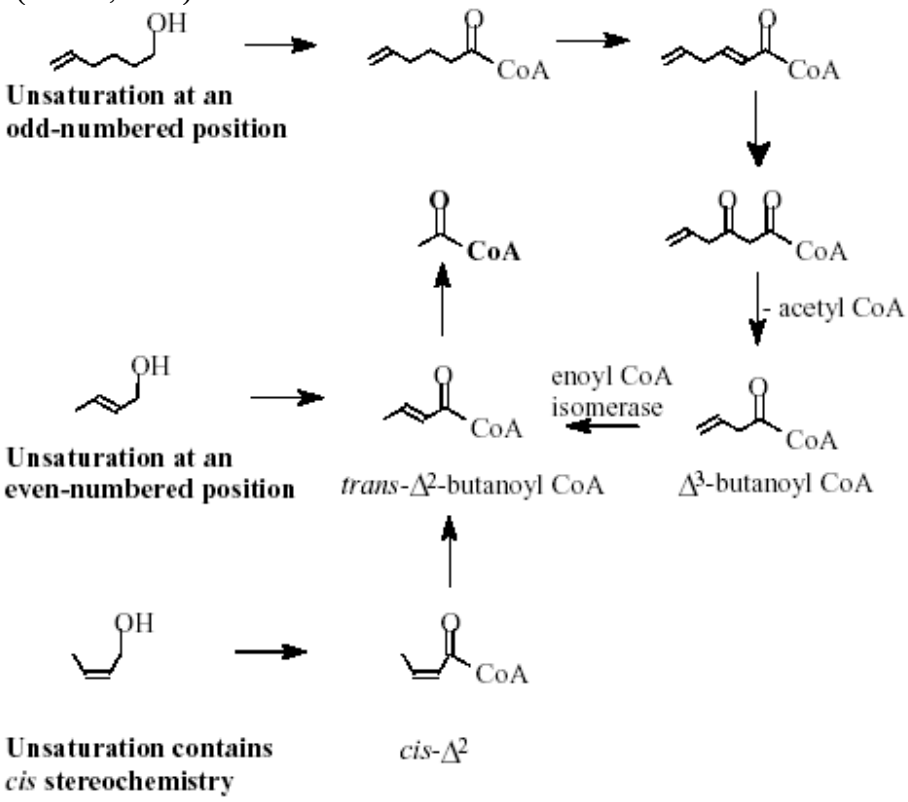


Figure III.2. *Metabolism of linear unsaturated carboxylic acid,*

The resulting linear saturated/unsaturated carboxylic acids participate in normal fatty acid metabolism (Figure III.2). In this pathway, the carboxylic acid is condensed with coenzyme A (CoA) followed by catalytic dehydrogenation mediated by acyl CoA dehydrogenase (Voet & Voet, 1990). The resulting trans-2,3-unsaturated ester (trans-delta^2-enoyl CoA) is converted to the 3-ketothioester, which undergoes beta-cleavage to yield an acetyl CoA fragment and a new thioester reduced by two carbons.

Cleavage of acetyl CoA units will continue along the carbon chain until the position of unsaturation is reached. If the unsaturation begins at an odd-numbered carbon, acetyl CoA fragmentation will eventually yield a delta^3-enoyl CoA, which cannot enter the fatty acid cycle until it is isomerised to the trans-delta^2-enoyl CoA by enoyl CoA isomerase. If unsaturation begins at an even-numbered carbon, acetyl CoA fragmentation yields a delta^2-enoyl CoA product, which is a substrate for further fatty acid oxidation. If the stereochemistry of the double bond is cis, it is isomerised to the trans double bond by the action of 3-

hydroxyacyl CoA epimerase prior to entering the fatty acid oxidation pathway. Even-numbered carbon acids continue to be cleaved to acetyl CoA while odd-numbered carbon acids yield acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly while propionyl CoA is transformed into succinyl CoA that then enters the citric acid cycle.

Alternate minor metabolic pathways have been characterised for linear long-chain fatty acids and short-chain carboxylic acids containing unsaturation. While linoleic and oleic acids participate in beta-oxidation and normal fatty acid metabolism in most tissues (Masoro, 1977), they may undergo omega-oxidation in the liver and alpha-oxidation in the brain (Wakil & Barnes, 1971; Gibson et al., 1982).

Unsaturated short-chain carboxylic acids may be metabolised via saturation to yield a substrate that may participate in the fatty acid pathway. For example, the mechanism for oxidative metabolism of 4-pentenoic acid has been studied in rat heart mitochondria. *In vitro* 4-pentenoic acid is converted to the CoA thioester, which is dehydrogenated to yield the trans-2,4-pentadienoyl CoA (Figure III.3). Two enzyme-catalysed processes then compete for this conjugated thioester. In the first pathway, NADPH-dependent enzyme-catalysed reduction of the delta^4-alkene leads to trans-2-pentenoic acid. The second pathway involves beta-oxidation to yield 3-keto-4-pentenoyl CoA. *In vitro* hydrogenation predominates to yield trans-2-pentenoic acid, which then participates in normal fatty acid oxidation (Schulz, 1983).

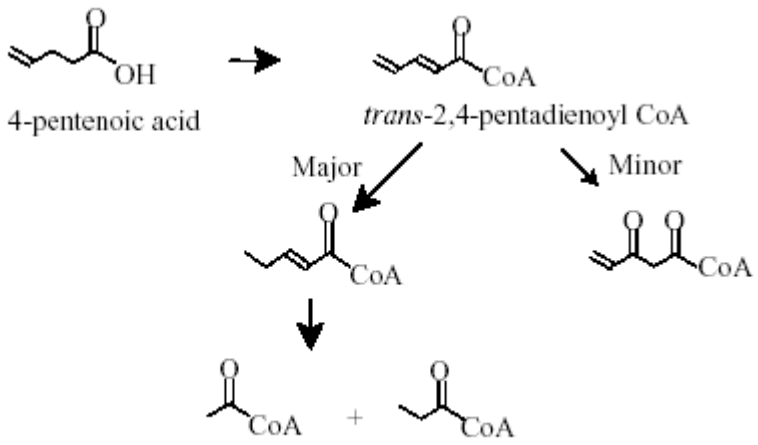


Figure III.3. *Metabolism of 4-pentenoic acid.*

III.3.3. Metabolism of Branched-chain Unsaturated Primary Alcohols, Aldehydes and Carboxylic Acids

Generally, branched-chain aliphatic alcohols are oxidized to the corresponding aldehydes, which in turn are oxidized to the corresponding carboxylic acids (Bosron & Li, 1980; Levi & Hodgson, 1989). Branched-chain aliphatic alcohols and aldehydes have been reported to be substrates for ADH (Hedlund & Kiessling, 1969a; Albro, 1975) and ALDH (Hedlund & Kiessling, 1969a), respectively. As carbon chain length increases, the substrate-enzyme binding affinity with ADH (Pietruszko et al., 1973) and the rates of ALDH-mediated oxidation also increase (Nakayasu et al., 1978).

Similar to their saturated analogs, unsaturated branched-chain aliphatic alcohols and aldehydes are converted by the pathways cited above to the corresponding carboxylic acids, which participate in the normal fatty acid metabolism (Voet & Voet, 1990).

Alternatively, they may undergo a combination of omega, omega-1, and beta-oxidation to yield polar metabolites, which are excreted as such or as glucuronic acid conjugates in the urine (Diliberto et al., 1990).

The principal metabolic pathways utilized for metabolisation of these branched-chain substances are determined primarily by four structural characteristics: carbon chain length, position of alkyl substituents, number of alkyl substituents and size of alkyl substituents.

Short-chain (< C6) branched aliphatic carboxylic acids undergo beta-oxidation, preferentially in the longer chain. Beta-cleavage of the branched aliphatic carboxylic acids yields linear carboxylic acid fragments, which are sources of carbon in the fatty acid metabolism pathway or tricarboxylic acid cycle (Voet & Voet, 1990). For example, a single oral dose of 4.5, 45, or 450 mg/kg [1-^{14}C]-isobutyric acid given to male Charles River CD rats by gavage was rapidly eliminated in the breath as expired $^{14}CO_2$. Within 24 hours of dosing, 77, 78, or 83 % of the 4.5, 45, or 450 mg/kg dose, respectively, was eliminated as CO_2 (DiVincenzo & Hamilton, 1979).

Methyl methacrylate given to rats by gavage was also eliminated mainly as CO_2 (Bratt & Hathway, 1977).
The hydrolysis of one candidate substance hex-3-enyl-2-ethylburtyrate [FL-no: 09.884] generates 2-ethylbutyric acid [FL-no: 08.045], which has some teratogenic potential (see Section 8.3). Although the 2-ethyl-branched acid is resistant to beta-oxidation, it can be further conjugated with glucuronic acid or undergo omega-oxidation. However, the candidate substance [FL-no: 09.884] cannot be anticipated to be metabolised to an innocuous product.

Terminal double bonds appear in eleven candidate substances [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176, 02.201, 05.143, 05.174, 09.612, 09.897 and 09.898]. Of these, six are unsaturated alcohols [FL-no: 02.125, 02.138, 02.170, 02.175, 02.176 and 02.201] two are unsaturated aldehydes [FL-no: 05.143 and 05.174], and three are unsaturated esters [FL-no: 09.612, 09.897, and 09.898]. These double bonds may be oxidized to the corresponding epoxides. Epoxides are highly reactive molecules, due to the large strain associated with the three membered ring structure, and they react easily with nucleophilic sites of cellular macromolecules. For this reason, several aliphatic alkene-derived epoxides have been demonstrated to be carcinogenic (e.g. ethylene, isoprene, butadiene, glycidol) (Melnick, 2002). Alternatively, epoxides can be conjugated with glutathione (GSH) by glutathione S-tansferases (GSTs) or hydrolysed to diols by epoxide hydrolases (EHs). The latter two reactions can be considered to be detoxifications.

It has been demonstrated that terminal double bonds may be oxidized at the double bond to give the corresponding epoxide or, alternatively, at the allylic carbon to give the allylic alcohol, as was demonstrated with 1-hexene with rat and human P450s (Chiappe et al., 1998). The ratio of epoxidation over allylic oxidation, as measured with different P450 isoforms (CYP) is ≥1, indicating that epoxide formation is generally favoured (Chiappe et al., 1998). Theoretically these pathways could occur with the candidate substances [FL-no: 02.125, 02.138, 02.175, 02.201, 06.143 and 05.174].

In the same paper (Chiappe et al., 1998) it was demonstrated that the biotransformation of 2-methyl-1-hexene proceeds exclusively via the epoxide, which was further hydrolysed by EH to the diol. This pathway might apply to the alcohols [FL-no: 02.170 and 02.176] and to the alcohol moiety of [FL-no: 09.612, 09.897 and 09.898]

However, the risk associated with the epoxidation of the terminal double bond of these candidate substances is expected to be low for several reasons:

1) epoxides can be metabolised by conjugation with glutathione or by epoxide-hydrolase mediated hydrolysis.
2) The terminal double bonds are all present in molecules that have alcohol- or aldehyde functions at the end distal from the double bond, or that are alcohol moieties of esters. The alcohol- and aldehyde functions can be expected to be readily attacked by oxidation processes, ultimately yielding unsaturated carboxylic acids, and also hydrolysis of the esters would yield the unsaturated alcohols, which will be oxidised to carboxylic acids. Biochemical attack of these

carboxylic acids via e.g. beta-oxidation or conjugation with glucuronic acid is expected to be much more efficient and rapid than microsomal oxidation.

Rats metabolised geraniol and citral (unsaturated branched-chain alcohol and aldehyde, respectively) largely via omega-oxidation to yield a mixture of diacids and hydroxy acids (Diliberto et al., 1990; Chadha & Madyastha, 1984). Geraniol related terpenoid alcohols (citronellol and nerol), and the aldehydes (geranial, citronellal and neral) exhibit similar pathways of metabolic metabolisation in animals (Figure III.4).

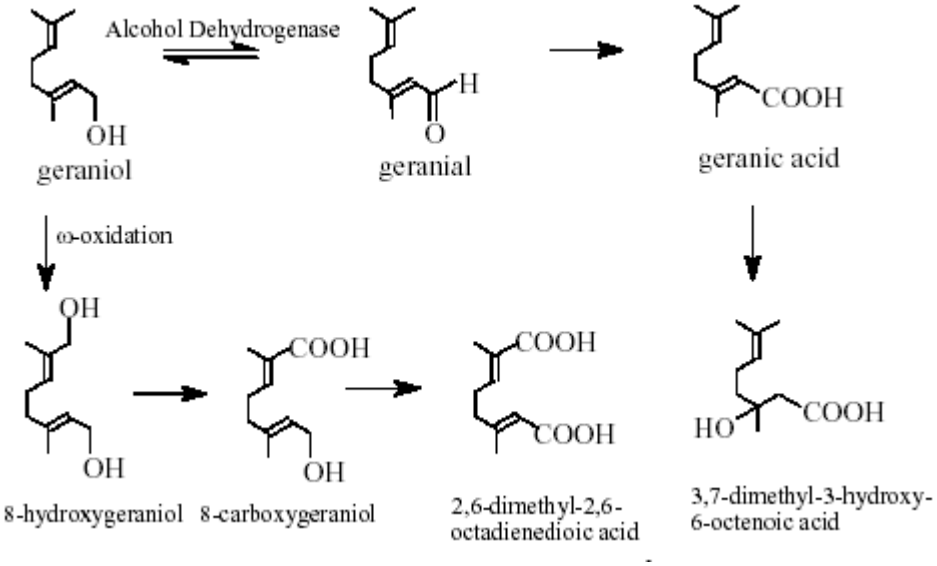


Figure III.4. *Metabolism of Geraniol in rats.*

Male rats were given repeated oral doses of 800 mg [1-^{3}H]-geraniol/kg bw by gavage daily for 20 days. Five urinary metabolites were identified via two primary pathways. In one pathway, the alcohol is oxidized to yield geranic acid (3,7-dimethyl-2,6-octadieneoic acid), which is subsequently hydrated to yield 3,7-dimethyl-3-hydroxy-6-octenoic acid. In a second pathway, the alcohol undergoes omega-oxidation mediated by liver cytochrome P-450 (Chadha & Madyastha, 1982) to yield 8-hydroxygeraniol. Selective oxidation at C-8 yields 8-carboxygeraniol, which undergoes further oxidation to the principal urinary metabolite 2,6-dimethyl-2,6-octadienedioic acid (Chadha & Madyastha, 1984).

Mono methyl substituted fatty acids are extensively metabolised to CO_2 via beta-oxidative cleavage in the fatty acid pathway. If more than one methyl group is substituted in the lower as well as higher molecular weight acids or ethyl or propyl substituents are present, beta-oxidation is inhibited. In those cases metabolism involves direct conjugation of the acid with glucuronic acid, or omega-oxidation followed by conjugation (Williams, 1959a; Deuel, 1957).

III.4. Summary and Conclusions

In summary, it is anticipated that the esters in the group of 48 candidate substances will undergo hydrolysis in the gastrointestinal tract, blood and liver to yield their corresponding aliphatic alcohols, aldehydes and carboxylic acids. Esters, aliphatic alcohols, aldehydes and carboxylic acids are expected to be absorbed from the gastrointestinal tract. Alcohols would be oxidized to their corresponding aldehydes and carboxylic acids, and aldehydes would be oxidized to their corresponding carboxylic acids. The resulting aliphatic carboxylic acids undergoes complete metabolism to CO_2 in the tricarboxylic acid cyclic and fatty acid pathway.

The following substances [FL-no: 02.170, 02.176, 09.612, 09.884, 09.341, 09.643, 09.871, 09.872, 09.831, 09.897 and 09.898] are not completely oxidized to CO_2 due to substitution in the beta-position or sterich hindrance. These substances, the esters after hydrolysis, are expected to undergo oxidation reactions and to be excreted as such or after conjugation with glucuronic acid. Hex-3-enyl-2-ethylburtyrate [FL-no: 09.884], is hydrolysed to 2-ethylbutyric acid and hex-3-enol, which can be further conjugated with glucuronic acid or undergo omega-oxidation. However, the candidate substance [FL-no: 09.884] cannot be anticipated to be metabolised to an innocuous product.

The risk associated with possible epoxidation of the candidate substances with terminal double bond is expected to be low for two reasons. Epoxides can be metabolised by conjugation with glutathione or by epoxide-hydrolase mediated hydrolysis. The terminal double bonds in this group of flavourings are all present in molecules that have alcohol- or aldehyde functions at the end distal from the double bond, and the alcohol and aldehyde functions are expected to be metabolised to carboxylic acids prior to epoxidation of the double bond.

ANNEX IV: TOXICITY

Acute toxicity data are available for four candidate substances of the present flavouring group of 48 substances from chemical groups 1 and 4, and for 42 supporting and structurally related substances evaluated by the JECFA at the 49th, 51st and 61st meetings (JECFA, 1998a; JECFA, 1999a; JECFA, 2004b). The supporting substances are listed in brackets.

Table IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD50 (mg/kg bw)	Reference	Comments
(4-Pentenoic acid [08.048])	Mouse	NR	Gavage	610	(Jenner et al., 1964)	
	Rat	M/F	Gavage	470	(Jenner et al., 1964)	
Pent-4-enal [05.174]	Rat	F	Gavage	620	(Smyth et al., 1962)	
(*cis*-3-Hexen-1-ol [02.056])	Mouse	M	Gavage	7000	(Gaunt et al., 1969)	
	Mouse	F	Gavage	7200	(Gaunt et al., 1969)	
	Rat	M/F	Oral	4700	(Moreno, 1973b)	
	Rat	M	Gavage	10100	(Gaunt et al., 1969)	
	Rat	F	Gavage	7300	(Gaunt et al., 1969)	
(*cis*-3-Hexenal [05.075])	Rat	M/F	Gavage	1560	(Palanker & Lewis, 1979)	
((Z,Z)-3,6-Nonadien-1-ol[1] [02.189])	Rat	M/F	Oral	2000	(Koike, 1996)	
(*cis*-6-Nonenal [05.059])	Mouse	NR	Oral	5000	(Moreno, 1978b)	
(9-Decenal[1] [05.139])	Mouse	M/F	Gavage	9500	(Johnson, 1980)	LD_{50} > 5 ml/kg.
(10-Undecenal [05.035])	Rat	NR	Oral	5000	(Hart & Wong, 1971)	
(10-Undecenoic acid [08.039])	Mouse	NR	Gavage	8150	(Newell et al., 1949)	
	Mouse	NR	Oral	2300-6600	(Tislow et al., 1950)	
	Rat	NR	Oral	2500	(Tislow et al., 1950)	
(Oleic acid [08.013])	Rat	NR	Oral	5000	(Moreno, 1977b)	
	Rat	NR	Oral	19000	(Briggs et al., 1976)	LD_{50} was > 21.5 ml for ocadecanoic acid (75 % oleic acid) and octadecadienoic acid (53 % linoleic acid, 23 % oleic acid).
(*cis*-3-Hexenyl propionate[1] [09.564])	Rat	NR	Oral	5000	(Moreno, 1976f)	
(*cis*-3-Hexenyl valerate[1])	Rat	NR	Oral	5000	(Moreno, 1978d)	1/10 rats died after a dose of 5000 mg/kg.
(Ethyl *cis*-4,7-octadienoate [09.290])	Rat	M/F	Gavage	10000	(Mondino, 1979)	
(Methyl 9-undecenoate [09.236])	Rat	M	Oral	3000	(Moreno, 1977b)	
(Ethyl 10-undecenoate [09.237])	Rat	NR	Oral	5000	(Moreno, 1977b)	
(Butyl 10-undecenoate [09.238])	Rat	NR	Oral	5000	(Moreno, 1977b)	
(Ethyl oleate [09.192])	Rat	NR	Oral	5000	(Bailey, 1976d)	1/10 rats died after a dose of 5000 mg/kg.
Methyl-3-but-3-en-1-ol [02.176]	Rat	NR	Oral	5440	(BASF, 1968)	
(2,6-Dimethyl-5-heptenal [05.074])	Rat	NR	Oral	5000	(Levenstein, 1974b)	
	Rat	M/F	Gavage	4550	(Mayyasi et al., 1981)	LD_{50} > 5 ml/kg.
Lavandulol [02.170]	Mouse	NR	Oral	5000	(Moreno et al., 1982)	4/10 mice died after a dose of 5000 mg/kg.
(3-Hexenyl isobutyrate[1] [09.563])	Rat	M/F	Gavage	25000	(Moran et al., 1980)	

Table IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD50 (mg/kg bw)	Reference	Comments
	Mouse	M/F	Gavage	25000	(Moran et al., 1980)	
(Hexyl 2-methyl-3&4-pentenoate [09.546])	Rat	M/F	Gavage	5000	(Elleman, 1979)	
(Ethyl 2-methyl-3,4-pentadienoate [09.540])	Mouse	M	Gavage	1316	(Babish, 1978c)	
	Mouse	F	Gavage	892	(Babish, 1978c)	
	Mouse	M/F	Gavage	770	(Moran et al., 1980)	
(Citronellyl formate [09.078])	Rat	M/F	Gavage	8400	(Calandra, 1971)	
(Geranyl formate [09.076])	Rat	M/F	Gavage	5460	(Weir & Wong, 1971a)	LD_{50} > 6 ml/kg. 1/5 rats died after 6 ml/kg.
(Neryl formate [09.212])	Rat	NR	Oral	5000	(Moreno, 1975f)	
(Rhodinyl formate [09.079])	Rat	NR	Oral	5000	(Moreno, 1974a)	1/10 rats died after a dose of 5000 mg/kg.
(Citronellyl acetate [09.012])	Rat	M/F	Gavage	6800	(Calandra, 1971)	
(Geranyl acetate [09.011])	Rat	M/F	Gavage	6330	(Jenner et al., 1964)	
(Neryl acetate [09.213])	Rat	M/F	Gavage	4550	(Levenstein & Wolven, 1972a)	LD_{50} > 5 ml/kg.
(Rhodinyl acetate [09.033])	Rat	M/F	Gavage	5000	(Levenstein, 1973a)	LD_{50} > 5 ml/kg.
(Citronellyl propionate [09.129])	Rat	NR	Oral	5000	(Moreno, 1973a)	3/10 rats died after a dose of 5000 mg/kg.
(Geranyl propionate [09.128])	Rat	NR	Oral	5000	(Russell, 1973a)	
(Neryl propionate [09.169])	Rat	NR	Oral	5000	(Moreno, 1975f)	
(Rhodinyl propionate [09.141])	Rat	NR	Oral	5000	(Moreno, 1976h)	
(Citronellyl butyrate [09.049])	Rat	NR	Oral	5000	(Moreno, 1972a)	3/10 rats died after a dose of 5000 mg/kg.
(Geranyl butyrate [09.048])	Rat	M/F	Gavage	10660	(Jenner et al., 1964)	
(Rhodinyl butyrate)	Rat	NR	Oral	5000	(Moreno, 1975f)	
(Geranyl hexanoate [09.067])	Rat	NR	Oral	5000	(Moreno, 1975f)	
(Citronellyl isobutyrate [09.421])	Rat	NR	Oral	5000	(Denine & Palanker, 1973a)	
(Geranyl isobutyrate [09.431])	Rat	NR	Oral	5000	(Shelanski & Moldovan, 1973a)	
(Neryl isobutyrate [09.424])	Rat	M	Oral	5000	(Moreno, 1980d)	
(Rhodinyl isobutyrate)	Rat	NR	Oral	5000	(Moreno, 1975f)	
(Geranyl isovalerate [09.453])	Rat	NR	Oral	5000	(Levenstein, 1975a)	
(Geranyl 2-ethylbutanoate [09.515])	Mouse	NR	Oral	8000	(Pellmont et al., 1968)	
Undec-10-en-1-ol [02.125]	Rat	M/F	Oral	5000	(Levenstein & Wolven, 1972c)	LD_{50} > 5 ml/kg.

NR: Not Reported

[1] A substance evaluated at the 61st JECFA meeting structurally related to candidate substances in FGE.06Rev1.

Subacute / subchronic / chronic /carcinogenicity toxicity data are available for 12 supporting substances of the present flavouring group. They were evaluated at the 49th and 51st JECFA meetings (JECFA, 1998a; JECFA, 1999a). No repeated dose studies are available on the candidate substances. The supporting substances are listed in brackets.

Table IV.2: Subacute / Subchronic / Chronic / Carcinogenicity Studies

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
(*cis*-3-Hexen-1-ol [02.056])	Rat; M, F 30	Drinking water	0, 310, 1250, 5000 ppm equal to M: 0, 30, 127, 410 mg/kg bw/day, F: 0, 42, 168, 721 mg/kg bw/day	98 days	127-168	(Gaunt et al., 1969)	NOAEL corresponds to 1250 mg/kg feed.
(10-Undecenoic acid [08.039])	Rat; M, F NR	Gavage	0, 100, 200, and 400 mg/kg bw/day	6 months	400	(Tislow et al., 1950)	Total number of animals studied was 152. Endpoints included body weight and changes in autopsy (only poorly reported abstract available).
	Rat; M 7	Diet	0, 5000, 10000 and 25000 mg/kg feed equivalent to 0, 500, 1000 and 2500 mg/kg bw/day	8 weeks	2500[3]	(Newell et al., 1949)	Reported only data on body weight. Study ongoing at the reporting time. There was a reduction in body weight gain at both concentration. Doses are considered very high.
(Oleic acid [08.013])	Rabbit; M, F 20	Diet	0, 150000 mg/kg feed equivalent to 4500 mg/kg bw/day	36 weeks	4500[3]	(Borgman & Wardlaw, 1975)	Groups: (1) olive oil and (2) semipurified oleic acid. Treatment included periods with diet supplemented with cholesterol. Serum cholesterol was the main endpoint. Rabbits fed oleic acid began to deteriorate by week 17th. Animals showed severe to slight hepatic fatty acid degeneration
	Mouse; NR 36 and 55	Diet	0, 1500 mg/kg feed equivalent to 0, 225 mg/kg bw/day	24 months	225[3]	(El-Khatib & Cora, 1981)	Groups were given (1) normal diet, or (2) normal diet + corn oil (10 %) + oleic acid (0.15%). Main endpoint was lipid content in the liver and pituitary gland. There was an increase. In 3 of 36 surviving mice given diet with corn oil + oleic acid adenocarcinoma of the colon was reported.
	Rabbit; M, F 38-42	Diet	0, 150000 mg/kg feed equivalent to 0, 4500 mg/kg bw/day	16 weeks	4500[3]	(Lee et al., 1986)	Treated animals were given a diet with 40 % casein and 15 % oleic acid. Examined for gallbladder content. The treated animals showed gallstones.
(Oleic acid/linoleic acid mixture [08.013] / [08.041])	Mouse; M, F 329-623	Oral (given on a separate dish)	0, 0 and ~ 64-100 mg/kg bw/day	≈ 24 months (long term, exact duration not reported)	64-100	(Szepsenwol & Boschetti, 1975)	A NOAEL was not determined. Groups: (1) untreated (2) refined corn oil, (3) refined corn oil with 15 mg/g oleic acid/linoleic acid mixture. Mice given treatment (3) had a higher incidence of stomach tumours as compared to the other two groups.
	Mouse; NR 195-328	Oral (given on a separate dish)	0, 0, 0, and ~ 85-100 mg/kg bw/day	≈ 24 months (long term, exact duration	85-100	(Szepsenwol, 1978)	A NOAEL was not determined. Groups: (1) untreated, (2) refined corn oil, (3) crude corn oil, and (4) refined corn oil + oleic acid/linoleic acid

Table IV.2: Subacute / Subchronic / Chronic / Carcinogenicity Studies

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
				not reported)			mixture. The mixture oleic acid/linoleic acid was carcinogenic, with an increased incidence of forestomach papilloma, squamous cell carcinoma and pyloric tumours.
(Hexanoic acid[1] [08.009])	Rat; M, F 10	Diet	100000 mg/kg feed equivalent to 5000 mg/kg bw/day	5 months	5000[3]	(Mori, 1953)	Endpoint was gastric lesions. No attempt was made to estimate the amount ingested by rats due to the volatility of fatty acid, which raises concerns on the validity of the results.
(2,6-Dimethyl-5-heptenal [05.074])	Rat; M, F 30	Diet	0, 9, 37, and 150 mg/kg bw/day	3 months	37	(Gaunt et al., 1983)	
(2-Ethylbutyric acid[1] [08.045])	Rat; M, F 6	Diet	6000 mg/kg feed equivalent to 300 mg/kg bw/day	3 months	300[3]	(Amoore et al., 1978)	
(Citronellyl acetate and geranyl acetate [09.012] and [09.011])	Mouse; M, F 20	Gavage	0, 125, 500, 1000, and 2000 mg/kg bw/day	13 weeks	1000	(NTP, 1987a)	The test material was composed of 71 % geranyl acetate and 29 % citronellyl acetate.
	Rat; M, F 20	Gavage	0, 250, 500, 1000, 2000, and 4000 mg/kg bw/day	13 weeks	2000	(NTP, 1987a)	The test material was composed of 71 % geranyl acetate and 29 % citronellyl acetate.
	Mouse; M, F 100	Gavage	0, 500, and 1000 mg/kg bw/day	2 years	500	(NTP, 1987a)	The test material was composed of 71 % geranyl acetate and 29 % citronellyl acetate. Survival among males was 62, 64 and 0 %, respectively. Survival among females was 50, 30, and 0 %, respectivel. The mixture was not considered to be carcinogenic.
(Citronellyl acetate and geranyl acetate [09.012] and [09.011], continued)	Rat; M, F 100	Gavage	0, 1000, and 2000 mg/kg bw/day	2 years	1000	(NTP, 1987a)	The test material was composed of 71 % geranyl acetate and 29 % citronellyl acetate. Survival among males was 68, 58 and 36%. Survival among females was 70, 56 and 66%, respectively. The mixture was not considered carcinogenic.
(Geranyl acetate [09.011])	Rat; M, F 20	Diet	0, 1000, 2500, and 10000 mg/kg feed equivalent to 0, 50, 125, 500 mg/kg bw/day	17 weeks	500[3]	(Hagan et al., 1967)	
(Geraniol[2] [02.012])	Rat; M, F 10	Diet	0, 10000 mg/kg feed equivalent to 500 mg/kg bw/day	16 weeks	500[3]	(Hagan et al., 1967)	
	Rat; M, F 10	Diet	0, 1000 mg/kg feed equivalent to 50 mg/kg bw/day	27 – 28 weeks	50[3]	(Hagan et al., 1967)	
(Citronellol[2] [02.011])	Rat; M, F 30	Diet	Incompletely reported	12 weeks	50	(Oser, 1967)	The test material was a mixture consisting of equal amounts of citronellol and linalool. The publication was not provided, only a FAO report referring to it. There was a slightly retarded growth of males, without effect on food

Table IV.2: Subacute / Subchronic / Chronic / Carcinogenicity Studies

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
							utilization. No other endpoints are mentioned.
(Citronellyl isobutyrate [09.421])	Rat; M, F 28	Diet	0, 14.7 mg/kg bw/day	3 months	14.7	(Damske et al., 1980a)	

NR = Not Reported.

NA = Not Applicable.

[1]A substance evaluated at the 49th JECFA meeting and structurally related to candidate substances in FGE.06.

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

[3] Conversion table for test chemical treatment dosed used in PAFA (FDA, 1993).

No developmental and reproductive toxicity studies are available for any candidate substance in the present flavouring group. One study was available for one supporting substance and for one hydrolysis product.

TABLE IV.3: DEVELOPMENTAL / REPRODUCTIVE TOXICITY STUDIES

Table IV.3: Developmental / Reproductive Toxicity Studies

Chemical name	Study type Duration	Species/sex No/group	Route	Dose levels	NOAEL mg/kg/day Including information on possible maternal toxicity	Reference	Comments
(10-Undecenoic acid [08.039])	One generation study 9 months	Rat; M, F NR	Gavage	NR	NR	(Tislow et al., 1950)	Only poorly reported abstract available.
(2-Ethylbutyric acid [08.045])	Developmental toxicity; dose administered gestation days 6-15	Rat; F 9-18	gavage	0, 150, 200 mg/kg bw	200	(Narotsky et al., 1994)	
	Developmental toxicity; dose administered gestation day 8	Mouse; F 15/group	Subcutaneous injection	0, 600 mg/kg bw	< 600	(Nau & Löscher, 1986)	1

NR = Not Reported.

1) In the present study valproic acid as well as a number of related substances was examined with respect to their teratogenic potential.Valproic acid was highly teratogenic at 600 mg/kg/day. The study showed that the teratogenic potential increased with the number of carbon-atoms in the 2-position.

In vitro mutagenicity/genotoxicity data are available for one candidate substances of the present flavouring group evaluation from chemical group 4 and for six supporting substances evaluated at the 49th and 51st JECFA meetings (JECFA, 1998a; JECFA, 1999a). Supporting substances are listed in brackets.

Table IV.4: GENOTOXICITY (*in vitro*)

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.
	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.
	Ames assay	*S. typh.* TA98, TA100, TA1535, TA1537,	Up to 50000 µg/plate	Negative[2]	(Heck et al., 1989)	No information concerning a possible cytotoxic effect nor on the number of concentrations

Table IV.4: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test system	Test Object	Concentration	Result	Reference	Comments
		TA1538				tested. The test guidelines do not require more than 5 mg/plate. The validity of this poorly reported 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 this poorly reported 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 this poorly reported 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 poorly reported study cannot be evaluated.
	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., 1987a)	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., 1987a)	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 poorly reported 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.

In vivo mutagenicity/genotoxicity data are available for two supporting substances of the present flavouring group. They were evaluated at the 49th JECFA meetings (JECFA, 1998a). The supporting substances are listed in brackets.

Table IV.5: GENOTOXICITY (*in vivo*)

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.

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ABBREVIATIONS

ADH	Alcohol dehydrogenase
ADI	Acceptable Daily Intake
ALDH	Aldehyde dehydrogenase
BW	Body weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids Chemical Abstract Service
CHO	Chinese hamster ovary (cells)
CoA	Co-enzyme A
CoE	Council of Europe
DNA	Deoxyribonucleic acid
EC	European Commission
EFSA	The European Food Safety Authority
EH	Epoxide hydrolase
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GSH	Glutathione
GST	Glutathione S-transferase
ID	Identity
IOFI	International Organization of the Flavour Industry
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal Dose, 50 %; Median lethal dose
MS	Mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide, reduced form
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate, reduced form
No	Number
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level

NTP	National Toxicology Program
SCE	Sister Chromatid Exchange
SCF	Scientific Committee on Food
SMART	Somatic Mutation and Recombination Test
TAMDI	Theoretical Added Maximum Daily Intake
UDS	Unscheduled DNA Synthesis
WHO	World Health Organisation