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Flavouring Group Evaluation 2, Revision 1: Branched- and straight-chain aliphatic saturated primary alcohols and related esters of primary alcohols and straight-chain carboxylic acids and one straight-chain aldehyde from chemical groups 1 and 2 (Commission Regulation (EC) No 1565/2000 of 18 July 2000) [1]

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

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PANEL MEMBERS

Fernando Aguilar, Herman Autrup, Susan Barlow, Laurence Castle, Riccardo Crebelli, Wolfgang Dekant, Karl-Heinz Engel, Nathalie Gontard, David Gott, Sandro Grilli, Rainer Gürtler, John Christian Larsen, Catherine Leclercq, Jean-Charles Leblanc, Xavier Malcata, Wim Mennes, Maria Rosaria Milana, Iona Pratt, Ivonne Rietjens*, Paul Tobback, Fidel Toldrá.

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) is asked to advise the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Scientific Panel is asked to evaluate 47 flavouring substances in the Flavouring Group Evaluation 2, Revision 1 (FGE.02Rev1), using the procedure as referred to in the Commission Regulation (EC) No 1565/2000. These 47 flavouring substances belong to chemical groups 1 and 2, Annex I of the Commission Regulation (EC) No 1565/2000.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission Flavouring Group Evaluation 2, Revision 1 (FGE.02Rev 1): Branched- and straight-chain aliphatic saturated primary alcohols and related esters of primary alcohols and straight-chain carboxylic acids and one straight-chain aldehyde from chemical groups 1 and 2

* *1 member of the Panel did not participate in the discussion due to a declared interest. For details see the minutes of the 21th AFC Panel meeting : http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Meetings424.htm*

The present Flavouring Group Evaluation deals with 47 branched- and straight-chain aliphatic saturated primary alcohols and related esters of primary alcohols and straight-chain carboxylic acids and one straight-chain aldehyde.

Eleven of the 47 flavouring substances in the group possess a chiral centre. For two of these substances the stereoisomeric composition has not been specified.

All 47 flavouring substances are assigned to structural class I according to the decision tree approach presented by Cramer et al., 1978.

Fourty-three of the substances in the present group of 47 candidate substances have been reported to occur naturally in a wide range of food items.

In its evaluation, the Panel as a default used the Maximised Survey-derived Daily Intake (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe. However, when the Panel examined the information provided by the European Flavouring Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach.

In the absence of more precise information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a modified Theoretical Added Maximum Daily Intake (mTAMDI) approach based on the normal use levels reported by Industry. In those cases where the mTAMDI approach indicated that the intake of a flavouring substance might exceed its corresponding threshold of concern, the Panel decided not to carry out a formal safety assessment using the Procedure. In these cases the Panel requires more precise data on use and use levels.

According to the default MSDI approach, the 47 flavouring substances in this group have intakes in Europe from 0.0012 to 6.7 microgram/*capita*/day, which are below the threshold of concern value for a structural class I substance of 1800 microgram/person/day.

On the basis of the reported annual production in Europe (MSDI approach), the combined intake of the 47 flavouring substances belonging to structural class I would result in a total intake of approximately 45 microgram/*capita*/day. This value is below the threshold of concern for structural class I substances of 1800 microgram/person/day. The total combined estimated intake of the 47 flavouring substances in the present group and the 64 structurally related substances from structural class I is approximately 8000 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.

All 47 flavouring substances in the present flavouring group evaluation are expected to be metabolised to innocuous products. The Panel noted that one substance in the present group of flavourings, 3,5,5-trimethylhexyl acetate, contains a tertiary butyl group. However, it is predicted that this ester is easily hydrolysed and either conjugated or further metabolised via common metabolic pathways.

Genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of the candidate substances using the Procedure.

It was noted, that where toxicity data were available on flavouring substances in the present flavouring group or on structurally related substances they were consistent with the conclusions in the present evaluation using the Procedure.

It is considered that on the basis of the default MSDI approach these 47 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 1500 to 3900 microgram/person/day for the 47 flavouring substances from structural class I. The intakes were all above the threshold of concern for a structural class I substance of 1800 microgram/person/day, except for one flavouring substance [FL-no: 05.152]. This substance, which have mTAMDI intake estimate below the threshold of concern for a structural class I substance, is also expected to be metabolised to innocuous products.

Thus, for 46 of the 47 flavouring substances considered in this opinion the intakes, estimated on the basis of the mTAMDI approach, exceed the relevant threshold for their structural class. Therefore, for these 46 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 toxicological data might become necessary.

In order to determine whether the conclusion for the 47 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 tests for the materials of commerce have been provided for 42 of the 47 flavouring candidate substances, except that information on chirality is missing for two of the substances [FL-no: 02.178 and 09.819]. For five of the substances [FL-no: 02.178, 09.180, 09.331, 09.583 and 09.642] the purity criteria are deficient in one of the parameters.

Thus, the final evaluation of the materials of commerce cannot be performed for six substances [FL-no: 02.178, 09.180, 09.331, 09.583, 09.642,and 09.819], pending further information. The remaining 41 substances [FL-no: 02.126, 02.154, 02.180, 02.196, 02.202, 05.152, 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587, 09.588, 09.589, 09.592, 09.593, 09.594, 09.598, 09.599, 09.600, 09.602, 09.651, 09.659, 09.660, 09.661, 09.662, 09.664, 09.665, 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816 and 09.820] would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

Key words: Flavourings, safety, branched- and straight-chain, aliphatic, saturated, primary alcohols, aldehydes, esters, carboxylic acids.

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BACKGROUND

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

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

The Flavouring Group Evaluation (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 first 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 positive 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, 1996).

HISTORY OF THE EVALUATION

FGE	Opinion Adopted by EFSA	Link	No. of Candidate Substances
FGE.02	Adopted by SCF 3 December 2003	http://europa.eu.int/comm/food/food/chemicalsafety/flavouring/scientificadvice_en.htm	41
FGE.02rev1	Adopted 3 July 2007	http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm	47

The present revision of FGE.02, FGE.02Rev1, includes the assessment of six additional flavouring substances [FL-no: 02.178, 09.180, 09.331, 09.583, 09.599 and 09.819]. For one new substance [FL-no: 09.819] one acute toxicity study was submitted. Additional information on nine flavouring substances [FL-no: 09.307, 09.358, 09.659 - 09.662 and 09.664 - 09.666] was made available since the FGE.02 was published.

TERMS OF REFERENCE

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

ACKNOWLEDGEMENT

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ASSESSMENT

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

1.1. Description

The present Flavouring Group Evaluation 2, Revision 1(FGE.02Rev1), using the procedure as referred to in the Commission Regulation (EC) 1565/2000 (the Procedure – shown in schematic form in Annex I), deals with 47 saturated alcohols, aldehydes and esters derived from aliphatic acyclic primary alcohols and linear aliphatic acyclic carboxylic acids. These 47 flavouring substances (candidate substances) belong to chemical groups 1 and 2, Annex I of Commission Regulation (EC) No 1565/2000 (EC, 2000).

The 47 candidate substances under consideration, with their chemical Register names, FLAVIS-(FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufactures Association- (FEMA-) numbers, structure and specifications, are listed in Table 1. Six of the 47 candidate substances are aliphatic acyclic primary alcohols [FL-no: 02.126, 02.154, 02.178, 02.180, 02.196 and 02.202]; one is an aliphatic acyclic aldehyde [FL-no: 05.152] and 40 are esters of aliphatic acyclic primary alcohols and linear aliphatic acyclic carboxylic acids [FL-no: 09.180, 09.307, 09.327, 09.331, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.583, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.599, 09.600, 09.602, 09.642, 09.651, 09.659 - 09.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, 09.819 and 09.820]. The hydrolysis products of the candidate esters are listed in Table 2b.

The 47 candidate substances are closely related structurally to 64 flavouring substances (supporting substances) evaluated at the 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) in the group "Esters of Aliphatic Acyclic Primary Alcohols with Aliphatic Linear Saturated Carboxylic Acids" (JECFA, 1998a; JECFA, 1999b). These 64 supporting substances evaluated by the JECFA, with the respective structural formulas, FEMA, CoE, and CAS register numbers, evaluation status by the Scientific Committee on Food (SCF), the JECFA, and by CoE and the European Maximised Survey-derived Daily Intake (MSDI) values, are listed in Table 3 (CoE, 1992; JECFA, 1999b; SCF, 1995).

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 variation of 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.).

Eleven of the 47 flavouring substances in the group possess a chiral centre [FL-no: 02.178, 09.307, 09.358, 09.659 - 09.662, 09.664 - 09.666 and 09.819]. Two of these 11 substances [FL-no: 02.178 and 09.819] have been presented without indication whether the commercial flavouring substance is dominated by one of the optical isomers (see Table 1).

1.3. Natural Occurrence in Food

Fourty-three of the substances in the present group of 47 candidate substances have been reported to occur naturally in a wide variety of fruits, wines and liquors, as well as in cheese, juice and other foods. Quantitative data on natural occurrence have been reported for 32 of the substances.

These reports include among others:

- Tetradecanol [FL-no: 02.126]: up to 7 mg/kg in whisky
- Butyl decanoate [FL-no: 09.327]: up to 5 mg/kg in oranges
- 2-Methylbutyl dodecanoate [FL-no: 09.307]: up to 0.14 mg/kg in cheese
- Heptadecanol [FL-no: 02.154]: up to 0.05 mg/kg in butter
- Hexadecanal [FL-no: 05.152]: 0.003 mg/kg in milk
- Methyl hexadecanoate [FL-no: 09.180]: up to 20 mg/kg in mushrooms, 5.3 mg/kg in elderberry fruit and up to 1.1 mg/kg in green tea.
- Methyl octadecanoate [FL-no: 09.651]: 0.009 mg/kg in milk powder

According to TNO four of the substances: isobutyl octadecanoate, pentyl dodecanoate, pentyl hexadecanoate, 3,5,5-trimethylhexyl acetate [FL-no: 09.592, 09.681, 09.682 and 09.819], respectively, have not been reported to occur naturally in any food items (TNO, 2000).

2. Specifications

Purity criteria for the 47 substances have been provided by the Flavouring Industry (EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad) (Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000), the purity criteria is adequate for the 47 candidate substances, except that identity tests are missing for four substances [FL-no: 02.178, 09.180, 09.331 and 09.583], the specific gravity range need to be specified for [FL-no: 09.642] and that information on chirality is needed for two candidate substances [FL-no: 02.178 and 09.819] (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, 1999).

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, 1999).

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 in 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, 2000). 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 Maximised Survey-derived Daily Intake (MSDI (SCF, 1999)) 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[2] (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, 1999).

In the present Flavouring Group Evaluation 02, Revision 1 (FGE.02Rev1) the total annual production volume of the 47 candidate substances for use as flavouring substances in Europe was reported to be 375 kg (EFFA, 2001a; EFFA, 2001d; EFFA, 2003s; EFFA, 2004ad). The total annual volume of production of the 64 supporting substances is 65000 kg (cited in (JECFA, 1999b)).

On the basis of the annual volume of production reported for the 47 candidate substances, MSDI values for each of these flavourings have been estimated (Table 2a).

More than 75% of the total annual volume of production for the candidate substances is accounted for by 12 of these flavourings [FL-no: 05.152, 09.180, 09.327, 09.334, 09.587, 09.593, 09.594, 09.598, 09.659, 09.665, 09.700 and 09.816]. The estimated daily *per capita* intake of these candidate substances from use as a flavourings is 2.4, 2.8, 6.7, 1.3, 3.0, 3.7, 1.8, 4.5, 2.1, 2.4, 1.3, and 2.6 microgram/day, respectively (Table 2a). The daily *per capita* intakes for each of the remaining substances are all less than 1.0 microgram (Table 2a).

[2] *EU figure 375 millions (Eurostat, 1998). 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*

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 47 candidate substances, information on food categories and normal and maximum use levels[3,4,5] were submitted by the Flavour Industry (EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad). The 47 candidate substances are used in flavoured food products divided into the food categories, outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000), as shown in Table 3.1. For the present calculation of mTAMDI, the reported normal use levels were used. In the case where different use levels were reported for different food categories the highest reported normal use level was used.

Table 3.1 Use of Candidate Substances

Food category	Description	Flavourings used
Category 1	Dairy products, excluding products of category 2	All
Category 2	Fats and oils, and fat emulsions (type water-in-oil)	All
Category 3	Edible ices, including sherbet and sorbet	All
Category 4.1	Processed fruits	All
Category 4.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	None
Category 5	Confectionery	All, except [FL-no: 09.331]
Category 6	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	All
Category 7	Bakery wares	All
Category 8	Meat and meat products, including poultry and game	All
Category 9	Fish and fish products, including molluscs, crustaceans and echinoderms	All, except [FL-no: 09.642]
Category 10	Eggs and egg products	None
Category 11	Sweeteners, including honey	None
Category 12	Salts, spices, soups, sauces, salads, protein products etc.	All
Category 13	Foodstuffs intended for particular nutritional uses.	All
Category 14.1	Non-alcoholic ("soft") beverages, excl. dairy products	All, except [FL-no: 09.599, 09.819]
Category 14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	All, except [FL-no: 09.331]
Category 15	Ready-to-eat savouries	All
Category 16	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	All

According to the Flavour Industry the normal use levels for the 47 candidate substances are in the range of 1 - 20 mg/kg food, and the maximum use levels are in the range of 10 - 100 mg/kg (EFFA, 2002i; EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad).

3 "Normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i)

4 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).

4 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).

The mTAMDI values for the 47 candidate substances from structural class I (see Section 5) range from 1500 to 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

Data for short and medium length linear- and branched-chain alcohols, aldehydes and esters (and their alcohol and carboxylic acid moieties), included in the present Flavouring Group Evaluation and general information for this class of chemicals, indicate that they are rapidly absorbed from the gastrointestinal tract, metabolised and excreted. Also, *in vitro* hydrolysis data from studies with the supporting substances, as well as other closely related substances, indicate that the esters included in the present evaluation can be hydrolysed to yield the corresponding alcohols and carboxylic acids (Gangolli & Shilling, 1968; Grundschober, 1977; Leegwater & Straten, 1974a; Longland et al., 1977).

General discussions on the biotransformation of linear aliphatic acids and aliphatic linear- and branched-chain alcohols and aldehydes, as well as hydrolysis of their esters, are provided in Annex III.

In summary, it is anticipated that the 40 candidate esters [FL-no: 09.180, 09.307, 09.327, 09.331, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.583, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.599, 09.600, 09.602, 09.642, 09.651, 09.659 - 9.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, 09.819 and 09.820] will undergo hydrolysis to yield their corresponding aliphatic alcohols and linear carboxylic acids. The resulting aliphatic alcohols and linear carboxylic acids, as well as the six aliphatic alcohols [FL-no: 02.126, 02.154, 02.178, 02.180, 02.196 and 02.202] and one linear aliphatic aldehyde [FL-no: 05.152] are expected to be completely oxidised to carbon dioxide via the fatty acid pathway followed by the tricarboxylic acid cycle. The branched-chain alcohols can also be conjugated in part and excreted via the urine (see Annex III).

The Panel noted that in the present group of flavourings, one substance contains a tertiary butyl group, 3,5,5-trimethylhexyl acetate [FL-no: 09.819]. However, it is predicted that this ester is easily hydrolysed and either conjugated or further metabolised via common metabolic pathways.

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 47 candidate substances from chemical groups 1 and 2 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the 47 substances are summarised in Table 2a.

Step 1

All 47 candidate substances are classified in structural class I according to the decision tree approach presented by Cramer et al. (Cramer et al., 1978).

Step 2

The 47 candidate substances can be predicted to be metabolised to innocuous products. The evaluation of these 47 candidate substances, therefore, proceeds via the A-side of the Procedure scheme (Annex I).

Step A3

The 47 candidate substances, which have all been assigned to structural class I, have current estimated European daily *per capita* intakes from 0.0012 to 6.7 microgram (EFFA, 2001d; EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad). These intakes are below the threshold of concern of 1800 microgram/person/day for a structural class I substance.

Based on results of the safety evaluation sequence all 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.

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

The estimated intakes for the 47 candidate substances in structural class I, based on the mTAMDI, range from 1500 to 3900 microgram/person/day. For 46 of the substances the mTAMDI is above the threshold of concern of 1800 microgram/person/day for a structural class I substance. For comparison of the intake estimates based on the MSDI approach and the mTAMDI approach see Table 6.1.

For these 46 candidate substances further information is required. This would include more reliable intake data and then, if required, additional toxicological data.

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)
02.126	Tetradecan-1-ol	0.061	3900	Class I	1800
02.154	Heptadecan-1-ol	0.0061	3900	Class I	1800
02.178	2-Methyloctan-1-ol	0.012	3900	Class I	1800
02.180	4-Methylpentan-1-ol	0.012	3900	Class I	1800
02.196	Octadecan-1-ol	0.12	3900	Class I	1800
02.202	Pentadecan-1-ol	0.024	3900	Class I	1800
05.152	Hexadecanal	2.4	1500	Class I	1800
09.180	Methyl hexadecanoate	2.8	3900	Class I	1800
09.307	2-Methylbutyl dodecanoate	0.49	3900	Class I	1800
09.327	Butyl decanoate	6.7	3900	Class I	1800
09.331	Butyl hexadecanoate	0.79	3500	Class I	1800
09.334	Butyl nonanoate	1.3	3900	Class I	1800
09.358	3,7-Dimethyloctyl acetate	0.0012	3900	Class I	1800
09.380	Ethyl pentadecanoate	0.012	3900	Class I	1800
09.390	Heptyl hexanoate	0.024	3900	Class I	1800
09.574	Hexadec-1-yl acetate	0.012	3900	Class I	1800

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)
09.579	Hexyl dodecanoate	0.24	3900	Class I	1800
09.582	Hexyl tetradecanoate	0.61	3900	Class I	1800
09.583	Hexyl valerate	0.79	3900	Class I	1800
09.587	Isobutyl decanoate	3.0	3900	Class I	1800
09.588	Isobutyl dodecanoate	0.61	3900	Class I	1800
09.589	Isobutyl hexadecanoate	0.24	3900	Class I	1800
09.592	Isobutyl octadecanoate	0.0012	3900	Class I	1800
09.593	Isobutyl octanoate	3.7	3900	Class I	1800
09.594	Isobutyl tetradecanoate	1.8	3900	Class I	1800
09.598	Isopentyl decanoate	4.5	3900	Class I	1800
09.599	Isopentyl heptanoate	0.011	2300	Class I	1800
09.600	Isopentyl hexadecanoate	0.12	3900	Class I	1800
09.602	Isopentyl tetradecanoate	0.24	3900	Class I	1800
09.642	Methyl formate	0.97	2700	Class I	1800
09.651	Methyl octadecanoate	0.73	3900	Class I	1800
09.659	2-Methylbutyl butyrate	2.1	3900	Class I	1800
09.660	2-Methylbutyl decanoate	0.85	3900	Class I	1800
09.661	2-Methylbutyl formate	0.97	3900	Class I	1800
09.662	2-Methylbutyl hexanoate	0.49	3900	Class I	1800
09.664	2-Methylbutyl octanoate	0.37	3900	Class I	1800
09.665	2-Methylbutyl propionate	2.4	3900	Class I	1800
09.666	2-Methylbutyl tetradecanoate	0.12	3900	Class I	1800
09.677	Octyl hexanoate	0.61	3900	Class I	1800
09.681	Pentyl dodecanoate	0.0012	3900	Class I	1800
09.682	Pentyl hexadecanoate	0.0012	3900	Class I	1800
09.700	Propyl decanoate	1.3	3900	Class I	1800
09.813	Propyl dodecanoate	0.61	3900	Class I	1800
09.814	Propyl hexadecanoate	0.73	3900	Class I	1800
09.816	Propyl octanoate	2.6	3900	Class I	1800
09.819	3,5,5-Trimethylhexyl acetate	0.011	2300	Class I	1800
09.820	Undecyl acetate	0.0012	3900	Class I	1800

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 Flavouring Group Evaluation 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, 2001a; EFFA, 2001d; EFFA, 2003s; EFFA, 2004ad), the combined estimated daily *per capita* intake is approximately 45

microgram, which does not exceed the threshold of concern for substances belonging to structural class I (1800 microgram/person/day).

The 47 candidate substances are structurally related to 64 supporting substances evaluated by JEFCA at 49th session (JECFA, 1999b). The total estimated combined intake of candidate and supporting substances (in Europe) would be 8000 microgram/*capita*/day (European data were not available for six of the supporting substances), which would exceed the threshold of concern for 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 candidate and supporting substances (Annex IV), the combined intake of these substances would not be expected to be of safety concern.

8. Toxicity

8.1. Acute Toxicity

Data are available for six candidate substances and for 20 supporting and structurally related supporting substances. The oral LD50 values range from 475 to 32000 mg/kg body weight (bw) in rats.

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

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

Data are available for one candidate substance [FL-no: 02.196] and for a series of supporting and structurally related supporting [FL-no: 02.001, 02.003, 02.005, 02.008, 02.056, 08.001, 09.001, 09.004, 09.038, 09.044, 09.069, 09.072, 09.075, 09.093, 09.101, 09.106, 09.107, 09.111, 09.117, 09.147, 09.246 and 09.251].

The repeated dose toxicity data are summarised in Annex IV, Table IV.2.

8.3. Developmental / Reproductive Toxicity Studies

Data are available on one candidate substance [FL-no: 02.196] and three supporting substances [FL-no: 09.004, 09.007 and 09.246] and one structurally related supporting substance [FL-no: 02.008].

The developmental and reproductive toxicity data are summarised in Annex IV, Table IV.3.

8.4. Genotoxicity Studies

For three [FL-no: 02.126, 02.196 and 09.642] out of 47 candidate substances, genotoxicity has been studied *in vitro* in bacteria. With all three candidate substances, negative results were obtained. *In vitro* genotoxicity data are also available for nine supporting substances [FL-no: 09.002, 09.004, 09.005, 09.023, 09.101, 09.117, 09.162, 09.246 and 09.251]. For eight of these nine substances bacterial gene mutation assays have been reported; all with negative results. For two of the nine supporting substances, methyl acetate [FL-no: 09.023] and propyl acetate, [FL-no: 09.002] induction of aneuploidy has been demonstrated in yeast cells, but this effect can be considered to be a threshold effect, which is probably not due to a genotoxic interaction with DNA. Further, it is questionable whether these positive findings with respect to aneuploidy in yeast can be extrapolated to humans. An assay for chromosomal aberrations in mammalian cells *in vitro* with butyl acetate [FL-no: 09.004] was reported to be negative.

There are no *in vivo* data available for the candidate substances. For one structurally related supporting substance [FL-no: 02.008] negative results were reported in a micronucleus test in the mouse, while for two other supporting substances [FL-no: 09.004 and 09.023] negative *in vivo* genotoxicity data (SCEs and chromosomal aberrations) have been reported in occupationally exposed people.

The genotoxicity data are summarised in Annex IV, Table IV.4 and IV.5.

Genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of the candidate substances using the Procedure.

9. Conclusions

The 47 candidate flavouring substances are branched- and straight-chain aliphatic saturated primary alcohols and related esters of primary alcohols and straight-chain carboxylic acids and one straight-chain aldehyde from chemical groups 1 and 2.

Eleven of the 47 flavouring substances in the group possess a chiral centre. For two of these substances the stereoisomeric composition has not been specified.

All 47 flavouring substances are assigned to structural class I according to the decision tree approach presented by Cramer et al., 1978.

Fourty-three of the substances in the present group of 47 candidate substances have been reported to occur naturally in a wide range of food items.

According to the default MSDI approach, the 47 flavouring substances in this group have intakes in Europe from 0.0012 to 6.7 microgram/*capita*/day, which are below the threshold of concern value for a structural class I substance of 1800 microgram/person/day.

On the basis of the reported annual production in Europe (MSDI approach), the combined intake of the 47 candidate substances belonging to structural class I would result in a total intake of approximately 45 microgram/*capita*/day. This value is below the threshold of concern for structural class I substances of 1800 microgram/person/day. The total combined estimated intake of the 64 supporting substances from structural class I and of the 47 candidate substances is approximately 8000 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.

All 47 flavouring substances in the present flavouring group evaluation are expected to be metabolised to innocuous products. The Panel noted that in the present group of flavourings, one substance, 3,5,5-trimethylhexyl acetate, contains a tertiary butyl group. However, it is predicted that this ester is easily hydrolysed and either conjugated or further metabolised via common metabolic pathways.

Genotoxicity data are available only for a limited number of substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of the candidate substances using the Procedure.

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

It is considered that on the basis of the default MSDI approach these 47 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 they ranged from 1500 to 3900 microgram/person/day for the 47 flavouring substances from structural class I. The intakes were all above the threshold of concern for a structural class I substance of 1800 microgram/person/day, except for one flavouring substance [FL-no: 05.152]. This substance, which has mTAMDI intake estimate below the threshold of concern for a structural class I substance, is also expected to be metabolised to innocuous products.

Thus, for 46 of the 47 flavouring substances considered in this opinion the intakes, estimated on the basis of the mTAMDI approach, exceed the relevant threshold for their structural class. Therefore, for these 46 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 toxicological data might become necessary.

In order to determine whether the conclusion for the 47 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 tests for the materials of commerce have been provided for 42 of the 47 flavouring candidate substances, except that information on chirality is missing for two of the substances [FL-no: 02.178 and 09.819] and for five of the substances [FL-no: 02.178, 09.180, 09.331, 09.583 and 09.642] the purity criteria are deficient in one of the parameters.

Thus, the final evaluation of the materials of commerce cannot be performed for six substances [FL-no: 02.178, 09.180, 09.331, 09.583, 09.642 and 09.819], pending further information. The remaining 41 substances [FL-no: 02.126, 02.154, 02.180, 02.196, 02.202, 05.152, 09.307, 09.327, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.587, 09.588, 09.589, 09.592, 09.593, 09.594, 09.598, 09.599, 09.600, 09.602, 09.651, 09.659, 09.660, 09.661, 09.662, 09.664, 09.665, 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816 and 09.820] 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 2, REVISION 1

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

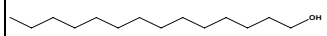
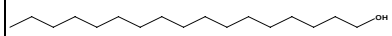
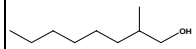
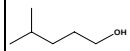
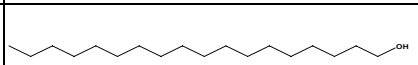
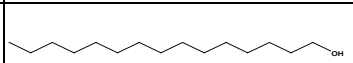
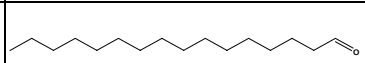
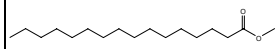
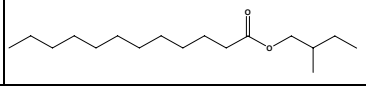
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
02.126	Tetradecan-1-ol		10314 112-72-1	Liquid $C_{14}H_{30}O$ 214.39	Insoluble 1 ml in 1 ml	170 (3 hPa) MS 95 %	1.435-1.441(40C) 0.819(40C)-0.825(40C	
02.154	Heptadecan-1-ol		- - 1454-85-9	Solid $C_{17}H_{36}O$ 256.47	Insoluble 1 ml in 1 ml	379 54 MS 95 %	n.a. n.a.	
02.178	2-Methyloctan-1-ol 6)		818-81-5	Liquid $C_9H_{20}O$ 144.26	Slightly soluble 1 ml in 1 ml	203 95 %	1.429-1.435 0.821-0.827	ID 7) CASrn in Register refers to the racemate,
02.180	4-Methylpentan-1-ol		10278 626-89-1	Liquid $C_6H_{14}O$ 102.18	Slightly soluble 1 ml in 1 ml	152 0 MS 95 %	1.411-1.417 0.810-0.816	
02.196	Octadecan-1-ol		- - 112-92-5	Solid $C_{18}H_{38}O$ 270.50	Insoluble 1 ml in 1 ml	210 (20 hPa) 59 MS 95 %	n.a. n.a.	
02.202	Pentadecan-1-ol		629-76-5	Solid $C_{15}H_{32}O$ 228.42	Insoluble 1 ml in 1 ml	133 (1 hPa) 45 MS 95 %	1.440-1.446 0.89-0.896	
05.152	Hexadecanal		10336 629-80-1	Solid $C_{16}H_{32}O$ 240.43	Insoluble 1 ml in 1 ml	144 (1 hPa) 36 MS 95 %	n.a. n.a.	
09.180	Methyl hexadecanoate		581 112-39-0	Liquid $C_{17}H_{34}O_2$ 270.45	Practically insoluble or insoluble 1 ml in 1 ml	181 (13 hPa) 99 %	1.448-1.454 0.877-0.883	ID 7)
09.307	2-Methylbutyl dodecanoate		10766 55195-19-2	Liquid $C_{17}H_{34}O_2$ 270.45	Insoluble 1 ml in 1 ml	308 MS 95 %	1.434-1.440 0.856-0.862	Racemate. CASrn to be changed to 93815-53-3,

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

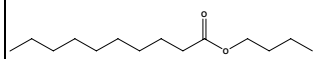
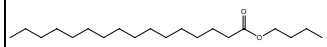
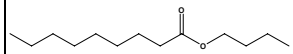
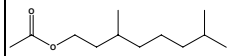
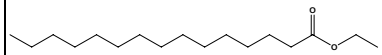
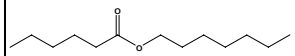
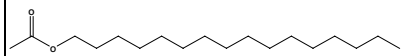
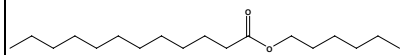
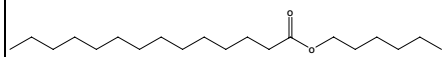
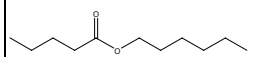
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.327	Butyl decanoate		10530 30673-36-0	Liquid $C_{14}H_{28}O_2$ 228.37	Insoluble 1 ml in 1 ml	123 (5 hPa) MS 95 %	1.427-1.433 0.858-0.864	
09.331	Butyl hexadecanoate		111-06-8	Solid $C_{20}H_{40}O_2$ 312.53	Practically insoluble or insoluble 1 ml in 1 ml	168 (13 hPa) 17 95 %	1.429-1,435 (50C) n.a.	ID 7)
09.334	Butyl nonanoate		50623-57-9	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble 1 ml in 1 ml	123 (3 hPa) MS 95 %	1.423-1.429 0.849-0.855	
09.358	3,7-Dimethyloctyl acetate		10899 20780-49-8	Liquid $C_{12}H_{24}O_2$ 200.32	Insoluble 1 ml in 1 ml	108 (19 hPa) MS 96 %	1.421-1.429 0.860-0.875	Racemate.
09.380	Ethyl pentadecanoate		10622 41114-00-5	Solid $C_{17}H_{34}O_2$ 270.45	Insoluble 1 ml in 1 ml	173 (20 hPa) 50 MS 95 %	n.a. 0.858-0.866	
09.390	Heptyl hexanoate		10666 6976-72-3	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble 1 ml in 1 ml	259 MS 95 %	1.421-1.427 0.859-0.865	
09.574	Hexadec-1-yl acetate		629-70-9	Solid $C_{18}H_{36}O_2$ 284.48	Insoluble 1 ml in 1 ml	200 (20 hPa) 24 MS 95 %	1.439-1.445 0.856-0.862	
09.579	Hexyl dodecanoate		34316-64-8	Liquid $C_{18}H_{36}O_2$ 284.48	Insoluble 1 ml in 1 ml	130 (1 hPa) NMR 95 %	1.436-1.442 0.855-0.86	
09.582	Hexyl tetradecanoate		42231-99-2	Solid $C_{20}H_{40}O_2$ 312.53	Insoluble 1 ml in 1 ml	215 (23 hPa) 84 NMR 95 %	n.a. 0.860-0.865	
09.583	Hexyl valerate		10696 1117-59-5	Liquid $C_{11}H_{22}O_2$ 186.29	1 ml in 1 ml	226 95 %	1.425-1.431 0.858-0.864	ID 7)

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

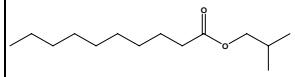
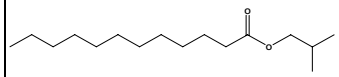
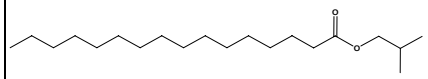
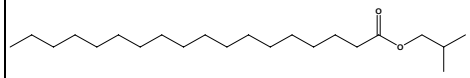
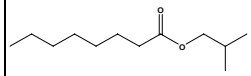
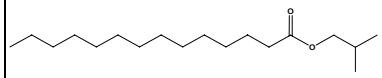
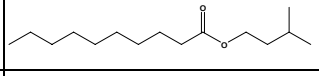
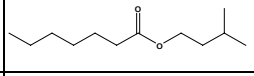
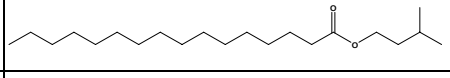
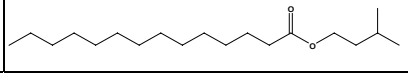
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.587	Isobutyl decanoate		10707 30673-38-2	Liquid $C_{14}H_{28}O_2$ 228.37	Insoluble 1 ml in 1 ml	272 MS 95 %	1.424-1.431 0.852-0.869	
09.588	Isobutyl dodecanoate		10708 37811-72-6	Liquid $C_{16}H_{32}O_2$ 256.43	Insoluble 1 ml in 1 ml	330 MS 95 %	1.428-1.436 0.852-0.861	
09.589	Isobutyl hexadecanoate		10715 110-34-9	Solid $C_{20}H_{40}O_2$ 312.53	Insoluble 1 ml in 1 ml	207 (20 hPa) 20 MS 95 %	n.a. n.a.	
09.592	Isobutyl octadecanoate		- - 646-13-9	Solid $C_{22}H_{44}O_2$ 340.59	Insoluble 1 ml in 1 ml	223 (20 hPa) 29 MS 95 %	n.a. n.a.	
09.593	Isobutyl octanoate		10714 5461-06-3	Liquid $C_{12}H_{24}O_2$ 200.32	Insoluble 1 ml in 1 ml	226 MS 95 %	1.416-1.426 0.852-0.864	
09.594	Isobutyl tetradecanoate		10712 25263-97-2	Solid $C_{18}H_{36}O_2$ 284.48	Insoluble 1 ml in 1 ml	330 47 MS 95 %	n.a. n.a.	
09.598	Isopentyl decanoate		2306-91-4	Liquid $C_{15}H_{30}O_2$ 242.40	Insoluble 1 ml in 1 ml	124 (4 hPa) MS 98 %	1.428-1.435 0.848-0.865	
09.599	Isopentyl heptanoate		10719 109-25-1	Liquid $C_{12}H_{24}O_2$ 200.32	Practically insoluble or insoluble 1 ml in 1 ml	112 (13 hPa) MS 95 %	1.420-1.426 0.856-0.864	
09.600	Isopentyl hexadecanoate		10723 81974-61-0	Solid $C_{21}H_{42}O_2$ 326.56	Insoluble 1 ml in 1 ml	365 80 NMR 95 %	1.429- 1.435(50C) n.a.	
09.602	Isopentyl tetradecanoate		10722 62488-24-8	Liquid $C_{19}H_{38}O_2$ 298.51	Insoluble 1 ml in 1 ml	342 58 NMR 95 %	n.a. n.a.	

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

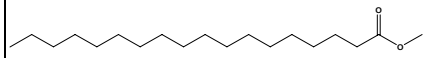
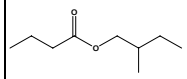
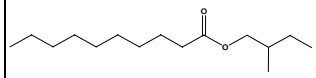
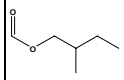
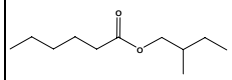
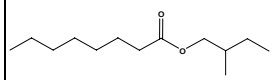
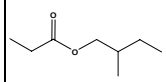
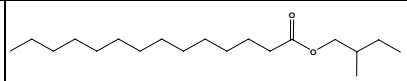
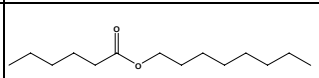
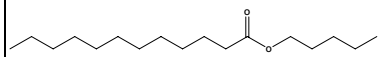
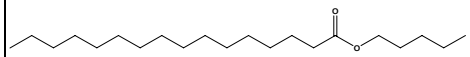
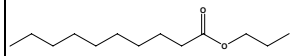
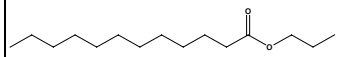
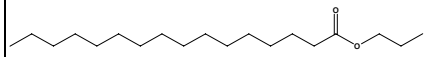
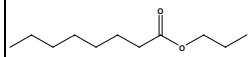
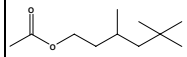
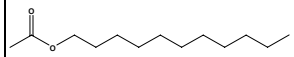
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
09.642	Methyl formate		10795 107-31-3	Liquid $C_2H_4O_2$ 60.05	Slightly soluble 1 ml in 1 ml	32 MS 99 %	1.341-1.346 0.960-0.985	Specific gravity range.
09.651	Methyl octadecanoate		10849 112-61-8	Solid $C_{19}H_{38}O_2$ 298.51	Insoluble 1 ml in 1 ml	210 (20 hPa) 38 MS 95 %	1.438-1.444 0.847(40C)- 0.853(40C	
09.659	2-Methylbutyl butyrate		51115-64-1	Liquid $C_9H_{18}O_2$ 158.24	Insoluble 1 ml in 1 ml	178 MS 95 %	1.408-1.414 0.862-0.868	Racemate.
09.660	2-Methylbutyl decanoate		10765 55195-23-8	Liquid $C_{15}H_{30}O_2$ 242.40	Insoluble 1 ml in 1 ml	151(13 hPa) MS 95 %	1.430-1.436 0.863-0.868	Racemate. CASrn to be changed to 68067-33-4.
09.661	2-Methylbutyl formate		35073-27-9	Liquid $C_6H_{12}O_2$ 116.16	Slightly soluble 1 ml in 1 ml	45 (0.01 hPa) NMR 95 %	1.389-1.410 0.874-0.894	Racemate.
09.662	2-Methylbutyl hexanoate		10768 2601-13-0	Liquid $C_{11}H_{22}O_2$ 186.29	Insoluble 1 ml in 1 ml	213 MS 95 %	1.417-1.423 0.856-0.862	Racemate.
09.664	2-Methylbutyl octanoate		10776 67121-39-5	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble 1 ml in 1 ml	252 (97 hPa) NMR 95 %	1.424-1.430 0.857-0.863	Racemate.
09.665	2-Methylbutyl propionate		10778 2438-20-2	Liquid $C_8H_{16}O_2$ 144.21	Slightly soluble 1 ml in 1 ml	157 MS 95 %	1.404-1.410 0.862-0.882	Racemate.
09.666	2-Methylbutyl tetradecanoate		10774 93805-23-3	Liquid $C_{19}H_{38}O_2$ 298.51	Insoluble 1 ml in 1 ml	197 (13 hPa) NMR 95 %	1.438-1.444 0.860-0.865	Racemate.
09.677	Octyl hexanoate		10865 4887-30-3	Liquid $C_{14}H_{28}O_2$ 228.37	Insoluble 1 ml in 1 ml	99 (1 hPa) MS 95 %	1.420-1.426 (30C) 0.850-0.856 (30C)	

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

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
09.681	Pentyl dodecanoate		5350-03-8	Solid $C_{17}H_{34}O_2$ 270.45	Insoluble 1 ml in 1 ml	325 50 MS 95 %	n.a. n.a.	
09.682	Pentyl hexadecanoate		- - 31148-31-9	Solid $C_{21}H_{42}O_2$ 326.56	Insoluble 1 ml in 1 ml	372 95 NMR 95 %	1.429- 1.435(50C) n.a.	
09.700	Propyl decanoate		30673-60-0	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble 1 ml in 1 ml	131 (15 hPa) MS 95 %	1.418-1.433 0.850-0.865	
09.813	Propyl dodecanoate		3681-78-5	Liquid $C_{15}H_{30}O_2$ 242.40	Insoluble 1 ml in 1 ml	291 MS 95 %	1.430-1.436 0.859-0.865	
09.814	Propyl hexadecanoate		10893 2239-78-3	Solid $C_{19}H_{38}O_2$ 298.51	Insoluble 1 ml in 1 ml	209 (29 hPa) 21 MS 95 %	1.436-1.442 0.827(60C)- 0.833(60C	
09.816	Propyl octanoate		10892 624-13-5	Liquid $C_{11}H_{22}O_2$ 186.29	Insoluble 1 ml in 1 ml	226 MS 95 %	1.418-1.424 0.861-0.867	
09.819	3,5,5-Trimethylhexyl acetate 6)		58430-94-7	Liquid $C_{11}H_{22}O_2$ 186.29	Practically insoluble or insoluble 1 ml in 1 ml	209 MS 95 %	1.418-1.424 0.862-0.868	CASrn in Register refers to the racemate.
09.820	Undecyl acetate		10906 1731-81-3	Liquid $C_{13}H_{26}O_2$ 214.35	Insoluble 1 ml in 1 ml	142 (20 hPa) MS 95 %	1.426-1.432 0.858-0.864	

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) *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)

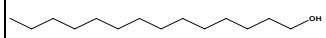
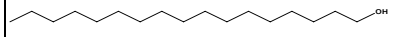
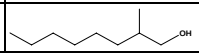
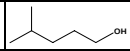
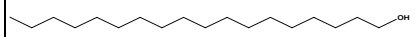
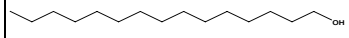
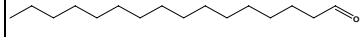
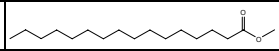
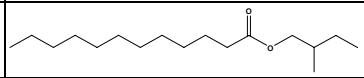
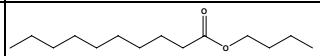
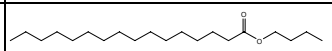
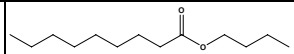
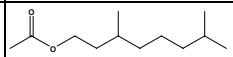
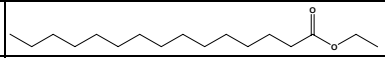
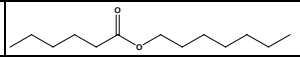
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.126	Tetradecan-1-ol		0.061	Class I A3: Intake below threshold	4)	6)	
02.154	Heptadecan-1-ol		0.0061	Class I A3: Intake below threshold	4)	6)	
02.178	2-Methyloctan-1-ol		0.012	Class I A3: Intake below threshold	4)	7)	
02.180	4-Methylpentan-1-ol		0.012	Class I A3: Intake below threshold	4)	6)	
02.196	Octadecan-1-ol		0.12	Class I A3: Intake below threshold	4)	6)	
02.202	Pentadecan-1-ol		0.024	Class I A3: Intake below threshold	4)	6)	
05.152	Hexadecanal		2.4	Class I A3: Intake below threshold	4)	6)	
09.180	Methyl hexadecanoate		2.8	Class I A3: Intake below threshold	4)	7)	
09.307	2-Methylbutyl dodecanoate		0.49	Class I A3: Intake below threshold	4)	6)	
09.327	Butyl decanoate		6.7	Class I A3: Intake below threshold	4)	6)	
09.331	Butyl hexadecanoate		0.79	Class I A3: Intake below threshold	4)	7)	
09.334	Butyl nonanoate		1.3	Class I A3: Intake below threshold	4)	6)	
09.358	3,7-Dimethyloctyl acetate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.380	Ethyl pentadecanoate		0.012	Class I A3: Intake below threshold	4)	6)	
09.390	Heptyl hexanoate		0.024	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)

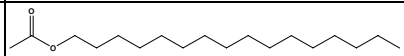
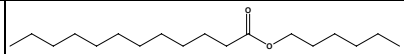
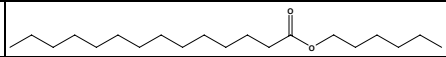
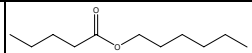
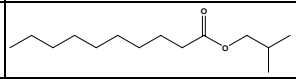
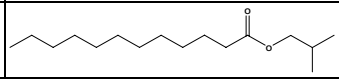
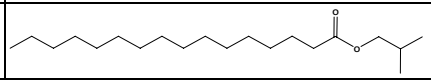
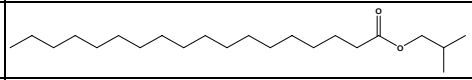
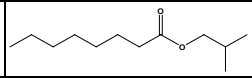
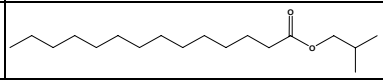
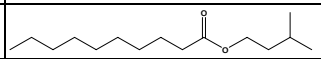
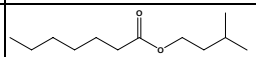
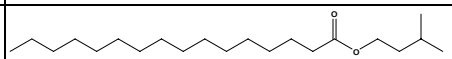
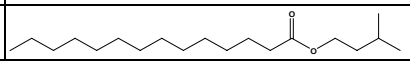
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.574	Hexadec-1-yl acetate		0.012	Class I A3: Intake below threshold	4)	6)	
09.579	Hexyl dodecanoate		0.24	Class I A3: Intake below threshold	4)	6)	
09.582	Hexyl tetradecanoate		0.61	Class I A3: Intake below threshold	4)	6)	
09.583	Hexyl valerate		0.79	Class I A3: Intake below threshold	4)	7)	
09.587	Isobutyl decanoate		3.0	Class I A3: Intake below threshold	4)	6)	
09.588	Isobutyl dodecanoate		0.61	Class I A3: Intake below threshold	4)	6)	
09.589	Isobutyl hexadecanoate		0.24	Class I A3: Intake below threshold	4)	6)	
09.592	Isobutyl octadecanoate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.593	Isobutyl octanoate		3.7	Class I A3: Intake below threshold	4)	6)	
09.594	Isobutyl tetradecanoate		1.8	Class I A3: Intake below threshold	4)	6)	
09.598	Isopentyl decanoate		4.5	Class I A3: Intake below threshold	4)	6)	
09.599	Isopentyl heptanoate		0.011	Class I A3: Intake below threshold	4)	6)	
09.600	Isopentyl hexadecanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.602	Isopentyl tetradecanoate		0.24	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)

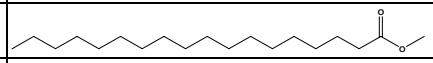
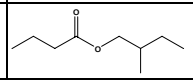
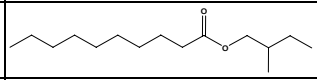
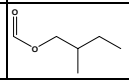
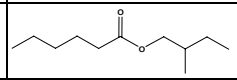
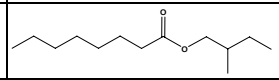
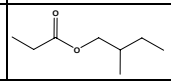
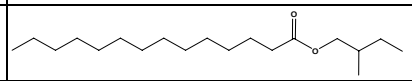
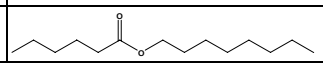
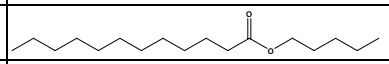
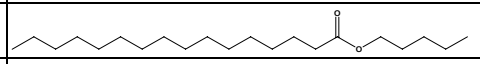
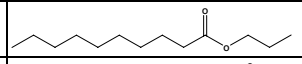
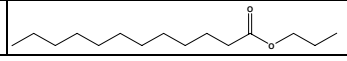
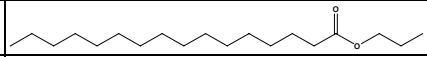
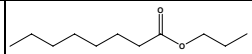
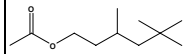
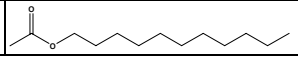
FL-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.642	Methyl formate		0.97	Class I A3: Intake below threshold	4)	7)	
09.651	Methyl octadecanoate		0.73	Class I A3: Intake below threshold	4)	6)	
09.659	2-Methylbutyl butyrate		2.1	Class I A3: Intake below threshold	4)	6)	
09.660	2-Methylbutyl decanoate		0.85	Class I A3: Intake below threshold	4)	6)	
09.661	2-Methylbutyl formate		0.97	Class I A3: Intake below threshold	4)	6)	
09.662	2-Methylbutyl hexanoate		0.49	Class I A3: Intake below threshold	4)	6)	
09.664	2-Methylbutyl octanoate		0.37	Class I A3: Intake below threshold	4)	6)	
09.665	2-Methylbutyl propionate		2.4	Class I A3: Intake below threshold	4)	6)	
09.666	2-Methylbutyl tetradecanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.677	Octyl hexanoate		0.61	Class I A3: Intake below threshold	4)	6)	
09.681	Pentyl dodecanoate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.682	Pentyl hexadecanoate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.700	Propyl decanoate		1.3	Class I A3: Intake below threshold	4)	6)	
09.813	Propyl dodecanoate		0.61	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
09.814	Propyl hexadecanoate		0.73	Class I A3: Intake below threshold	4)	6)	
09.816	Propyl octanoate		2.6	Class I A3: Intake below threshold	4)	6)	
09.819	3,5,5-Trimethylhexyl acetate		0.011	Class I A3: Intake below threshold	4)	7)	
09.820	Undecyl acetate		0.0012	Class I A3: Intake below threshold	4)	6)	

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

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

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

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

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

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

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

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

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

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

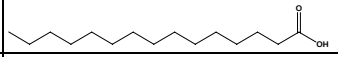
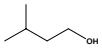
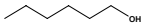
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
-	Pentadecanoic acid		Not evaluated as flavouring substance		Not in EU-Register.
-	Methanol		Not evaluated as flavouring substance		Not in EU-Register.
02.001	2-Methylpropan-1-ol 251		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.002	Propan-1-ol 82		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.003	Isopentanol 52		Category 1 a) No safety concern d) Category A c)	Class I A3: Intake below threshold	
02.004	Butan-1-ol 85		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.005	Hexan-1-ol 91		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.006	Octan-1-ol 97		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.009	Hexadecan-1-ol 114		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	

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

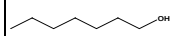
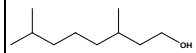
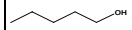
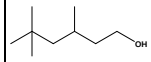
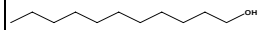
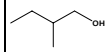
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
02.021	Heptan-1-ol 94		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.026	3,7-Dimethyloctan-1-ol 272		No safety concern b) Category B c)	Class I A3: Intake below threshold	
02.040	Pentan-1-ol 88		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.055	3,5,5-Trimethylhexan-1-ol 268		Category 2 a) No safety concern b) Category B c)	Class I A3: Intake below threshold	
02.057	Undecan-1-ol 106		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.076	2-Methylbutan-1-ol 1199		Category 1 a) No safety concern e) Category B c)	Class I A3: Intake below threshold	
02.078	Ethanol 41		Category 1 a) No safety concern d)	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.
08.001	Formic acid 79		Category 1 a) No safety concern b) Deleted c)	Class I A3: Intake below threshold	
08.002	Acetic acid 81		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
08.003	Propionic acid 84		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	

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

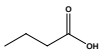
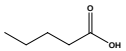
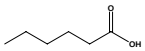
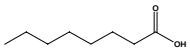
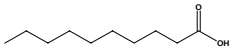
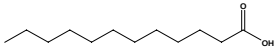
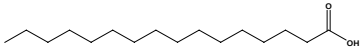
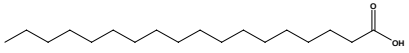
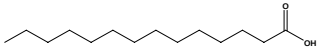
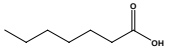
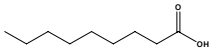
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
08.005	Butyric acid 87		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
08.007	Valeric acid 90		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
08.009	Hexanoic acid 93		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
08.010	Octanoic acid 99		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
08.011	Decanoic acid 105		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
08.012	Dodecanoic acid 111		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
08.014	Hexadecanoic acid 115		Category 1 a) No safety concern b) Deleted c)	Class I A3: Intake below threshold	
08.015	Octadecanoic acid 116		Category 1 a) No safety concern b) Deleted c)	Class I A3: Intake above threshold, A4: Endogenous	
08.016	Tetradecanoic acid 113		Category 1 a) No safety concern b) Deleted c)	Class I A3: Intake below threshold	
08.028	Heptanoic acid 96		Category 1 a) No safety concern b) Category A 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
08.029	Nonanoic acid 102		Category 1 a) No safety concern b) Category A c)	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, Class II = 540, 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) (SCF, 1995).

b) (JECFA, 1999b).

c) (CoE, 1992).

d) (JECFA, 1997a).

e) (JECFA, 2004a).

TABLE 3: SUPPORTING SUBSTANCES SUMMARY

Table 3: Supporting Substances Summary

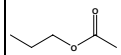
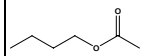
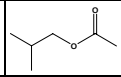
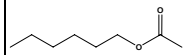
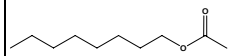
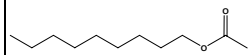
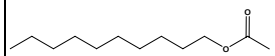
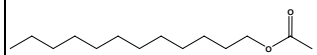
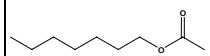
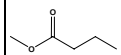
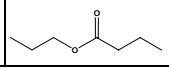
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.002	Propyl acetate		2925 192 109-60-4	126 JECFA specification (JECFA, 1997b)	160	No safety concern a) Category A b)	
09.004	Butyl acetate		2174 194 123-86-4	127 JECFA specification (JECFA, 1997b)	1000	No safety concern a) Category A b)	
09.005	Isobutyl acetate		2175 195 110-19-0	137 JECFA specification (JECFA, 1997b)	990	No safety concern a) Category A b)	
09.006	Hexyl acetate		2565 196 142-92-7	128 JECFA specification (JECFA, 1997b)	2800	No safety concern a) Category A b)	
09.007	Octyl acetate		2806 197 112-14-1	130 JECFA specification (JECFA, 1997b)	72	No safety concern a) Category A b)	
09.008	Nonyl acetate		2788 198 143-13-5	131 JECFA specification (JECFA, 1997b)	5.6	No safety concern a) Category A b)	
09.009	Decyl acetate		2367 199 112-17-4	132 JECFA specification (JECFA, 1997b)	6.2	No safety concern a) Category A b)	
09.010	Dodecyl acetate		2616 200 112-66-3	133 JECFA specification (JECFA, 2000d)	7.9	No safety concern a) Category A b)	
09.022	Heptyl acetate		2547 212 112-06-1	129 JECFA specification (JECFA, 1997b)	47	No safety concern a) Category A b)	
09.023	Methyl acetate		2676 213 79-20-9	125 JECFA specification (JECFA, 1997b)	400	No safety concern a) Category A b)	
09.038	Methyl butyrate		2693 263 623-42-7	149 JECFA specification (JECFA, 1997b)	180	Category 1 c) No safety concern a) Category A b)	
09.040	Propyl butyrate		2934 266 105-66-8	150 JECFA specification (JECFA, 1997b)	63	Category 1 c) No safety concern a) Category A b)	

Table 3: Supporting Substances Summary

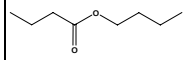
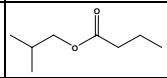
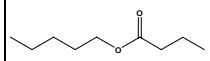
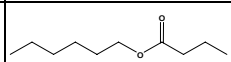
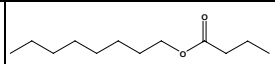
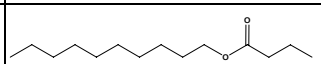
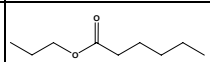
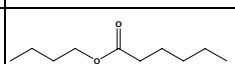
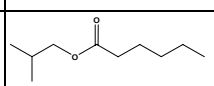
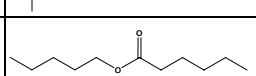
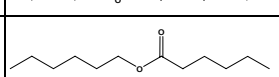
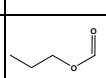
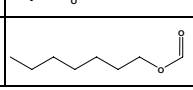
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.042	Butyl butyrate		2186 268 109-21-7	151 JECFA specification (JECFA, 1997b)	330	No safety concern a) Category A b)	
09.043	Isobutyl butyrate		2187 269 539-90-2	158 JECFA specification (JECFA, 1997b)	40	No safety concern a) Category A b)	
09.044	Pentyl butyrate		2059 270 540-18-1	152 JECFA specification (JECFA, 1997b)	380	Category 1 c) No safety concern a) Category A b)	
09.045	Hexyl butyrate		2568 271 2639-63-6	153 JECFA specification (JECFA, 1997b)	91	Category 1 c) No safety concern a) Category A b)	
09.046	Octyl butyrate		2807 272 110-39-4	155 JECFA specification (JECFA, 2000d)	14	Category 1 c) No safety concern a) Category A b)	
09.047	Decyl butyrate		2368 273 5454-09-1	156 JECFA specification (JECFA, 2000d)	0.0	Category 1 c) No safety concern a) Category A b)	
09.061	Propyl hexanoate		2949 311 626-77-7	161 JECFA specification (JECFA, 1997b)	12	No safety concern a) Category A b)	
09.063	Butyl hexanoate		2201 313 626-82-4	162 JECFA specification (JECFA, 1997b)	12	No safety concern a) Category A b)	
09.064	Isobutyl hexanoate		2202 314 105-79-3	166 JECFA specification (JECFA, 2000d)	5.2	No safety concern a) Category A b)	
09.065	Pentyl hexanoate		2074 315 540-07-8	163 JECFA specification (JECFA, 1997b)	7.4	No safety concern a) Category A b)	
09.066	Hexyl hexanoate		2572 316 6378-65-0	164 JECFA specification (JECFA, 1997b)	120	No safety concern a) Category A b)	
09.073	Propyl formate		2943 340 110-74-7	117 JECFA specification (JECFA, 2003b)	4.3	No safety concern a) Category A b)	
09.074	Heptyl formate		2552 341 112-23-2	121 JECFA specification (JECFA, 2000d)	0.0	No safety concern a) Category A b)	

Table 3: Supporting Substances Summary

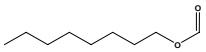
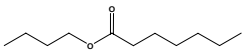
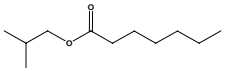
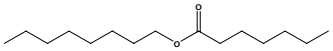
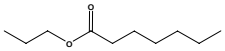
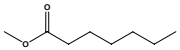
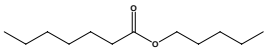
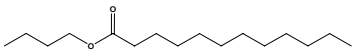
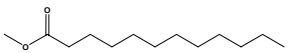
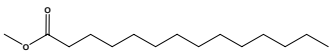
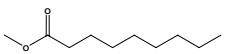
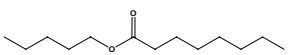
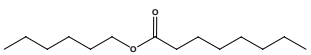
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (μg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.075	Octyl formate		2809 342 112-32-3	122 JECFA specification (JECFA, 1997b)	0.12	No safety concern a) Category A b)	
09.091	Butyl heptanoate		2199 363 5454-28-4	169 JECFA specification (JECFA, 2000d)	0.0	No safety concern a) Category A b)	
09.092	Isobutyl heptanoate		2200 364 7779-80-8	172 JECFA specification (JECFA, 2001c)	0.012	No safety concern a) Category A b)	
09.094	Octyl heptanoate		2810 366 5132-75-2	171 JECFA specification (JECFA, 2000d)	0.18	No safety concern a) Category B b)	
09.095	Propyl heptanoate		2948 367 7778-87-2	168 JECFA specification (JECFA, 2000d)	0.12	No safety concern a) Category A b)	
09.096	Methyl heptanoate		2705 368 106-73-0	167 JECFA specification (JECFA, 1997b)	4.9	No safety concern a) Category A b)	
09.098	Pentyl heptanoate		2073 370 7493-82-5	170 JECFA specification (JECFA, 2003b)	0.52	No safety concern a) Category B b)	
09.100	Butyl dodecanoate		2206 376 106-18-3	181 JECFA specification (JECFA, 1997b)	0.0	Category 1 c) No safety concern a) Category A b)	
09.101	Methyl dodecanoate		2715 377 111-82-0	180 JECFA specification (JECFA, 2003b)	4.4	Category 1 c) No safety concern a) Category A b)	
09.106	Methyl tetradecanoate		2722 387 124-10-7	183 JECFA specification (JECFA, 1997b)	54	Category 1 c) No safety concern a) Category B b)	
09.108	Methyl nonanoate		2724 389 1731-84-6	179 JECFA specification (JECFA, 1997b)	0.73	Category 1 c) No safety concern a) Category A b)	
09.112	Pentyl octanoate		2079 393 638-25-5	174 JECFA specification (JECFA, 1997b)	2.9	Category 1 c) No safety concern a) Category A b)	
09.113	Hexyl octanoate		2575 394 1117-55-1	175 JECFA specification (JECFA, 1997b)	1.1	Category 1 c) No safety concern a) Category B b)	

Table 3: Supporting Substances Summary

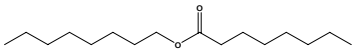
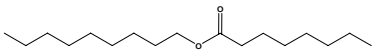
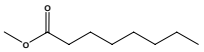
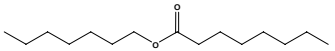
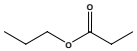
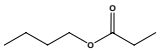
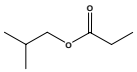
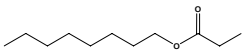
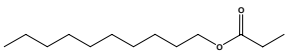
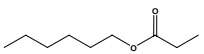
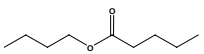
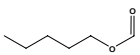
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.114	Octyl octanoate		2811 395 2306-88-9	177 JECFA specification (JECFA, 2000d)	0.024	Category 1 c) No safety concern a) Category B b)	
09.115	Nonyl octanoate		2790 396 7786-48-3	178 JECFA specification (JECFA, 2001c)	0.12	Category 1 c) No safety concern a) Category B b)	
09.117	Methyl octanoate		2728 398 111-11-5	173 JECFA specification (JECFA, 1997b)	8.3	Category 1 c) No safety concern a) Category A b)	
09.118	Heptyl octanoate		2553 399 4265-97-8	176 JECFA specification (JECFA, 2000d)	0.61	Category 1 c) No safety concern a) Category B b)	
09.122	Propyl propionate		2958 403 106-36-5	142 JECFA specification (JECFA, 1997b)	8.2	No safety concern a) Category A b)	
09.124	Butyl propionate		2211 405 590-01-2	143 JECFA specification (JECFA, 1997b)	8.8	No safety concern a) Category A b)	
09.125	Isobutyl propionate		2212 406 540-42-1	148 JECFA specification (JECFA, 1997b)	10	No safety concern a) Category A b)	
09.126	Octyl propionate		2813 407 142-60-9	145 JECFA specification (JECFA, 1997b)	0.0	No safety concern a) Category A b)	
09.127	Decyl propionate		2369 408 5454-19-3	146 JECFA specification (JECFA, 1997b)	0.0	No safety concern a) Category A b)	
09.134	Methyl propionate		2742 415 554-12-1	141 JECFA specification (JECFA, 1997b)	7.9	No safety concern a) Category A b)	
09.139	Hexyl propionate		2576 420 2445-76-3	144 JECFA specification (JECFA, 1997b)	4.9	No safety concern a) Category A b)	
09.148	Butyl valerate		2217 466 591-68-4	160 JECFA specification (JECFA, 1997b)	3.2	Category 1 c) No safety concern a) Category A b)	
09.159	Pentyl formate		2068 497 638-49-3	119 JECFA specification (JECFA, 2003b)	24	No safety concern a) Category A b)	

Table 3: Supporting Substances Summary

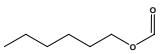
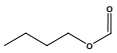
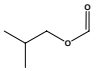
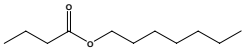
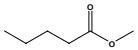
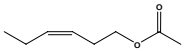
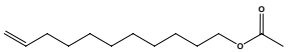
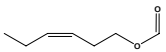
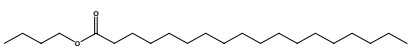
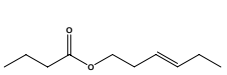
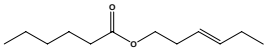
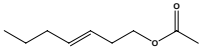
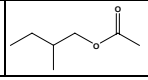
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
09.161	Hexyl formate		2570 499 629-33-4	120 JECFA specification (JECFA, 1997b)	5.1	No safety concern a) Category A b)	
09.163	Butyl formate		2196 501 592-84-7	118 JECFA specification (JECFA, 1997b)	18	No safety concern a) Category A b)	
09.164	Isobutyl formate		2197 502 542-55-2	124 JECFA specification (JECFA, 1997b)	4.0	No safety concern a) Category A b)	
09.166	Heptyl butyrate		2549 504 5870-93-9	154 JECFA specification (JECFA, 2000d)	5.1	Category 1 c) No safety concern a) Category A b)	
09.182	Methyl valerate		2752 588 624-24-8	159 JECFA specification (JECFA, 1997b)	26	Category 1 c) No safety concern a) Category A b)	
09.197	Hex-3(cis)-enyl acetate		3171 644 3681-71-8	134 JECFA specification (JECFA, 1997b)	550	No safety concern a) Category B b)	
09.214	Undec-10-enyl acetate		3096 2062 112-19-6	136 JECFA specification (JECFA, 1997b)	0.71	No safety concern a) Category B b)	
09.240	Hex-3(cis)-enyl formate		3353 2153 33467-73-1	123 JECFA specification (JECFA, 1997b)	37	No safety concern a) Category B b)	
09.246	Butyl octadecanoate		2214 2189 123-95-5	184 JECFA specification (JECFA, 2001c)	4.4	No safety concern a) Deleted b)	
09.270	Hex-3-enyl butyrate		3402 11859 16491-36-4	157 JECFA specification (JECFA, 1997b)	130	No safety concern a)	JECFA evaluated cis-3-hexenyl butyrate (CASrn as in Register). CASrn in Register refers to the (Z)-isomer.
09.271	Hex-3-enyl hexanoate		3403 11779 31501-11-8	165 JECFA specification (JECFA, 2000d)	35	No safety concern a)	JECFA evaluated cis-3-hexenyl hexanoate (CASrn as in Register). CASrn in Register refers to the (Z)-isomer.
09.275	Hept-3(trans)-enyl acetate		3493 10662 1576-77-8	135 JECFA specification (JECFA, 1997b)	0.21	No safety concern a)	JECFA CASrn 34942-91-1. CASrn in Register refers to (E)-isomer.

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
09.286	2-Methylbutyl acetate		3644 10762 624-41-9	138 JECFA specification (JECFA, 1997b)	110	No safety concern a)	

ND) No intake data reported.

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) (JECFA, 1999b).

b) (CoE, 1992).

c) (SCF, 1995).

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, 2000), 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, 1999), 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[6] (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[7] (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.

[6] *"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).*

[7] *"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).*

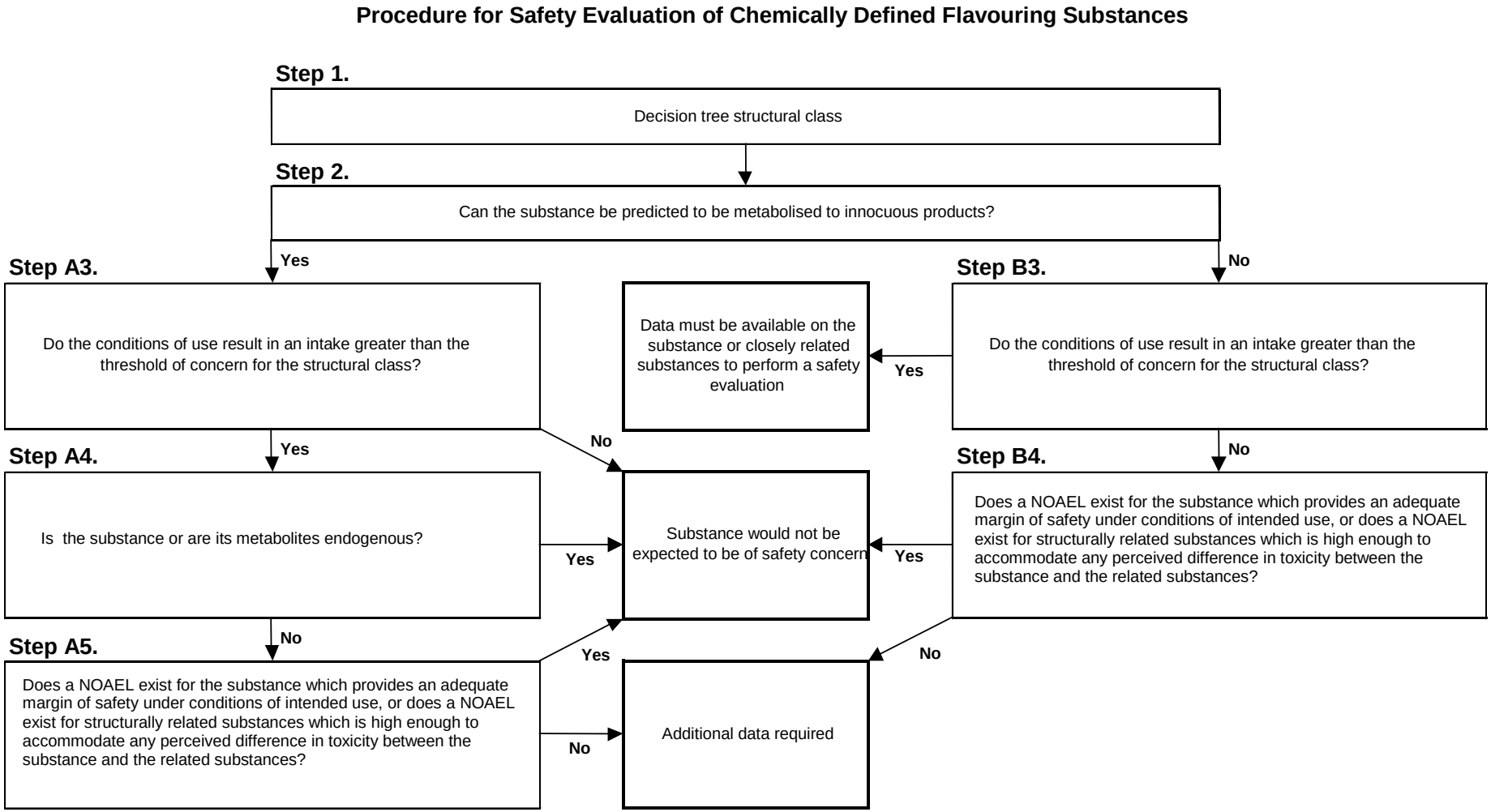


Figure I.1 *Procedure for Safety evaluation of Chemically Defined Flavouring Substances*

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, 2000). 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 (EC, 2000) 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, 2000)

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 the 47 candidate substances in the present flavouring group (Table II.1.2).

Table II.1.2. Normal and Maximum use levels (mg/kg) for candidate substances in FGE.02Rev1 (EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad)

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
02.126	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
02.154	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
02.178	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	2 25
02.180	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
02.196	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
02.202	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
05.152	3 15	2 10	3 15	2 10	- -	4 20	2 10	4 20	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
09.180	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
09.307	7 35	5 25	10 50	5 25	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
09.327	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
09.331	7 35	5 25	10 50	7 35	- -	- -	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	- -	20 100	5 25
09.334	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
09.358	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
09.380	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
09.390	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
09.574	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
09.579	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
09.582	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
09.583	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
09.587	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
09.588	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
09.589	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
09.592	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
09.593	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	85	75	100	90	-	100	75	100	50	50	-	-	25	50	25	100	100	25
09.594	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
09.598	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	50	25	50	35	-	100	25	50	10	10	-	-	25	50	50	100	100	25
09.599	7	5	10	7	-	10	5	10	2	2	-	-	5	10	-	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	-	50	100	25
09.600	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
09.602	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
09.642	5	5	10	7	-	5	5	5	2	-	-	-	5	10	2	5	20	5
	35	25	50	35	-	50	25	50	10	-	-	-	25	50	25	50	100	25
09.651	7	5	10	5	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	25	-	50	25	50	10	10	-	-	25	50	25	50	100	25
09.659	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
09.660	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
09.661	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
09.662	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
09.664	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
09.665	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
09.666	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
09.677	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
09.681	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
09.682	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
09.700	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	100	100	35	-	100	25	100	10	10	-	-	25	50	25	100	100	25
09.813	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
09.814	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
09.816	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	100	10	10	-	-	25	50	25	50	100	25
09.819	7	5	10	7	-	10	5	10	2	2	-	-	5	10	-	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	-	50	100	25
09.820	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

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 consumes 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, 2000) 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, 2000)
- 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, 2000)
- Exception a (SCF, 1995) corresponds to food category 5 and 11 (EC, 2000)
- Exception b (SCF, 1995) corresponds to food category 15 (EC, 2000)
- Exception c (SCF, 1995) corresponds to food category 14.2 (EC, 2000)
- Exception d (SCF, 1995) corresponds to food category 12 (EC, 2000)
- 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, 2000) 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	Dairy products, excluding products of category 02.0	Food		
02	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03	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	Confectionery			Exception a
06	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07	Bakery wares	Food		
08	Meat and meat products, including poultry and game	Food		
09	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10	Eggs and egg products	Food		
11	Sweeteners, including honey			Exception a
12	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13	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	Ready-to-eat savouries			Exception b
16	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 Evaluation, for which Industry has provided use and use levels (EFFA, 2001a; EFFA, 2003s; EFFA, 2004ad). The mTAMDI values are only given for highest reported normal use.

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)
02.126	Tetradecan-1-ol	3900	Class I	1800
02.154	Heptadecan-1-ol	3900	Class I	1800
02.178	2-Methyloctan-1-ol	3900	Class I	1800
02.180	4-Methylpentan-1-ol	3900	Class I	1800
02.196	Octadecan-1-ol	3900	Class I	1800
02.202	Pentadecan-1-ol	3900	Class I	1800
05.152	Hexadecanal	1500	Class I	1800
09.180	Methyl hexadecanoate	3900	Class I	1800
09.307	2-Methylbutyl dodecanoate	3900	Class I	1800
09.327	Butyl decanoate	3900	Class I	1800
09.331	Butyl hexadecanoate	3500	Class I	1800
09.334	Butyl nonanoate	3900	Class I	1800
09.358	3,7-Dimethyloctyl acetate	3900	Class I	1800
09.380	Ethyl pentadecanoate	3900	Class I	1800
09.390	Heptyl hexanoate	3900	Class I	1800
09.574	Hexadec-1-yl acetate	3900	Class I	1800
09.579	Hexyl dodecanoate	3900	Class I	1800
09.582	Hexyl tetradecanoate	3900	Class I	1800
09.583	Hexyl valerate	3900	Class I	1800
09.587	Isobutyl decanoate	3900	Class I	1800
09.588	Isobutyl dodecanoate	3900	Class I	1800
09.589	Isobutyl hexadecanoate	3900	Class I	1800
09.592	Isobutyl octadecanoate	3900	Class I	1800
09.593	Isobutyl octanoate	3900	Class I	1800
09.594	Isobutyl tetradecanoate	3900	Class I	1800
09.598	Isopentyl decanoate	3900	Class I	1800
09.599	Isopentyl heptanoate	2300	Class I	1800
09.600	Isopentyl hexadecanoate	3900	Class I	1800
09.602	Isopentyl tetradecanoate	3900	Class I	1800
09.642	Methyl formate	2700	Class I	1800
09.651	Methyl octadecanoate	3900	Class I	1800
09.659	2-Methylbutyl butyrate	3900	Class I	1800
09.660	2-Methylbutyl decanoate	3900	Class I	1800
09.661	2-Methylbutyl formate	3900	Class I	1800
09.662	2-Methylbutyl hexanoate	3900	Class I	1800
09.664	2-Methylbutyl octanoate	3900	Class I	1800
09.665	2-Methylbutyl propionate	3900	Class I	1800
09.666	2-Methylbutyl tetradecanoate	3900	Class I	1800
09.677	Octyl hexanoate	3900	Class I	1800
09.681	Pentyl dodecanoate	3900	Class I	1800
09.682	Pentyl hexadecanoate	3900	Class I	1800
09.700	Propyl decanoate	3900	Class I	1800
09.813	Propyl dodecanoate	3900	Class I	1800
09.814	Propyl hexadecanoate	3900	Class I	1800
09.816	Propyl octanoate	3900	Class I	1800
09.819	3,5,5-Trimethylhexyl acetate	2300	Class I	1800
09.820	Undecyl acetate	3900	Class I	1800

ANNEX III: METABOLISM

III.1 Absorption, Distribution and Excretion

Data for short- and medium-length linear alcohols, aldehydes and esters (and their component alcohols and carboxylic acids) included in this evaluation, and more general information for this class of chemicals, indicate that they are rapidly absorbed from the gastrointestinal tract (JECFA, 1999b). Information on distribution and excretion of these compounds has not been submitted, but these flavouring substances can be expected to be extensively metabolised to substances that are easily excreted (see below).

The relevant and specific information available on the absorption, distribution and excretion of the flavouring substances included in this monograph or chemical analogues follows:

Methyl formate [FL-no: 09.642]

Methyl formate is expected to be hydrolysed in the gastrointestinal (GI) tract to methanol and formic acid (see below). Methanol and formic acid are rapidly absorbed from the GI tract of man (Lund, 1948; Malorny, 1969a). The biological half-lives of formic acid and methanol in man following ingestion are approximately 45 minutes (Malorny, 1969a) and 7 hours (estimated from data in (Leaf & Zatman, 1952)), respectively. In comparison the corresponding biological half-lives of formic acid in rats and guinea pigs are approximately 12 minutes and 22 minutes, respectively (Malorny, 1969a).

2-Methylbutan-1-ol [FL-no: 02.076]

Small amounts of the amyl alcohols pentan-1-ol [FL-no: 02.040], 2-methylbutan-1-ol [FL-no: 02.076], and 3-methylbutan-1-ol [FL-no: 02.003] were excreted via expired air (0.088 to 5.6 % of total dose) or urine (0.27 to 2.0 % of total dose) following 1 g/kg dose i.p. injection to rats (Haggard et al., 1945). The maximum blood alcohol concentrations ranged from 14 to 55 mg/100 ml and were no longer detectable in the blood after 4 to 9 hours. Rapid metabolism probably accounted for the low blood alcohol levels reported. The closely related branched-chain aliphatic candidate chemical alcohol, 4-methylpentan-1-ol [FL-no: 02.180], would be expected to follow a similar pattern of absorption, distribution, metabolism and excretion.

The branched chain candidate chemical ester, 2-methylbutyl formate [09.661] would be expected to follow a very similar pattern of absorption, distribution and excretion as described for methyl formate [FL-no: 09.642] and 2-methylbutan-1-ol [FL-no: 02.076].

Hexadecan-1-ol [FL-no: 02.009]

Data for the C16 aliphatic alcohol, hexadecan-1-ol (cetyl alcohol), indicate that of the 34 % total absorbed (recovered in thoracic duct lymph, carcass, liver, expired CO_2, and urine) of a dose in corn oil administered by oral gavage to male Sprague-Dawley rats, 75 % was found in the thoracic duct lymph after 24 hours and that 85 % of this material had been converted to fatty acid, presumed to be palmitic acid (Baxter et al., 1967). Another study corroborates this result in that cetyl alcohol was well absorbed (63 to 96 %, based on the difference between amount administrated and amount recovered from the intestinal tract and faeces) when fed to rats. From 31 to 64 % of the absorbed material was recovered from the thoracic lymph lipids. About 15 % of this amount was present as unchanged cetyl alcohol. The remainder had been oxidised to palmitic acid and subsequently incorporated into triglycerides and phospholipids. The main part of this oxidation process took

place during the passage of the lipids through the intestinal mucosa cells (Blomstrand & Rumpf, 1954). The C14 and C15 linear-chain aliphatic candidate chemical alcohols, i.e. tetradecan-1-ol [FL-no: 02.126] and pentadecan-1-ol [FL-no: 02.202], would be expected to follow a similar pattern of absorption, distribution and excretion as the closely related C16 linear-chain aliphatic alcohol, hexadecan-1-ol.

III.2 Biotransformation

A general discussion of the biotransformation of esters of aliphatic linear or branched chain alcohols and linear aliphatic acids and their alcohol and acid moieties, as well as specific discussions of the metabolic pathways for propyl alcohol [FL-no: 02.002], 2-ethylbutyl alcohol [FL-no: 02.043], isobutyl alcohol [FL-no: 02.001], isoamyl alcohol [FL-no: 02.003], isobutyraldehyde [FL-no: 05.004], acetaldehyde [FL-no: 05.001], isobutyric acid [FL-no: 08.006], isovaleric acid [FL-no: 08.008], and 2-methylbutyric acid [FL-no: 08.046] are provided by JECFA (JECFA, 1999b). These discussions and conclusions apply equally well to the candidate substances as they do to the supporting substances.

The following additional discussion on the metabolism of the short and medium-length linear or branched aliphatic alcohols, aldehydes, esters of linear carboxylic acids, and linear or branched chain-carboxylic acids is structured according to the general metabolic reactions that have been demonstrated for these or similar chemicals. The likelihood that the candidate substances undergo these metabolic reactions depends on their chain length and degree of branching and functional groups. It is likely that multiple metabolic reactions will occur for some substances. The probable metabolic reactions are the following:

III.2.1 Ester Hydrolysis

III.2.2 Oxidation of Alcohols and Aldehydes to Acids

III.2.3 Reduction of Aldehydes to Alcohols

III.2.4 Metabolism to Glucuronides and Sulphates

III.2.5 beta-Oxidation of Linear Carboxylic Acids

III.2.6 omega-Oxidation of Carboxylic Acids

III.2.7 Other Biotransformation Reactions

III.2.1 Ester Hydrolysis

The esters included in this monograph are expected to be hydrolysed enzymatically to carboxylic acids and alcohols via carboxylesterases found in most tissues throughout the body, the most important of which are the beta-esterases. beta-Esterases have been demonstrated in almost all mammalian tissues with the highest concentration of esterase activity towards simple aliphatic and aromatic substrates invariably localised in the liver (Heymann, 1980).

In a study of the influence of the alkyl (C1-C7) and acyl chain length (C1-C7) of aliphatic esters on kinetic parameters of rat liver carboxylesterase, it was found that an elongation of the alcohol chain up to C4 leads to a linear increase of the Km values approaching a plateau from C4 to C7. A variation on the length of the acyl part had no significant influence on Km (Arndt & Krisch, 1973). In a later study with similar substrates, other authors (Junge & Heymann, 1979) found that short

chain unbranched aliphatic esters are good substrates for pig-liver carboxyl esterase with respect to reaction rates and affinity. However, different isoenzymes showed striking differences in the hydrolysis rates. In the case of variation of the acyl chain, isoenzyme V had an optimum for the C5 compound (methyl pentanoate), while with acetate esters of varying chain length of the alcohol moiety, this isoenzyme exhibited a minimum activity with butyl and pentyl acetate. In contrast, the activity of isoenzyme I increased constantly with increasing chain length of both, the acyl and the alcohol moieties. The authors concluded that it appears reasonable to assume a cooperative and complementary function, which is fulfilled by the different substrate specificities of the esterase isoenzymes.

While no hydrolysis data have been provided for the esters of the present group of flavourings, there are in vitro hydrolysis data for some structurally related esters. Structurally related esters were shown to be hydrolysed rather slowly in artificial gastric juice (half-life T1/2 146-770 min) (Longland et al., 1977; Gangolli & Shilling, 1968). Hydrolysis in artificial pancreatic juice/pancreatin was found to be faster than in artificial gastric juice (Gangolli & Shilling, 1968; Longland et al., 1977; Leegwater & Straten, 1974a; Grundschober, 1977). However, there is a variation in the degree of hydrolysis between different structurally related esters. Hydrolysis by artificial pancreatic juice was rather fast for some esters (T1/2 of ethylbutyrate, isoamyl butyrate, ethyl hexanoate, ethyl heptanoate, ethyl nonanoate, and ethyl laurate were 6, 11, 3, 10, 6, and 6 min, respectively) and relatively slow for other esters (T1/2 of butyl acetate and isoamyl hexanoate were 66 and 38 min., respectively). Rat liver homogenate and small intestinal mucosa preparation were found to be much more efficient in hydrolysing esters. While half lives of butyl acetate were 491 and 108 sec. for hydrolysis by liver homogenate and intestinal mucosa preparation, respectively, half lives of isoamyl butyrate, ethyl hexanoate, and ethyl heptanoate were less than 1 second in liver homogenate or small intestinal mucosa preparation (Longland et al., 1977).

The Panel noted that in the present group of flavourings one substance contains a tertiary butylgroup, 3,5,5-trimethylhexyl acetate [FL-no: 09.819]. However, it is predicted that this ester is easily hydrolysed and either conjugated or further metabolised via common metabolic pathways.

Based on these data on substances structurally related to the esters included in this evaluation it can be expected that the 40 esters included in this evaluation will be hydrolysed to their corresponding acids and alcohols in humans within a relatively short time. The expected hydrolysis products for the 40 esters, and their evaluation status when used as flavouring substances, are shown in Table 2b.

III.2.2 Oxidation of Alcohols and Aldehydes to Acids

Linear and branched chain saturated alcohols and aldehydes are oxidised to corresponding carboxylic acids by high capacity NAD+/NADH-dependent enzymes (Parkinson, 1996a; Feron et al., 1991).

Alcohol dehydrogenase (ADH) enzymes are cytosolic enzymes that are primarily responsible for the oxidation of alcohols to their corresponding aldehydes. Alcohols also can be oxidised to aldehydes by non-ADH enzymes present in the microsomes and peroxisomes, but these are generally quantitatively less important than ADH for ethanol oxidation. Aldehyde dehydrogenases (ALDH) oxidise aldehydes to their corresponding carboxylic acids. Of the several ALDH enzymes involved in the oxidation of aldehydes, Class I ALDH enzymes are responsible for the oxidation of the widest variety of aldehydes (Parkinson, 1996a) and would be expected to be responsible for the oxidation of the candidate substances. Branched-chain aliphatic alcohols and aldehydes are also good substrates for ADH and ALDH (Hedlund & Kiessling, 1969a; Albro, 1975).

III.2.3 Reduction of Aldehydes to Alcohols

Aldehydes also may be reduced to alcohols, but reduction has a minor overall impact on aldehyde metabolism. Reduction is a reversible reaction, while oxidation is irreversible and the Km of ALDH is substantially lower (higher affinity) than the Km of the reductases for the aldehydes (Sladek et al., 1989, as cited in (Feron et al., 1991)).

III.2.4 Metabolism to Glucuronides and Sulphates

Hydroxyl and carboxyl functional groups are sensitive to conjugation reactions with glucuronide and sulphate (Parkinson, 1996a). Conjugation of hydroxyl and carboxyl groups with glucuronide and sulphate and subsequent urinary excretion is expected to compete with the other metabolic reactions described in this annex. Based on the metabolic profiles available, these conjugation reactions apparently comprise a small fraction of the overall metabolic disposition of short- and medium-length branched chain alcohols, acids, aldehydes and esters. Conjugation with glucuronide may account for the elimination of up to 10 % of the dose for linear aliphatic alcohols with a chain length of about 6 to 8 carbon atoms. For linear alcohols with shorter chain length, this conjugation with glucuronic acid is even less important (Kamil et al., 1953a).

III.2.5 beta-Oxidation of Linear Carboxylic Acids

beta-Oxidation is a major route of metabolism for the candidate chemicals included in this monograph. beta-Oxidation of fatty acids produces acetyl coenzyme A as a result of sequential removal of two-carbon units from carboxylic acids. The process is repeated until the end products are acetate or propionate. The products of fatty acid oxidation depend on the chain length of the chemical. Acetyl coenzyme A is utilised for energy via the citric acid cycle or converted to acetoacetate and subsequently to other ketone bodies. Ketone bodies may be oxidised or excreted in the urine. Propionate originates from odd numbered-chain acids and is converted to succinyl-CoA for entry into the citric acid cycle (Voet & Voet, 1990). The candidate chemicals included in this monograph are prime candidates for fatty acid beta-oxidation since the esters are expected to be hydrolysed to acids and alcohols, and the alcohols and aldehydes will be oxidised to carboxylic acids.

III.2.6 omega-Oxidation of Carboxylic Acids

Medium- and long-chain fatty acids may also be partly oxidised via omega-oxidation, producing dicarboxylic acids, which may be attacked from either end by beta-oxidation. omega-Oxidation may occur when capacity for beta-oxidation is either exceeded because of a large dose of the chemical or blocked because of substitution in the alpha- or beta-position. Short-chain acids, such as butyric, caproic and caprylic acids may be converted to longer-chain fatty acids for incorporation into normal intermediary metabolism (Voet & Voet, 1990).

III.2.7 Other Biotransformation Reactions

2-Methylbutan-1-ol [FL-no: 02.076]

This and other short chain amyl alcohols were rapidly metabolised after peritoneal injection to rats (1 g/kg). The alcohols were oxidised to their corresponding aldehydes, which were assumed to be further oxidised to their corresponding acids (Haggard et al., 1945) (Haggard et al., 1945). The oxidation of alcohols to aldehydes appeared to occur mainly in the liver, for this reaction was inhibited in partially hepatectomized rats. As a minor pathway, primary alcohols may be conjugated directly with glucuronide. In a study of the glucuronic acid conjugation of aliphatic alcohols in rabbit, 2-methylbutanol yielded about 10 % of non-reduced glucuronide. Non-branched primary alcohols (C1-C18) showed a very low extent of conjugation (less than 10 %) while some branched primary alcohols were conjugated to much higher percentages (Kamil et al., 1953a).

III.3 Conclusion

It is anticipated that the 40 candidate esters [FL-no: 09.180, 09.307, 09.327, 09.331, 09.334, 09.358, 09.380, 09.390, 09.574, 09.579, 09.582, 09.583, 09.587 - 09.589, 09.592 - 09.594, 09.598, 09.599, 09.600, 09.602, 09.642, 09.651, 09.659 - 9.662, 09.664 - 09.666, 09.677, 09.681, 09.682, 09.700, 09.813, 09.814, 09.816, 09.819 and 09.820] will undergo hydrolysis to yield their corresponding linear or branched chain aliphatic alcohols and linear carboxylic acids. The hydrolysis products of the 40 esters, the four linear aliphatic alcohols [FL-no: 02.126, 02.154, 02.196, and 02.202], the two branched-chain alcohol [FL-no: 02.178 and 02.180] and the one candidate linear aldehyde [FL-no: 05.152], are all expected to be absorbed rapidly from the gastrointestinal tract. Any remaining non-hydrolysed candidate esters are expected to be absorbed rapidly from the gastrointestinal tract as well, after which they are also expected to be hydrolysed.

Linear alcohols, resulting from ester hydrolysis and the four primary linear candidate alcohols, would be oxidised to their corresponding aldehydes and these and the one candidate linear aldehyde would be oxidised to their linear carboxylic acids, which can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle.

Branched-chain alcohols, resulting from ester hydrolysis and the two primary branched-chain candidate alcohols, would be oxidised to their corresponding aldehydes and further to their corresponding branched chain carboxylic acids, which can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle. Metabolism to glucuronides may also take place.

Similarly, linear carboxylic acids resulting from ester hydrolysis can be assumed to be metabolised to carbon dioxide via the fatty acid pathways and the carboxylic acid cycle.

The Panel noted that in the present group of flavourings one substance contains a tertiary butylgroup, 3,5,5-trimethylhexyl acetate [FL-no: 09.819]. However, it is predicted that this ester is easily hydrolysed and either conjugated or further metabolised via common metabolic pathways.

ANNEX IV: TOXICITY

Oral acute toxicity data are available for six candidate substances of the present flavouring group evaluation from chemical groups 1 and 2, and for 20 supporting and structurally related supporting, of which 18 were evaluated by the JECFA at the 46th and 49th meetings. The supporting substances are listed in brackets.

TABLE IV.1: ACUTE TOXICITY

Table IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD_{50} (mg/kg bw)	Reference	Comments
Methyl formate [09.642]	Rat	NR	Oral	1500	(BASF, 1979a)	
	Rat	NR	Oral	475	(Eastman Kodak Co., 1994a)	
	Mouse	NR	Oral	675	(Eastman Kodak Co., 1994a)	
	Rabbit	NR	Oral	1621	(Munch, 1972)	
	Rabbit	NR	Oral	1600	(Gosselin et al., 1984)	
	Rabbit	NR	Oral	1622	(RTECS, 2002)	
(Formic Acid [08.001])	Rat	NR	Oral	1830	(Sporn et al., 1962)	2
	Mouse	NR	Oral	1100	(Malorny, 1969a)	2
(Isoamyl formate [09.162])	Rabbit	NR	Oral	3016	(Munch, 1972)	2
	Rat	NR	Oral	9840	(Jenner et al., 1964)	2
(Methyl acetate [09.023])	Rat	NR	Oral	6970	(Smyth et al., 1962)	1
	Rabbit	NR	Oral	3700	(Munch, 1972)	1
(Lauryl acetate [09.010])	Rat	NR	Oral	>5000	(Moreno, 1974b)	1
(cis-3-Hexenyl acetate [09.197])	Rat	NR	Oral	>5000	(Wohl, 1974b)	1
	Rat	NR	Oral	5000	(Sauer & Robbins, 1979)	1
(10-Undecen-1-yl acetate [09.214])	Rat	NR	Oral	>5000	(Levenstein, 1974a)	1
(Isobutyl acetate [09.005])	Rat	NR	Oral	>15,400	(Smyth et al., 1962)	1
(2-Ethylhexyl acetate [09.381])	Rat	NR	Oral	3000	(Smyth & Carpenter, 1944)	In FGE.04
(Methyl propionate [09.134])	Rat	NR	Oral	>5000	(Myers et al., 1977c)	1
	Mouse	NR		3460	(Lewis, 1996a)	1
	Rabbit	NR	Oral	2025	(Munch, 1972)	1
(Amyl butyrate [09.044])	Rat	NR	Oral	12,210	(Jenner et al., 1964)	1
	Guinea pig	NR	Oral	11,950	(Jenner et al., 1964)	1
(Hexyl butyrate [09.045])	Rat	NR	Oral	>5000	(Myers et al., 1977c)	1
(Heptyl butyrate [09.166])	Rat	NR	Oral	>5000	(Moreno, 1982b)	1
(Decyl butyrate [09.047])	Rat	NR	Oral	9,800	(Smyth et al., 1951a)	1
(cis-3-Hexenyl butyrate [09.270])	Rat	NR		>5,000	(Moreno, 1978b)	1
(Isobutyl butyrate [09.043])	Rabbit	NR	Oral	9,504	(Munch, 1972)	1
	Rat	NR	Oral	>5,000	(Moreno, 1975d)	1
4-Methylpentan-1-ol [02.180]	Rat	NR	Oral	6,500	(Wang & Bai, 1998)	
(Methyl valerate [09.182])	Rat	NR	Oral	>5,000	(Moreno, 1978a)	1
(cis-3-Hexenyl hexanoate [09.271])	Rat	NR	Oral	>5,000	(Moreno, 1978c)	1

Table IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD_{50} (mg/kg bw)	Reference	Comments
(Isobutyl hexanoate [09.064])	Rat	NR	Oral	>5,000	(Moreno, 1975e)	1
(Methyl decanoate [09.251])	Rat	NR	Oral	>2000	(Kästner, 2000a)	Assumes a density of 1 g/ml. Evaluated by SCF/COE.
Tetradecan-1-ol [02.126]	Rat	NR	Oral	33000	(Wang & Bai, 1998)	
	Rat	NR	Oral	>8000	(Egan & Portwood, 1974)	
Heptadecan-1-ol [02.154]	Rat	NR		51600	(Wang & Bai, 1998)	
Octadecan-1-ol [02.196]	Rat	NR	Oral	>5000	(Kästner, 2000a)	
	Rat	NR	Oral	>8000	(Egan & Portwood, 1974)	
(Butyl stearate [09.246])	Rat	M	Oral	>32000	(Smith, 1953b)	1
3,5,5-Trimethylhexyl acetate [FL-no: 09.819]	Rat	NR	Oral	> 4250	(Moreno, 1973af)	

NR = not reported; M = Male.

1. Summarised by JECFA, 49th meeting (JECFA, 1998a).

2. Summarised by JECFA 46th meeting (JECFA, 1997a).

Subacute / subchronic / chronic / carcinogenic toxicity data are available for one candidate substance of the present flavouring group evaluation from chemical groups 1 and 2 and for 22 supporting and structurally related supporting substances, of which 19 have been evaluated by the JECFA at the 46th and 49th meetings. The supporting substances are listed in brackets.

TABLE IV.2: SUBACUTE / SUBCHRONIC / CHRONIC / CARCINOGENICITY STUDIES

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

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels (mg/kg bw/day)	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
(Formic Acid [08.001])	Rat/ NR	Diet		42	<1250	(Sporn et al., 1962)	Food note 2. Bulgarian report.
	Rat/ NR	Drinking water		42	250	(Sporn et al., 1962)	Food note 2. Bulgarian report.
	Rat/ NR	Drinking water		7-189	160	(Sollmann, 1921)	Food note 2. Poorly reported.
	Human/ M	Oral		28	>8	(Sollmann, 1921)	Food note 2. Poorly reported.
(Ethyl formate [09.072])	Rat; 10 M, 10 F	Diet	0, 1000, 2500, 10000 ppm, equivalent to 0, 50, 125, 500 mg/kg bw/day.	17 weeks	500	(Hagan et al., 1967)	Food note 2.
(Butyl acetate [09.004])	Rat; 40	Oral	0, 0.005, 0.05, 0.5 mg/kg bw/day.	180 days	0.5	(Petrovskaya & Bul'bin, 1969)	Food note 1.
(Octyl acetate [09.075])	Rat;20 M, 20 F	Gavage	0, 100, 500, 1000 mg/kg bw/day, five days a week.	13 weeks	500	(Daughtrey et al., 1989a)	Food note 1.
(2-Methyl-1-propanol [02.001])	Rat; 10 M, 10 F	Drinking water	0, 1000, 4000, 16000 ppm, calculated by author to 0, 80, 340, 1450 mg/kg bw/day.	90 days	1450	(BASF, 1992a)	Food note 1.
(Methyl butyrate [09.038])	Rat; 10	Diet	0, 100 mg/animal/day, equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.
(Amyl butyrate [09.044])	Rat; 10 M, 10 F	Diet	0, 1000, 2500, 10000 ppm, equivalent to 0, 50, 125, 500 mg/kg bw/day.	16 weeks	500	(Hagan et al., 1967)	Food note 1.
(3-Methylbutyl alcohol [02.003])	Rat; 15 M, 15 F	Gavage	0, 150, 500, 1000 mg/kg bw/day.	17 weeks	1000	(Carpanini et al., 1973b)	Food note 1.
(Ethyl pentanoate [09.147])	Rat; 10 M, 10 F	Diet	0. 1000, 2500, 10000 ppm, equivalent to 0, 50, 125, 500 mg/kg bw/day.	17 weeks	500	(Hagan et al., 1967)	Food note 2.
(Hexyl alcohol [02.005])	Rat/ M, F	Diet		13 weeks	577	(Eibert, 1992)	Food note 1. Poorly reported.
	Dog/NR	Gelatin capsules	0, 0.5%, 1%.	13 weeks	230-695	(Eibert, 1992)	Food note 1. Poorly reported.
(Methyl hexanoate [09.069])	Rat; 10	Diet	0, 100 mg/animal/day, equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.

(cis-3-Hexenol [02.056])	Rat; 15 M, 15 F	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	150	(Gaunt et al., 1969)	Food note 1.
(Ethyl heptanoate [09.093])	Rat; 10 M, 10 F	Diet	0, 1000, 10000 ppm, equivalent to 0, 50, 500 mg/kg bw/day.	13 weeks	500	(Hagan et al., 1967)	Food note 2.
(Methyl octanoate [09.117])	Rat; 10	Diet	0, 100 mg/animal/day equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.
	Rat; 15 M, 15 F	Diet	0, 3.2, 3.6 mg/kg bw/day.	90 days	3.6	(Oser et al., 1965)	Food note 1.
(Ethyl octanoate [09.111])	Rat; 10 M, 10 F	Diet	0, 1000, 2500, 10000 ppm, equivalent to 0, 50, 125, 500 mg/kg bw/day.	17 weeks	500	(Hagan et al., 1967)	Food note 2.
(Ethyl nonanoate [09.107])	Rat; 5 M, 5 F	Diet	0, 10000 ppm, equivalent to 0, 500 mg/kg bw/day.	16 weeks	500	(Hagan et al., 1967)	Food note 2.
	Rat; 5 M, 5 F	Diet	0, 1 %, equivalent to 0 and 500 mg/kg bw/day.	16 weeks	500	(FDA, 1954)	Food note 2.
(Methyl decanoate [09.251])	Rat; 10	Diet	0, 100 mg/animal/day, equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.
(Methyl laurate [09.101])	Rat; 10	Diet	0, 100 mg/animal/day, equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.
(Dodecan-1-ol [02.008])	Rat; 12 M, 12 F	Diet	0, 1500, 7500, 30000 ppm, equal to 0, 100, 500, 2000 mg/kg bw/day.	37 days	100	(Institute of Toxicology, 1992b)	.
(Methyl myristate [09.106])	Rat; 10	Diet	0, 100 mg/animal/day, equivalent to 0, 250 mg/kg bw/day.	12 weeks	250 (Rat weight 400 mg) 300 (JECFA)	(Alfin-Slater et al., 1965)	Food note 1.
Octadecan-1-ol [02.196]	Rat/ M, F	Gavage	0, 100, 500, 1000 mg/kg bw/day, five days a week.	28 days	1000	(Potokar, 1986)	
(Ethyl acetate [09.001])	Rat; M 20, F 20	Drinking water	0, 0.004 %, equivalent to 0, 2 mg/kg bw/day.	371-392 days	2	(Johannsen & Purchase, 1969)	Food note 2.
(Butyl stearate [09.246])	Rat; 16 M	Diet	0, 0.01, 0.05, 0.25, 1.25, 6.25 %, equivalent to 0, 5, 25, 125, 625, 3100 mg/kg bw/day.	Two year	3100	(Smith, 1953b)	Food note 1. No dose-related effect, including no histological changes, even at highest dose: 6.25 % corresponding to 3100 mg/kg bw/day.

NR = Not reported; M = male; F = Female.

1. Summarised by JECFA, 49th meeting (JECFA, 1998a).

2. Summarised by JECFA 46th meeting (JECFA, 1997a).

Developmental and reproductive toxicity data are available for one candidate substance of the present flavouring group evaluation from chemical groups 1 and 2 and for four supporting and structurally related supporting substance evaluated by JECFA at the 49th meetings. Supporting substances are listed in brackets.

TABLE IV.3: DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Table IV.3: Developmental and Reproductive Toxicity Studies

Chemical Name [FL-no]	Study type Durations	Species/Sex No / group	Route	Dose levels	NOAEL (mg/kg bw /day), Including information of possible maternel toxicity	Reference	Comments
(Butyl acetate [09.004])	Multigeneration repro./ 8 months	Rat; 48	Gavage	2 mg on alternating days. 24, 84 and 208 mg/animal prior to the 1st, 2nd and 3rd generation.	590 No statistically significant changes in the number of pregnancies, the number of born offspring, the number of viable offspring, the birth weight of offspring or the weight of offspring after 7 and 21 days.	(Sporn et al., 1963)	1
(Octyl acetate [09.007])	Dev. Toxicity/ Day 6 to 15 of gestation	Rat; F	Gavage	0, 100, 500, 1000 mg7kg bw/day.	Maternal NOEL 100 Develop. NOEL 500 Decreased maternal body weight and food consumption at 500 and 1000 mg/kg/day. Increased incidence of litters with at least one malformed fetus at 1000 mg/kg/day.	(Daughtrey et al., 1989b)	1
(Dodecan-1-ol [02.008])	One generation repro./ 14 days premating. 5 weeks total	Rat; 12 M, 12 F	Diet	0, 100, 500, 2000 mg7kg bw/day.	2000 No effects on reproductive or developmental parameter.	(Institute of Toxicology, 1992a)	
Octadecan-1-ol [02.196]	One generation repro./ 14 days premating; 5 weeks total	Rat; 12 M, 12 F	Diet	0, 100, 500, 2000 mg7kg bw/day.	2000 No effects on reproductive or developmental parameter.	(Institute of Toxicology, 1992b)	
(Butyl stearate [09.246])	One generation repro./ 10 weeks premating	Rat; 20 M, 20 F	Diet	0, 3125 mg7kg bw/day.	3100 No adverse effects on fertility, litter size or survival of offspring observed.	(Smith, 1953b)	1

F = Female; M = Male.

1. Summarised by JECFA, 49th meeting (JECFA, 1998) (JECFA, 1998a).

In vitro mutagenicity/genotoxicity data are available for three candidate substances of the present flavouring group evaluation from chemical groups 1 and 2 and for nine supporting and structurally related supporting substances, some evaluated by JECFA at the 49th meeting. Supporting substances are listed in brackets.

TABLE IV.4: GENOTOXICITY (*IN VITRO*)

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

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
Methyl formate [09.642]	Ames	S. typh. TA1535, TA100, TA1537, TA98	20-5000µg/plate	Neg.	(BASF, 1990)	With and without metabolic activation.
	Ames	S. typh. TA100, TA1535, TA97, TA98	100-10,000µg/plate	Neg.	(Zeiger et al., 1992)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	667-10,000µg/plate	Neg.	(Hoechst-Celanese Corp., 1989a)	With and without metabolic activation.
(Isoamyl formate [09.162])	Rec assay	B. subtilis	Up to 18µg/disk	Neg.	(Oda et al., 1979)	1
	Rec assay	B. subtilis	20 µl/disk in DMSO	Neg.	(Yoo, 1986)	1, With and without metabolic activation.
	Chrom. Abs	CHO fibroblast	Up to 2 mg/ml in DMSO	Neg.	(Ishidate et al., 1984)	1, Without metabolic activation.
	Ames	S.typh. TA92, TA1535, TA100, TA1537, TA94, TA98, TA2637	Up to 10 mg/plate in	Neg.	(Ishidate et al., 1984)	1, With and without metabolic activation.
(Methyl acetate [09.023])	Ames	S. typh. TA97, TA98, TA102, TA104, TA1535, TA1538	Up to 10 mg/plate	Neg.	(Zeiger et al., 1992)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100,TA1535, TA1537,TA1538	NR	Neg.	(Hoechst AG, 1988)	With and without metabolic activation.
	Ames	E. coli	NR	Neg.	(Hoechst AG, 1988)	With and without metabolic activation.
	Induction of aneuploidy	S. cerevisiae D61.M	Up to 3.85 %	See comments	(Zimmermann et al., 1985a)	Only pos. after cold-shock during mitosis
	Mitotic recomb. and point mutation	S. cerevisiae D61.M	Up to 3.85 %	Neg.	(Zimmermann et al., 1985a)	
(Propyl acetate [09.002])	Induction of aneuploidy	S.cerevisiae D61.M	Up to 1.23%	See comments	(Zimmermann et al., 1985a)	Only pos. at cytotoxic levels
(Butyl acetate [09.004])	Chrom. Abs.	CH fibroblast cells	2 mg/ml in DMSO	Neg.	(Ishidate et al., 1984)	1, Without metabolic activation.
	Ames	S. typh. TA97, TA98, TA102, TA104, TA1535,TA1538	Up to 10 mg/plate in DMSO	Neg.	(Zeiger et al., 1992)	1, With and without metabolic activation.
	Ames	S.typh. TA92, TA94, TA98, TA100, TA1535, TA1537, TA2637	Up to 10 mg/plate in DMSO	Neg.	(Ishidate et al., 1984)	1, With and without metabolic activation.
	Mod. Ames	S.typh. TA98, TA100, TA1535, TA1537, TA1538, E.coli WP2, uvrA	1-5000 µg/plate	Neg	(Shimizu et al., 1985)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	NR	Neg.	(Huels, 1988)	With and without metabolic activation.
	Induction of aneuploidy	S.cerevisiae D61.M	2.5 to 4.0 mg/ml	Neg.	(Zimmermann et al., 1985a)	Without metabolic activation.
(Isobutyl acetate [09.005])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	Up to 5000 µg/ml	Neg.	(Huels-Bericht, 1988)	With and without metabolic activation.
(Methyl octanoate [09.117])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1.5 – 5000 µg/plate	Neg.	(Banduhn, 1988)	With and without metabolic activation.

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

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(Methyl decanoate [09.251])	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538	1.5-5000 µg/plate	Neg.	(Banduhn, 1988)	With and without metabolic activation.
(Methyl laurate [09.101])	Ames	S. typh. TA98, TA100, TA1535, TA1538, C12	NR	Neg.	(Banduhn, 1992a)	With and without metabolic activation.
Tetradecan-1-ol [02.126]	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	1.5 – 5000 µg/plate.	Neg.	(Wallat, 2000b; Wallat, 2000a)	With and without metabolic activation.
Octadecan-1-o l[02.196]	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	0.63 – 20 µg/plate.	Neg.	(Wallat, 2000c)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	50 µg/plate.	Neg.	(Anonymous, 1985a)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	0.033-10 mg/plate.	Neg.	(Prival et al., 1991)	With and without metabolic activation.
	Ames	E. coli, WP2.	0.033-10 mg/plate	Neg.	(Prival et al., 1991)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	0.3-10,000 µg/plate (TA100); 10 – 3333 µg/plate (other strains).	Neg.	(Mortelmans & Tanaka, 1989)	With and without metabolic activation.
	Ames	E. coli, WP 2	10-3333 mg/plate.	Neg.	(Mortelmans & Tanaka, 1989)	With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537.	0.3 µmol/plate.	Neg.	(Florin et al., 1980)	With and without metabolic activation.
(Butyl stearate [09.246])	Reversion Assay	S. typh. TA97, TA98, TA100, TA102, TA1537, E. coli, WP2.	100-5000µg/plate in acetone with Tween 80.	Neg.	(Hachiya, 1987)	1, With and without metabolic activation.
	Ames	S. typh. TA98, TA100, TA1535, TA1537, TA1538.	0.04-4 µl/plate.	Neg.	(Mobil Oil Corp., 1982)	With and without metabolic activation.

In vivo mutagenicity/genotoxicity data are available for none of the candidate substance of the present flavouring group evaluation from chemical groups 1 and 2 but for three supporting substances evaluated by JECFA at the 49th meeting. Supporting substances are listed in brackets.

TABLE IV.5: GENOTOXICITY (*IN VIVO*)

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

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
(Methyl acetate [09.023])	Humans	SCE & Chrom. Aberrations (Occ. exp.)	Inhalation	3-169 mg/m^3	Negative	(Haglund et al., 1980)	1
(Butyl acetate [09.004])	Humans	SCE & Chrom. Aberrations (Occ. exp.)	Inhalation	7-1676 mg/m^3	Negative	(Haglund et al., 1980)	1
(Dodecan-1-ol [02.008])	Mouse	Micronucleus	gavage	5000 mg/kg bw	Negative	(Banduhn, 1992b)	1

1) Summarised by JECFA, 49th meeting (JECFA, 1998a).

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