EFSA Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 47, Revision 1: Bi- and tricyclic secondary, ketones and related esters from chemical groups 7 and 8

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Link to article, DOI:
10.2903/j.efsa.2012.2637

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 47, Revision 1 (FGE.47Rev1):

Bi- and tricyclic secondary alcohols, ketones and related esters from chemical group 8[1]

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

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to evaluate six flavouring substances in the Flavouring Group Evaluation 47, including an additional two substances in this Revision 1, using the Procedure in Commission Regulation (EC) No 1565/2000. None of the substances were considered to have genotoxic potential. The substances were evaluated through a stepwise approach (the Procedure) that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. The Panel concluded that the six substances [FL-no: 02.119, 07.171, 07.196, 09.584, 09.848 and 09.888] do not give rise to safety concern at their levels of dietary intake, estimated on the basis of the MSDI approach. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been considered. Adequate specifications including complete purity criteria and identity for the materials of commerce have been provided for all six candidate substances.

KEY WORDS

1 On request from the European Commission, Question No EFSA-Q-2011-01049 & EFSA-Q-2011-01050, adopted on 22 March 2012.

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

Suggested citation: EFSA Panel on Food Contact Material, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 47, Revision 1: Bi- and tricyclic secondary, ketones and related esters from chemical groups 7 and 8. EFSA Journal 2012;10(3):2637. [43 pp.] doi:10.2903/j.efsa.2012.2637. Available online: www.efsa.europa.eu/efsajournal

Tricyclic secondary alcohol, bicyclic secondary alcohols and related esters, bicyclic ketones flavourings, safety, FGE.47.

SUMMARY

The European Food Safety Authority (EFSA) asked the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) 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 Panel is asked to evaluate six flavouring substances in the Flavouring Group Evaluation 47, Revision 1 (FGE.47Rev1), using the Procedure as referred to in the Commission Regulation EC No 1565/2000. These six flavouring substances belong to chemical group 7 and 8, Annex I of the Commission Regulation EC No 1565/2000.

The present revision of FGE.47, FGE.47Rev1, comprises the evaluation of six candidate flavouring substances. Four of these have been evaluated in the previous version (FGE.47). Two additional candidate substances, cedrenol [FL-no: 02.119] and pin-2-en-4-one [FL-no: 07.196], have now been included, following their separate evaluation for genotoxic potential in FGE.211 and FGE.212Rev1, because of the presence of structural alerts for genotoxicity.

The six candidate substances are one tricyclic alcohol [FL-no: 02.119], two bicyclic ketones [FL-no: 07.171 and 07.196] and three esters of bicyclic secondary alcohols [FL-no: 09.584, 09.848 and 09.888].

All six candidate substances possess one or more chiral centres. The stereoisomeric composition has been specified for all six substances.

Four candidate substances belong to structural class I and two candidate substances belong to structural class II according to the decision tree approach as presented by Cramer et al., 1978.

Three candidate substances [FL-no: 02.119, 07.171 and 07.196] in the present group have been reported to occur naturally.

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 candidate substances in this group have intakes in Europe from 0.011 to 34 microgram/*capita*/day, which are below the thresholds of concern values for structural class I (1800 microgram/person/day) and structural class II (540 microgram/person/day) substances.

On the basis of the reported annual production volumes in Europe (MSDI approach), the combined intake of the four candidate substances belonging to structural class I would result in a combined intake of approximately 35 microgram/*capita*/day and for the two substances assigned to structural class II to 15 microgram/day. These values are lower than the thresholds of concern for structural class

I or class II substances (1800 or 540 microgram/person/day, respectively). The total combined intakes of candidate and supporting substances in Europe are approximately 1200 and 70 microgram/*capita*/day, for structural class I substances and for structural class II substances, respectively, which do not exceed the thresholds of concern for structural class I and II.

For two of the candidate substances [FL-no: 02.119 and 07.196] it has been concluded in FGE.211 and FGE.212Rev1, respectively, that a concern for genotoxicity, indicated by the presence of a structural alert, could be ruled out based on experimental data for structurally related substances. Thus, these two substances can be evaluated through the Procedure. For the remaining four substances, genotoxicity data are available only for a limited number of supporting substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of these four candidate substances using the Procedure.

The six candidate substances are expected to be metabolised to innocuous products.

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

It is considered that on the basis of the default MSDI approach the six 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 for the four candidate substances in structural class I from 1900 to 3900 microgram/person/day. These intakes are above the threshold of concern for structural class I of 1800 microgram/person/day. The estimated intake of the two candidate substances [FL-no: 07.171 and 07.196] assigned to structural class II, based on the mTAMDI approach, is 1000 microgram/person/day each, which is above the threshold of concern for structural class II of 540 microgram/person/day.

Thus, for the four candidate substances from structural class I and for the two candidate substances allocated to structural class II, the intakes, estimated on the basis of the mTAMDI approach, exceed the relevant threshold for the structural class. Therefore, for all six substances more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be reconsidered using the Procedure. Subsequently, additional toxicity data might become necessary.

In order to determine whether the conclusion for the candidate substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria for the materials of commerce have been provided for all six candidate substances.

Thus, for all six candidate substances [FL-no: 02.119, 07.171, 07.196, 09.584, 09.848 and 09.888], the Panel concluded that they would present no safety concern at the level of intake estimated on the basis of the MSDI approach.

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BACKGROUND

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

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

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

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

HISTORY OF THE EVALUATION

The Flavouring Group Evaluation 47, FGE.47 dealt with one bicyclic ketone and three esters of bicyclic secondary alcohols. The original submissions from Industry (EFFA, 2005f; EFFA, 2006ac) included two candidate substances [FL-no: 02.119 and 07.196], which are alpha, beta-unsaturated ketones, for which further evaluation of genotoxic potential was required before they could be evaluated using the Procedure. The two substances were evaluated with respect to genotoxicity in FGE.211 and FGE.212.

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.47	22 May 2008	http://www.efsa.europa.eu/en/efsajournal/pub/743.htm	4
FGE.47Rev1	22 March 2012		6

The present revision of FGE.47, FGE.47Rev1, includes the assessment of the two additional candidate substances [FL-no: 02.119 and 07.196] considered with respect to genotoxicity in FGE.211 and FGE.212Rev1 (EFSA, 2011e; EFSA, 2011f). In these FGEs the Panel concluded that the data available ruled out the concern for genotoxicity and thus concluded that these two substances can be evaluated through the Procedure.

No further toxicity and/or metabolism data were provided by Industry for these two substances. A search in open literature provided additional information on the acute toxicity of cedrenol [FL-no: 02.119]. This information has also been included in this revision.

FGE.47Rev1 also includes additional information submitted by the Industry (EFFA, 2010a) on specifications for [FL-no: 07.171, 09.584, 09.848 and 09.888], which had been requested in FGE.47.

During the revision process the Panel recognised that although *d*-camphor [FL-no: 07.215] could not be used as a supporting substance for acute toxicity of the candidate substances in this FGE, it is

sufficiently structurally related to support the evaluation of the candidate substances in this FGE with respect to chronic toxicity, reproductive toxicity and genotoxicity. Therefore, data on *d*-camphor have been introduced in this revision of FGE.47.

TERMS OF REFERENCE

The European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances in the Register (Commission decision 1999/217/EC), according to Commission Regulation (EC) No 1565/2000 (EC, 2000a), prior to their authorisation and inclusion in the Union list (Regulation (EC) No 1334/2008). The evaluation programme was finalised at the end of 2009.

After the finalisation of the evaluation programme, in their letters of the 7th May 2010 and 3rd June, the Commission requested EFSA, based on additional submitted data on genotoxicity, to carry out re-evaluation of the flavouring substances pin-2-en-4-one [FL-no: 07.196] and cedrenol [FL-no: 02.119], and depending on the outcome, to proceed to the evaluation of these flavouring substances through the Procedure, also according to Commission Regulation (EC) No 1565/2000 (EC, 2000a).

ASSESSMENT

1. Presentation of the Substances in Flavouring Group Evaluation 47, Revision1

1.1. Description

The present Flavouring Group Evaluation 47, Revision 1 (FGE.47Rev1), using the Procedure as referred to in the Commission Regulation EC No 1565/2000 (EC, 2000a) (The Procedure – shown in schematic form in Annex I of this FGE), deals with one tricyclic secondary alcohol [FL-no: 02.119], two bicyclic ketone [FL-no: 07.171 and 07.196] and three esters of bicyclic secondary alcohols [FL-no: 09.584, 09.848 and 09.888]. All six flavouring substances (candidate substances) belong to chemical group 8, according to Annex I of Commission Regulation (EC) No 1565/2000 (EC, 2000a).

The six flavouring substances under consideration, as well as 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.

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

The six candidate substances are structurally related to 16 flavouring substances (supporting substances) evaluated at the 63rd meeting of the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) in the group "Monocyclic and Bicyclic Secondary Alcohols, Ketones and Related Esters" (JECFA, 2006a).

The names and structures of the 16 supporting substances are listed in Table 3, together with their evaluation status (CoE, 1992; SCF, 1995; JECFA, 2006a).

1.2. Stereoisomers

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

substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number, etc.).

The six candidate substances, cedrenol [FL-no: 02.119], isopinocamphone [FL-no: 07.171], pin-2-en-4-one [FL-no: 07.196], isobornyl isobutyrate [FL-no: 09.584], (1*S*-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol acetate [FL-no: 09.848] and isobornyl 2-methylbutyrate [FL-no: 09.888], possess one or more chiral centres. For all six substances the stereoisomeric composition has been specified (See Table 1).

1.3. Natural Occurrence in Food

Three candidate substances have been reported to occur in apricot, citrus fruits, mango, cloudberry and essential oils (TNO, 2000; TNO, 2011). Quantitative data on the natural occurrence have been reported for these substances:

- Cedrenol [FL-no: 02.119]: up to 500 mg/kg in citrus fruits
- Isopinocamphone [FL-no: 07.171]: up to 2.2 mg/kg in apricot
- Pin-2-en-4-one [FL-no: 07.196]: up to 500 mg/kg in citrus fruits, 3.5 mg/kg in apricot, 2.7 mg/kg in mango.

The remaining three substances (isobornyl isobutyrate [FL-no: 09.584], (1*S*-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol acetate [FL-no: 09.848] and isobornyl 2-methylbutyrate [FL-no: 09.888]) have not been reported to occur naturally in any food items according to TNO (TNO, 2000).

2. Specifications

Purity criteria for the six substances have been provided by the Flavour Industry (EFFA, 2005f; EFFA, 2006ac).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000a), this information is adequate for all six candidate substances (see Section 1.2 and Table 1).

3. Intake Data

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

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

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

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

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

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

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

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

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

In the present FGE.47Rev1, the total annual production volume of the candidate substances for use as flavouring substances in Europe has been reported to be approximately 400 kg (EFFA, 2005f; EFFA, 2006ac). For the supporting substances, the total annual volume of production has been reported by the JECFA to be approximately 9700 kg (isobornyl acetate [FL-no: 09.218] accounts for 7300 kg, (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one [FL-no: 07.215] for 410 kg, borneol [FL-no: 02.016] for 1100 kg and fenchyl alcohol [FL-no: 02.038] for 450 kg) (JECFA, 2005c; JECFA, 2009c).

On the basis of the annual volume of production reported for the candidate substances, the daily *per capita* intakes for each of these flavourings have been estimated. The estimated MSDI of cedrenol [FL-no: 02.119] from use as a flavouring substance is 34 microgram and that of pin-2-en-4-one [FL-no: 07.196] is 15 microgram. For each of the remaining substances the estimated daily *per capita* intake is equal to or less than 0.085 microgram for each (Table 2a).

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

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

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

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

For all six candidate substances information on food categories and normal and maximum use levels[5,6,7] were submitted by the Flavour Industry (EFFA, 2005f; EFFA, 2006ac; EFFA, 2007a). The 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, 2000a), 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
01.0	Dairy products, excluding products of category 2	All
02.0	Fats and oils, and fat emulsions (type water-in-oil)	All
03.0	Edible ices, including sherbet and sorbet	All
04.1	Processed fruits	All
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	None
05.0	Confectionery	All
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	All
07.0	Bakery wares	All
08.0	Meat and meat products, including poultry and game	All
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	All
10.0	Eggs and egg products	None
11.0	Sweeteners, including honey	None
12.0	Salts, spices, soups, sauces, salads, protein products etc.	All
13.0	Foodstuffs intended for particular nutritional uses	All
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	Only [FL-no: 02.119]
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	All
15.0	Ready-to-eat savouries	All except [FL-no: 09.888]
16.0	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 six candidate substances are in the range of 1 - 20 mg/kg food, and the maximum use levels are in the range of 5 - 100 mg/kg (EFFA, 2002i; EFFA, 2005f; EFFA, 2006ac; EFFA, 2007a) (see Table II.1.2, Annex II).

The mTAMDI values for the four candidate substances from structural class I range from 1900 to 3900 microgram/person/day. For both candidate substances from structural class II the mTAMDI is 1000 microgram/person/day.

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

[5] "Normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i).
[6] The normal and maximum use levels in different food categories (EC, 2000) have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).
[7] The use levels from food category 5 "Confectionery" have been inserted as default values for food category 14.2 "Alcoholic beverages" for substances for which no data have been given for food category 14.2 (EFFA, 2007a).

4. Absorption, Distribution, Metabolism and Elimination

The available data indicate that the three esters in this group [FL-no: 09.584, 09.848 and 09.888] are readily hydrolysed to the corresponding bicyclic secondary alcohols which are subsequently conjugated with glucuronic acid and excreted in the urine. Similarly conjugation with glucuronide will also occur with the free tri-cyclic alcohol cedrenol [FL-no: 02.119]. The major metabolic pathway of the two bicyclic ketones [FL-no: 07.171 and 07.196], involves reduction to the corresponding secondary alcohols, which will be excreted primarily as the glucuronic acid conjugate. In addition to reductive pathways, alicyclic ketones and, to a lesser extent, secondary alcohols containing an alkyl side-chain undergo oxidation of the side-chain to form polar oxygenated metabolites that are excreted mainly in the urine, either unchanged or as glucuronide or sulphate conjugates. It is therefore concluded that the candidate substances can be anticipated to be metabolised to innocuous products.

For more detailed information, see Annex III.

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

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach. Where the mTAMDI approach indicates that the intake of a flavouring substance might exceed its corresponding threshold of concern, a formal safety assessment is not carried out using the Procedure. In these cases the Panel requires more precise data on use and use levels. For comparison of the intake estimations based on the MSDI approach and the mTAMDI approach, see Section 6.

For the safety evaluation of the six candidate substances from chemical group 7 and 8 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the substances are summarised in Table 2a.

Step 1

Four candidate substances are classified into structural class I [FL-no: 02.119, 09.584, 09.848 and 09.888] and two [FL-no: 07.171 and 07.196] into structural class II according to the decision tree approach presented by Cramer et al. (Cramer et al., 1978).

Step 2

All six candidate substances in this group are expected to be metabolised to innocuous products. The evaluation of these substances therefore proceeded via the A-side of the Procedure scheme.

Step A3

The candidate substances [FL-no: 02.119, 07.171, 07.196, 09.584, 09.848 and 09.888] have estimated European daily per capita intakes ranging from 0.011 to 34 microgram (Table 2a). These intakes are below the threshold of concern of 1800 microgram/person/day for structural class I and 540 microgram/person/day for structural class II substances.

Based on results of the safety evaluation sequence of the Procedure, these six candidate substances, proceeding via the A-side of the Procedure scheme, do not pose a safety concern when used as flavouring substances at the 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 four candidate substances in structural class I based on the mTAMDI range from 1900 to 3900 microgram/person/day. For all these substances the mTAMDI is above the threshold of concern of 1800 microgram/person/day.

The estimated intake of the two substances assigned to structural class II, based on the mTAMDI, is 1000 microgram/person/day each, which is above the threshold of concern for structural class II substances of 540 microgram/person/day.

Thus, for all candidate substances [FL-no: 02.119, 07.171, 07.196, 09.584, 09.848 and 09.888] further information is required. This would include more reliable intake data and then, if necessary, additional toxicological data.

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

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

FL-no	EU Register name	MSDI (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.119	Cedrenol	34	3900	Class I	1800
09.584	Isobornyl isobutyrate	0.085	2300	Class I	1800
09.848	(1S-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate	0.011	2300	Class I	1800
09.888	Isobornyl 2-methylbutyrate	0.061	1900	Class I	1800
07.171	Isopinocamphone	0.024	1000	Class II	540
07.196	Pin-2-en-4-one	15	1000	Class II	540

7. Considerations of Combined Intakes from Use as Flavouring Substances

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

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

On the basis of the reported annual production volumes in Europe (EFFA, 2005f; EFFA, 2006ac) the combined estimated *per capita* intake as flavouring of the four candidate substances assigned to structural class I is 35 microgram/day, and of the two substances assigned to structural class II, 15 microgram/day. These values do not exceed the thresholds of concern for substances belonging to structural class I and II of 1800 and 540 microgram/person/day, respectively.

The candidate substances are structurally related to 16 flavouring substances (13 are structural class I substances, three are structural class II substances) evaluated by JECFA at its 63rd session (JECFA, 2006a). The estimated total combined intake of candidate and supporting substances (in Europe) would be 1200 microgram/*capita*/day for structural class I substances, which is below the threshold of concern for structural class I of 1800 microgram/person/day. The estimated total combined intake of candidate and supporting substances (in Europe) would be 70 microgram/*capita*/day for structural class II substances, which is below the threshold of concern for structural class II of 540 microgram/person/day.

8. Toxicity

8.1. Acute Toxicity

Data are available on the candidate substance cedrenol [FL-no: 02.119] and on nine supporting substances. For cedrenol an oral LD_{50} value of > 5000 mg/kg bw has been reported for rats (Opdyke, 1975b). For the supporting substances LD_{50} values ranging from 5000 mg/kg bw to more than 10000 mg/kg body weight (bw) have been reported. The Panel noted that due to the limited reporting, the validities of these LD_{50} are difficult to assess.

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

The Panel is aware that there are acute toxicity data on adults and children for one supporting substance, (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (camphor [FL-no: 07.215]), mostly arising from the accidental ingestion of camphor-containing medications. The probable lethal oral bolus dose has been reported to be in the range of 50 to 500 mg/kg bw. No acute toxicity was reported after doses lower than 2 mg/kg bw and clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher, whereas clinically manifest toxicity in sensitive persons would require doses higher than 30 mg/kg bw. The Panel therefore suggested that maximum limits should be set to ensure that exposure to camphor does not exceed 2 mg/kg bw on a single day in any age group (EFSA, 2008l).

As discussed in Annex III, camphor is rapidly metabolised to hydroxylated products which are then excreted. Under the anticipated conditions of dietary exposure from a food matrix, these metabolic pathways are the major routes for detoxification and would not be expected to be saturated. The reduction of camphor to borneol and isoborneol is only a minor metabolic pathway. In rat liver preparations, the 2-keto group of *d*-camphor underwent no detectable reduction; l-camphor was reduced to a small extent. Rabbit liver cytosol mediated a vigorous stereospecific *endo*-reduction of d-camphor to borneol; a small amount (1 %) of isoborneol was also formed. After oral administration of camphor to rabbits a reduction to borneol was observed to some extent, whereas in dogs only excretion of hydroxylated camphor was reported. In humans admitted to hospital in a state of acute intoxication after ingestion of 6 - 10 g camphor, no reduction products but only 5- and 8-(or 9)-hydroxycamphor and their conjugates were detected as metabolites. Thus, the acute toxicity of camphor is not likely to be attributable to metabolism to borneol or isoborneol, which are hydrolysis products of three of the candidate substances in this FGE.

The Panel therefore considers that the acute human toxicity findings on camphor, a substance structurally related to the candidate substances in this FGE, are not relevant for the safety assessment of the candidate flavouring substances or their hydrolysis products.

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

There are no data available on the candidate substances, but there are data on four of the supporting substances.

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

8.3. Developmental / Reproductive Toxicity Studies

There are no data available on the candidate substances, but there are data on one supporting substance.

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

8.4. Genotoxicity Studies

There are no genotoxicity data available for the candidate substances. Therefore the genotoxic potential of the candidate substances in this FGE was assessed from data available for supporting substances.

Due to the presence of a structural alert for genotoxicity ("alpha,beta-unsaturated carbonyl moiety") for two candidate substances [FL-no: 02.119 and 07.196], these two substances had to be further assessed in separate FGEs:

- In FGE.211 it was concluded for candidate substance [FL-no: 02.119] that based on new *in vitro* genotoxicity data on 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930], no genotoxic potential is indicated.

- In FGE.212Rev1 it was concluded for candidate substance [FL-no: 07.126] that based on additional genotoxicity information on isophorone [FL-no: 07.126], no genotoxic potential is indicated.

Therefore, these two substances [FL-no: 02.119 and 07.126] can be evaluated using the Procedure.

In vitro

Borneol [FL-no: 02.016] and isobornyl propionate [FL-no: 09.131] were consistently tested negative in the Ames assay when a variety of *Salmonella typhimurium* strains including TA97, TA98, TA100, TA1535, TA1537 and TA1538 were incubated with up to 5,000 µg/plate with or without metabolic activation (Azizan and Blevins, 1995; Simmon et al., 1977; Wild et al., 1983).

Borneol showed no mutagenic activity when tested in *Escherichia coli* WP2 uvrA at concentrations up to 3,200 µg/plate (Yoo, 1986).

In the Rec-assay, borneol was reported to induce growth inhibition in *Bacillus subtilis* strain M45- when tested at concentrations of up to 10 mg/disk (Yoo, 1986). This test has very limited relevance for the genotoxicity evaluation.

No indication of genotoxic activity was obtained in four bacterial reverse mutation assays in *Salmonella typhimurium* and in two SCE assays in Chinese hamster ovary cells with the supporting substance (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one [FL-no: 07.215] (*d*-camphor). A bacterial reverse mutation assay with *d,l*-camphor was also negative.

In vivo

The genotoxic potential of isobornyl propionate [FL-no: 09.131] to induce somatic mutations in adult *Drosophila melanogaster* was studied in a Basc test. No increased frequency of mutation was observed when a 10 mM solution of isobornyl propionate was fed to the flies for 3 days (Wild et al., 1983).

In the micronucleus test, groups of NMRI mice administered intraperitoneal doses of 841, 1,893 or 2,944 mg/kg bw isobornyl propionate showed no increase in micronucleated erythrocytes in bone marrow samples, 30 hours post administration (Wild et al., 1983).

No indication for enhanced micronucleus formation was obtained with the supporting substance *d,l*-camphor in mouse erythrocytes in peripheral blood after topical administration (NTP, 1999c).

Conclusion on genotoxicity

For two candidate substances [FL-no: 02.119 and 07.196] it was concluded in FGE.211 (EFSA, 2011e) and FGE.212Rev1 (EFSA, 2011f) that a concern for genotoxicity, indicated by the presence of a structural alert, could be ruled out based on experimental data for structurally related substances. For the remaining four substances [FL-no: 07.171, 09.584, 09.848 and 09.888], genotoxicity data are available only for a limited number of supporting substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of these four candidate substances using the Procedure.

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

9. Conclusions

The present revision of FGE.47, FGE.47Rev1, comprises the evaluation of six candidate flavouring substances. Four of these were evaluated in the previous version (FGE.47). Two additional candidate substances [FL-no: 02.119 and 07.196] were included following their separate evaluation for genotoxic potential in FGE.211 and FGE.212Rev1, due to the presence of structural alerts for genotoxicity.

The six candidate substances are one tricyclic alcohol [FL-no: 02.119], two bicyclic ketone [FL-no: 07.171 and 07.196] and three esters of bicyclic secondary alcohols [FL-no: 09.584, 09.848 and 09.888].

All candidate substances possess one or more chiral centres. The stereoisomeric composition has been specified for all six substances.

Four candidate substances belong to structural class I and two candidate substances have been assigned to structural class II according to the decision tree approach as presented by Cramer et al., 1978.

Three candidate substances [FL-no: 02.119, 07.171 and 07.196] in the present group have been reported to occur naturally.

According to the default MSDI approach, the candidate substances in this group have intakes in Europe from 0.011 to 34 microgram/*capita*/day, which are below the thresholds of concern values for structural class I (1800 microgram/person/day) and structural class II (540 microgram/person/day) substances.

On the basis of the reported annual production volumes in Europe (MSDI approach), the combined intake of the four candidate substances belonging to structural class I would result in a combined intake of approximately 35 microgram/*capita*/day and to 15 microgram/day for the two substances assigned to structural class II. These values are lower than the thresholds of concern for structural class I or class II substances (1800 or 540 microgram/person/day, respectively). The total combined intakes of candidate and supporting substances in Europe are approximately 1200 and 70 microgram/*capita*/day, for structural class I substances and for structural class II substances, respectively, which also do not exceed the thresholds of concern for structural class I and II.

For two of the candidate substances it has been concluded in FGE.211 and FGE.212Rev1, respectively, that a concern for genotoxicity, indicated by the presence of a structural alert, could be ruled out based on experimental data for structurally related substances. Thus, these two substances can be evaluated through the Procedure. For the remaining four substances, genotoxicity data are available only for a limited number of supporting substances, and the genotoxicity could not be assessed adequately. However, the data available do not preclude the evaluation of these four candidate substances using the Procedure.

The six candidate substances are expected to be metabolised to innocuous products.

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

It is considered that on the basis of the default MSDI approach the 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 1900 to 3900 microgram/person/day for the four candidate substances from structural class I. These intakes are above the threshold of concern for structural class I of 1800 microgram/person/day. The estimated intake of the two candidate substances [FL-no: 07.171 and 07.196] assigned to structural class II, based on the mTAMDI approach, is 1000 microgram/person/day each, which is above the threshold of concern for structural class II of 540 microgram/person/day.

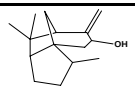
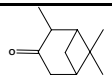
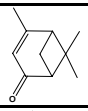
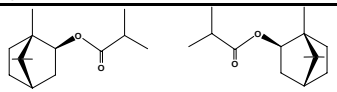
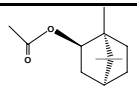
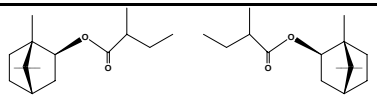
Thus, for the four candidate substances from structural class I and for the two candidate substances allocated to structural class II, the intakes, estimated on the basis of the mTAMDI approach, exceed the relevant threshold for the structural class. Therefore, for all six candidate substances more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be reconsidered using the Procedure. Subsequently, additional toxicity data might become necessary.

In order to determine whether the conclusion for the candidate substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria for the materials of commerce have been provided for all six candidate substances.

Thus, for all six candidate substances [FL-no: 02.119, 07.171, 07.196, 09.584, 09.848 and 09.888], the Panel concluded that they would present no safety concern at the level of intake estimated on the basis of the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN FGE.47REV1

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 47Rev1

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
02.119	Cedrenol		10189 28231-03-0	Solid $C_{15}H_{24}O$ 220.35	Practically insoluble or insoluble Soluble	98 (0.27 hPa) 128 MS 95 %	n.a. n.a.	Complex mixture of diastereoisomers (EFFA, 2012g). (Stereoisomeric composition not specified).
07.171	Isopinocamphone		4198 11125 18358-53-7	Liquid $C_{10}H_{16}O$ 152.24	Insoluble Freely soluble	70 (7 hPa) MS 95 %	1.472-1.478 0.963-0.969	Mixture of diastereoisomers. Approx. 25 % of each (EFFA, 2012g).
07.196	Pin-2-en-4-one		4216 11186 80-57-9	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Freely soluble	90 (16 hPa) NMR MS 95 %	1.492-1.498 0.975-0.981	Racemate (EFFA, 2012g). Mixture of (+/-)-verbenone.
09.584	Isobornyl isobutyrate		4146 85586-67-0	Liquid $C_{14}H_{24}O_2$ 224.34	Insoluble Freely soluble	132 (25 hPa) MS 95 %	1.460-1.466 0.958-0.964	Racemate (±) = *DL*-Isobornyl isobutyrate. CASrn in Register refers to (1*R*,2*R*,4*R*)-rel. Register name to be changed to *DL*-Isobornyl isobutyrate (EFFA, 2011m).
09.848	(1*S*-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate		5655-61-8	Solid $C_{12}H_{20}O_2$ 196.29	Insoluble Freely soluble	225 29 NMR MS 95 %	1.456-1.462 0.981-0.987	Name to be changed to (-)-bornyl acetate.
09.888	Isobornyl 2-methylbutyrate		4147 94200-10-9	Solid $C_{15}H_{26}O_2$ 238.37	Insoluble Freely soluble	336 84 MS 95 %	n.a. n.a.	Mixture of diastereoisomers. CASrn = 94200-10-9 (EFFA, 2010a). 25 % of each (EFFA, 2012g).

1) Solubility in water, if not otherwise stated.

2) Solubility in 95 % ethanol, if not otherwise stated.

3) At 1013.25 hPa, if not otherwise stated.

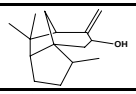
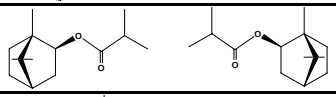
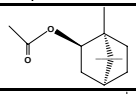
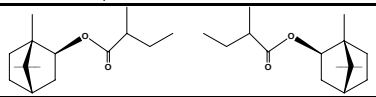
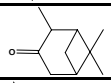
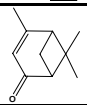
4) At 20°C, if not otherwise stated.

5) At 25°C, if not otherwise stated.

6) Stereoisomeric composition not specified.

TABLE 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
02.119	Cedrenol		34	Class I A3: Intake below threshold	4)	6)	a)
09.584	Isobornyl isobutyrate		0.085	Class I A3: Intake below threshold	4)	6)	
09.848	(1S-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate		0.011	Class I A3: Intake below threshold	4)	6)	
09.888	Isobornyl 2-methylbutyrate		0.061	Class I A3: Intake below threshold	4)	6)	
07.171	Isopinocamphone		0.024	Class II A3: Intake below threshold	4)	6)	
07.196	Pin-2-en-4-one		15	Class II A3: Intake below threshold	4)	6)	b)

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

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

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

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

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

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

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

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

a) Evaluated in FGE.211, genotoxicity concern could be ruled out.

b) Evaluated in FGE.212Rev1, genotoxicity concern could be ruled out.

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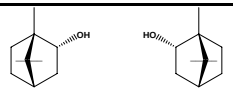
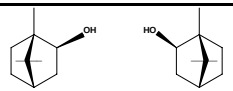
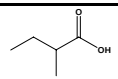
TABLE 2B: EVALUATION STATUS OF HYDROLYSIS PRODUCTS OF CANDIDATE ESTERS

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
02.016	Borneol 1385		No safety concern a) Category B b)	Class I A3: Intake below threshold	
02.059	Isoborneol 1386		No safety concern a) Category B b)	Class I A3: Intake below threshold	
08.002	Acetic acid 81		Category 1 c) No safety concern d) Category A b)	Class I A3: Intake above threshold, A4: Endogenous	
08.006	2-Methylpropionic acid 253		Category 1 c) No safety concern d) Category A b)	Class I A3: Intake below threshold	
08.046	2-Methylbutyric acid 255		Category 1 c) No safety concern d) Category A b)	Class I A3: Intake below threshold	

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

2) No safety concern at estimated levels of intake.

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

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

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

a) (JECFA, 2005c).

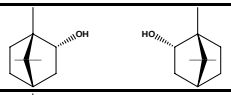
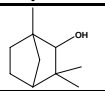
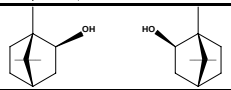
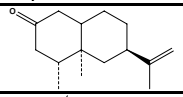
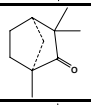
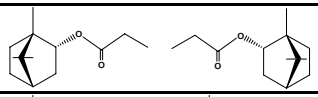
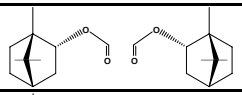
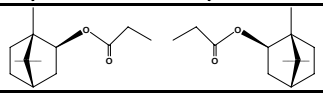
b) (CoE, 1992).

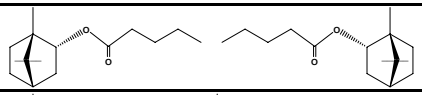
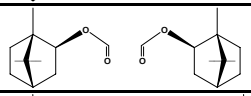
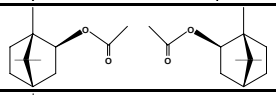
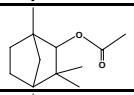
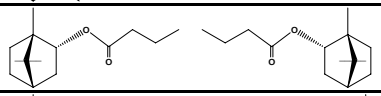
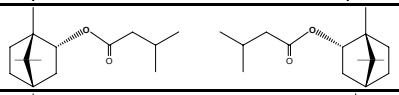
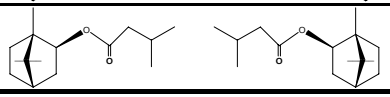
c) (SCF, 1995).

d) (JECFA, 1999b).

TABLE 3: SUPPORTING SUBSTANCES SUMMARY

Table 3: Supporting Substances Summary

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
02.016	Borneol		2157 64 507-70-0	1385 JECFA specification (JECFA, 2005b)	130	No safety concern a) Category B b)	
02.038	Fenchyl alcohol		2480 87 1632-73-1	1397 JECFA specification (JECFA, 2005b)	55	No safety concern a) Category B b)	
02.059	Isoborneol		2158 2020 124-76-5	1386 JECFA specification (JECFA, 2005b)	21	No safety concern a) Category B b)	
07.153	1,10-Dihydronootkatone		3776 20489-53-6	1407 JECFA specification (JECFA, 2005b)	0.24	No safety concern a)	
07.159	d-Fenchone		2479 551 4695-62-9	1396 JECFA specification (JECFA, 2005b)	6.3	No safety concern a)	
07.215	(1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one		2230 140 464-49-3	1395 JECFA specification (JECFA, 2005b)	50	No safety concern a)	JECFA evaluated *d*-camphor (CASrn as in Register). CASrn in Register refers to (1*R*,4*R*)-1,7,7-Trimethylbicyclo(2.2.1)-heptan-2-one (*d*-camphor).
09.017	Bornyl acetate		2159 207 76-49-3	1387 JECFA specification (JECFA, 2005b)	18	No safety concern a) Category B b)	
09.082	Bornyl formate		2161 349 7492-41-3	1389 JECFA specification (JECFA, 2005b)	1.2	No safety concern a) Category B b)	
09.131	Isobornyl propionate		2163 412 2756-56-1	1391 JECFA specification (JECFA, 2005b)	2.6	No safety concern a) Category B b)	

09.153	Bornyl valerate		2164 471 7549-41-9	1392 JECFA specification (JECFA, 2005b)	3.7	No safety concern a) Category B b)
09.176	Isobornyl formate		2162 565 1200-67-5	1390 JECFA specification (JECFA, 2005b)	0.61	No safety concern a) Category B b)
09.218	Isobornyl acetate		2160 2066 125-12-2	1388 JECFA specification (JECFA, 2005b)	890	No safety concern a) Category B b)
09.269	Fenchyl acetate		3390 11769 13851-11-1	1399 JECFA specification (JECFA, 2005b)	2.9	No safety concern a)
09.319	Bornyl butyrate		3907 13109-70-1	1412 JECFA specification (JECFA, 2005b)	6.1	No safety concern a)
09.456	Bornyl isovalerate		2165 451 76-50-6	1393 JECFA specification (JECFA, 2005b)	0.12	No safety concern a) Category B b)
09.457	Isobornyl isovalerate		2166 452 7779-73-9	1394 JECFA specification (JECFA, 2005b)	0.012	No safety concern a) Category B b)

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, 2005c).

b) (CoE, 1992).

ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

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

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

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

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

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

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

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

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

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

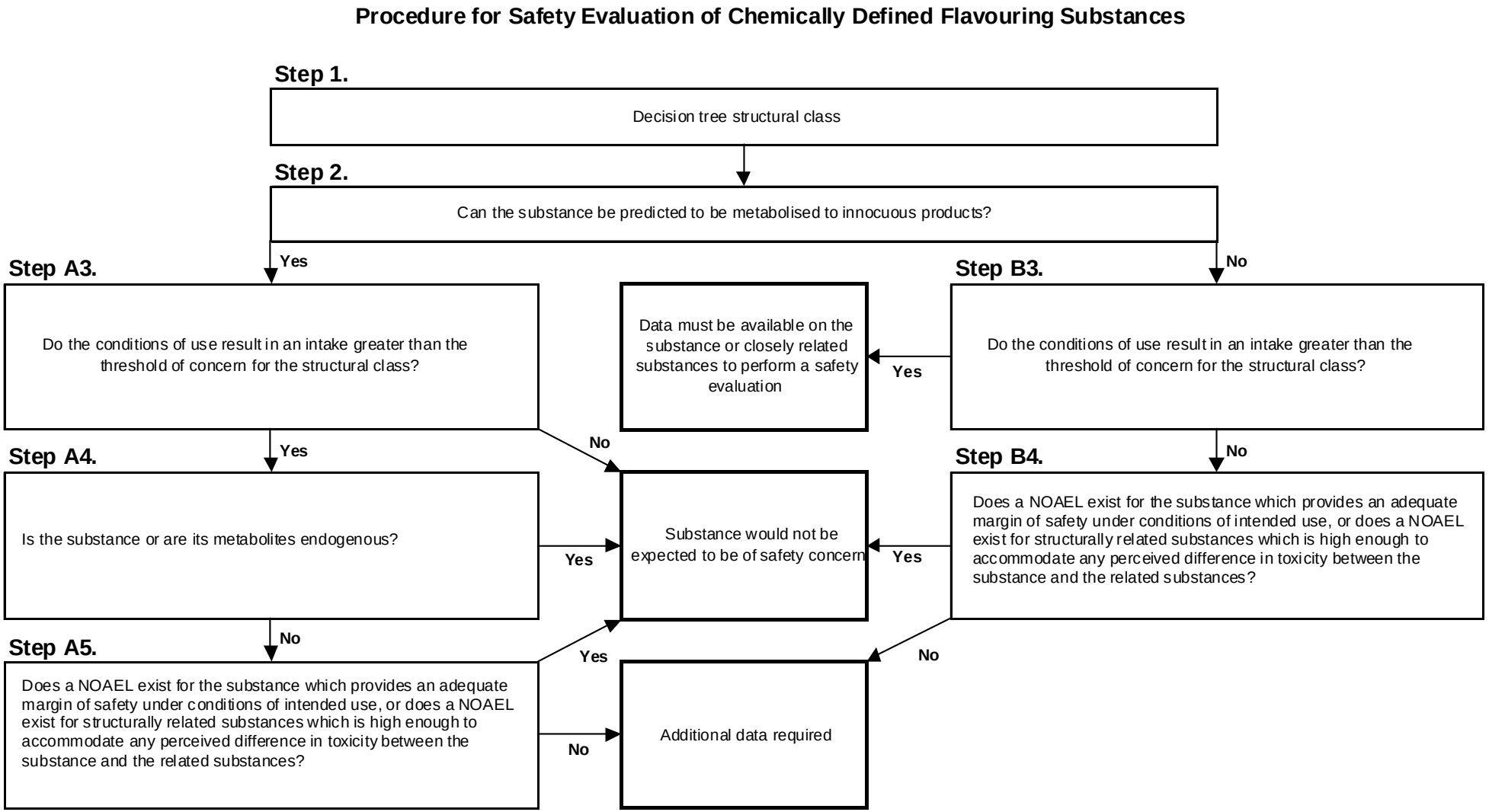


Figure I.1 *Procedure for Safety Evaluation of Chemically Defined Flavouring Substances*

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, 2000a). According to the Industry the "normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

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

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

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

Table II.1.2 Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.47Rev1 (EFFA, 2005f; EFFA, 2006ac; EFFA, 2007a)

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
02.119	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
07.171	3	2	3	2	-	4	2	5	1	1	-	-	2	3	-	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	-	20	25	10
07.196	3	2	3	2	-	4	2	5	1	1	-	-	2	3	-	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	-	20	25	10
09.584	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
09.848	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
09.888	7	5	10	7	-	10	5	10	2	2	-	-	5	10	-	10	-	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	-	50	-	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 may consume

the amount of flavourable foods and beverages listed in Table II.2.1. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

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

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

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

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

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

	Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories		
Key	Food category	Food	Beverages	Exceptions
01.0	Dairy products, excluding products of category 02.0	Food		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03.0	Edible ices, including sherbet and sorbet	Food		
04.1	Processed fruit	Food		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Food		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07.0	Bakery wares	Food		
08.0	Meat and meat products, including poultry and game	Food		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10.0	Eggs and egg products	Food		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Food		

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

	Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories	
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts		Exception c
15.0	Ready-to-eat savouries		Exception b
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0	Food	

The mTAMDI values (see Table II.2.3) are presented for each of the four flavouring substances in the present flavouring group, for which Industry has provided use and use levels (EFFA, 2005f; EFFA, 2006ac; EFFA, 2007a). The mTAMDI values are only given for the highest reported normal use levels.

TableII.2.3 Estimated intakes based on the mTAMDI approach

FL-no	EU Register name	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.119	Cedrenol	3900	Class I	1800
09.584	Isobornyl isobutyrate	2300	Class I	1800
09.848	(1*S*-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate	2300	Class I	1800
09.888	Isobornyl 2-methylbutyrate	1900	Class I	1800
07.171	Isopinocamphone	1000	Class II	540
07.196	Pin-2-en-4-one	1000	Class II	540

ANNEX III: METABOLISM

III.1. Introduction

The present FGE consists of six substances of which three are esters of bicyclic secondary alcohols [FL-no: 09.584, 09.848 and 09.888], one is a tricyclic alcohol [FL-no: 02.119] and two are bicyclic ketones [FL-no: 07.171 and 07.196].

III.2. Absorption, Distribution, Metabolism and Excretion

III.2.1 Hydrolysis of Esters

The esters within this group are expected to be hydrolysed in humans to their component alcohols and aliphatic carboxylic acids. Subsequently, the carboxylic acids are completely metabolised through recognised biochemical pathways (Nelson and Cox, 2000a). Ester hydrolysis is catalysed by classes of enzymes recognised as carboxylesterases (Heymann, 1980; White et al., 1990), the most important of which are the B-esterases. In mammals, these enzymes occur in most tissues (Heymann, 1980; Anders, 1989), but predominate in hepatocytes (Heymann, 1980).

III.2.2 Absorption, Distribution, Metabolism and Excretion of the alcohols and ketones

III.2.2.1 Absorption, Distribution and Excretion

In rabbits, more than 90 % of an oral dose of *d*-, *l*-, or *d,l*-bornyl acetate was excreted in the urine as the glucuronic acid conjugate of borneol [FL-no: 02.016] (Williams, 1959a).

Studies in humans, dogs and rabbits, have shown that the secondary alcohols and ketones of this group are rapidly absorbed, distributed, metabolised and excreted mainly in the urine as glucuronide conjugates. Small amounts may be expired in exhaled air.

Case reports, in which ingestion of the structurally related substance camphor [FL-no: 07.215] resulted in toxicity in both adults and children within minutes of exposure (Jacobziner and Raybin, 1962; Phelan, 1976; Kopelman et al., 1979; Gibson et al., 1989), demonstrate rapid absorption of this substance. Rabbits gavaged with 1.9 - 3.5 mmol/kg bw [289 - 533 mg/kg bw] *d*-camphor excreted 59.1 % of the dose conjugated with glucuronic acid in the urine within 24 hours (Robertson and Hussain, 1969). A group of 50 Sprague-Dawley rats was administered a single dose of 1,000 mg of 40 % camphor in cottonseed oil/kg bw (approximately 400 mg camphor) by gavage and killed at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0 or 10.0 hours following treatment. Blood samples were taken prior to death. Peak blood concentration of camphor occurred at 96 min, with an absorption half-life of 38 min and a plasma elimination half-life of 142 min. The authors considered these data to compare favourably to those in man (Dean et al., 1992).

The toxicokinetics of *d,l*-camphor were studied in B6C3F1 mice and F344 rats. In mice, camphor was rapidly eliminated from the plasma following a single intravenous injection of 50 mg/kg bw with an elimination rate constant of 0.0337 and 0.0335/min for males and females, respectively, and a half-live of 21 minutes. In rats, camphor underwent biphasic elimination from plasma following a single intravenous injection of 6 mg/kg bw with an elimination rate constant of 0.0038 and 0.0059/min for males and females, respectively, and half-lives of 185 (males) and 118 (females) minutes (Grizzle et al., 1996).

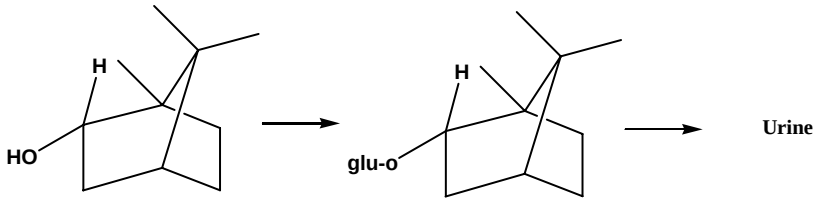
In a case report, a pregnant woman (week 40) accidentally ingested 12 g camphorated oil (% camphor not specified) and 36 hours later gave birth to a cyanotic baby exhibiting no respiration. The baby died within 30 min. The presence of camphor was noted at 15 min in maternal circulation, at 20 hours in amniotic fluid, and at 36 hours in cord blood, infant brain, liver and kidneys (Riggs et al., 1965).

Approximately 80 % of a 2,000 mg oral dose of *d*-borneol [FL-no: 02.016] given to humans (sex and number not specified) was excreted within 10 hours (Williams, 1959a).

III.2.2.2 Metabolism

The major metabolic pathway of the ketones involves reduction to the corresponding secondary alcohols, which are subsequently excreted primarily as the glucuronic acid conjugates (Williams, 1959a; Lington and Bevan, 1994; Topping et al., 1994). Metabolites excreted into the bile containing a double bond may be reduced to the corresponding dihydro derivatives by the gut microflora (Krasavage et al., 1982). In addition to reductive pathways, alicyclic ketones and, to a lesser extent, secondary alcohols containing an alkyl side-chain undergo oxidation of the side-chain to form polar poly-oxygenated metabolites that are excreted mainly in the urine, either unchanged or as the glucuronide or sulphate conjugates.

The bicyclic secondary alcohols are rapidly conjugated in humans, dogs and rabbits with glucuronic acid and excreted via the urine. In humans (Figure III.1), 81 and 94 % of an oral dose of 1,000 and 2,000 mg of borneol [FL-no: 02.016], respectively, was excreted as the glucuronic acid conjugate within 24 hours (Wagreich et al., 1941). At 10 hours following ingestion of 2,000 mg of borneol, 81 % of the dose was detected as the glucuronic acid conjugate in human urine (Quick, 1928b). At a higher dose level (i.e., 3,500 mg borneol), 69 % of the dose was detected in human urine after 6 hours (Quick, 1928b). Similar conjugation has been reported in dogs (Quick, 1927; Pryde and Williams, 1934) and an increased level of β-glucuronidase has been reported in several tissues of dogs orally administered borneol (Fishman, 1940). At oral doses of 100 mg/kg per day and higher, rats fed borneol over a period of 10 days showed an increase in the urinary levels of total glucuronic acid, o-glucuronide and ascorbic acid (Tamura et al., 1962). Fenchyl alcohol administered by gavage to rabbits was also excreted via urine as a glucuronide conjugate (Hämäläinen, 1912).



FigureIII.1 *Metabolism of borneol in humans*

In rats, pre-treated for 3 days with borneol (intraperitoneal or dietary exposure), increases of approximately 25 % were reported in the activities of biphenyl 4-hydroxylase, glucuronyl transferase, 4-nitrobenzoate reductase and CYP-450 (Parke and Rahman, 1969). Rats (4/group) given 250 mg/kg bw of l-borneol by intraperitoneal injection daily for 3 days showed no significant increase in liver UDP-glucuronosyltransferase (UDPGT) activity. After daily treatment for up to four weeks slight increases in the activity were observed. The authors concluded that over the short periods of exposure, detoxication of borneol does not require the induction of UDPGT; however, longer exposure periods, at high dose levels, necessitate UDPGT induction (Boutin et al., 1983). Conversely, in rats intubated with 3 mmol/kg bw of borneol [463 mg/kg bw in olive oil], the activity of hepatic *S*-3-hydroxy-3-methylglutaryl coenzyme A reductase was decreased by approximately 50 %, 17 hours after dosing (Clegg et al., 1980).

Cytochrome P4502B1 was induced in rat liver microsomes isolated from rats injected intraperitoneally with 300 mg/kg bw borneol (Hiroi et al., 1995), indicating that oxidation may occur to a limited extent. Rats injected intraperitoneally with 1,000 mg/kg bw isobornyl acetate [FL-no: 09.218] for 3 days showed a minimum 2.0-fold increase in the activities of *N*-demethylase and NADPH cytochrome c reductase, and in CYP-450 content indicating that isobornyl acetate induces the microsomal mixed-function oxidase system (Cinti et al., 1976), which also suggests that oxidation of ring positions and ring substituents may occur.

Ingestion of 6 to 10 gram of camphor by humans resulted in urinary excretion of 3-, 5-, 8- and 9-hydroxycamphor, 5-ketocamphor and the carboxylic acid of either 8- or 9-hydroxycamphor, unconjugated or conjugated with glucuronic acid (Köppel et al., 1982). A minor amount was exhaled in expired air. Hydroxylation products, predominantly 5-endo- and 5-exo-hydroxycamphor and a compound resembling 3-endo-hydroxycamphor, have also been reported when camphor was orally administered to dogs (1,000 mg per animal, 4 times per day via gelatine capsule for 7 days) or rabbits (300 mg per animal, single dose by gavage) (Leibman and Ortiz, 1973). The same camphor hydroxylation products, with a small amount of 2,5-bornanedione, were similarly identified *in vitro* following incubation with rat and rabbit liver fractions (Leibman and Ortiz, 1973). Similar hydroxylation products (4- and 5-hydroxyfenchone and p-apofenchone-3-carboxylic acid) were detected in the urine of dogs fed d-fenchone (Reinartz and Zanke, 1936). The metabolism of *d*-fenchone also demonstrates that hydroxylation of ring methyl substituents leads to the corresponding carboxylic acid derivatives.

In rabbit liver cytosol, *d*-camphor was reduced via an NADPH-dependent pathway to borneol and a small amount of isoborneol (Robertson and Hussain, 1969; Leibman and Ortiz, 1973). In rat liver, camphor induced members of the P450IIB sub-family, most likely P450*b* and/or P450*e* (Austin et al., 1988). Female Swiss albino mice gavaged with 50, 150 or 300 mg camphor/kg bw per day in olive oil for 20 days showed a statistically significant increase in CYP-450 and cytochrome *b5*, aryl hydrocarbon hydrolase and glutathione *S*-transferase activities only at the highest dose level (Banerjee et al., 1995).

Other minor routes of metabolism of the cyclic secondary alcohols include hydroxylation of an allylic position and oxidative cleavage of the strained ring in the cyclic substance.

III.3. Conclusion

The available data indicate that the three esters in this group [FL-no: 09.584, 09.848 and 09.888] are readily hydrolysed to the corresponding bicyclic secondary alcohols which are subsequently conjugated with glucuronic acid and excreted in the urine. Similarly conjugation with glucuronide will also occur with the free tri-cyclic alcohol cedrenol [FL-no: 02.119]. The major metabolic pathway of the bicyclic ketones [FL-no: 07.171 and 07.196], involves reduction to the corresponding secondary alcohol, which will be excreted primarily as the glucuronic acid conjugates. In addition to reductive pathways, alicyclic ketones and, to a lesser extent, secondary alcohols containing an alkyl side-chain undergo oxidation of the side-chain to form polar oxygenated metabolites that are excreted mainly in the urine, either unchanged or as glucuronide or sulphate conjugates. It is therefore concluded that the candidate substances can be anticipated to be metabolised to innocuous products.

ANNEX IV: TOXICITY

Oral acute toxicity data are available for one candidate substance of the present Flavouring Group Evaluation, and for nine supporting substances evaluated by the JECFA at the 63th meeting (JECFA, 2006a). The supporting substances are listed in brackets.

TABLE IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	LD_{50} (mg/kg bw)	Reference	Comments
Cedrenol [02.119]	Rat	NR	> 5000	(Opdyke, 1975b)	
(Bornyl isovalerate [09.456])	Rat	NR	>5000	(Denine, 1973b)	
(Isoborneol [02.059])	Rat	NR	5200	(Moreno, 1977abp)	
(Isobornyl formate [09.176])	Rat	NR	>5000	(Levenstein, 1975p)	
(Isobornyl acetate [09.218])	Rat	M	>10,000	(Fogleman and Margolin, 1970)	
(Isobornyl propionate [09.131])	Rat	NR	>5000	(Moreno, 1973al)	
(Fenchyl alcohol [02.038])	Rat	NR	ND	(Moreno, 1976ad)	
(Fenchyl acetate [09.269])	Rat	NR	>5000	(Moreno, 1975s)	
(1,10 Dihydronootkatone [07.153])	Rat	NR	>5 ml/kg	(Sedlacek, 1985)	
((1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one [07.215])	Rat	NR	>5000	(Moreno, 1976ac)	
	Mice	NR	1310	(Opdyke, 1978d)	

M=Male; F=Female; NR=Not Reported; ND=No Data.

Subacute / Subchronic / Chronic / Carcinogenic toxicity data are available for none of the candidate substances of the present Flavouring Group Evaluation but for four supporting substances evaluated by the JECFA at the 63th meeting (JECFA, 2006a). The supporting substances are listed in brackets.

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

Chemical Name [FL-no]	Species; Sex[1] No./Group[2]	Route	Dose levels	Duration	NOAEL (mg/kg bw/day)	Reference	Comments
(Borneol [02.016])	Dog; NR 1/3	Gavage	526 mg/kg bw /day	31 days	526[3]	(Miller et al., 1933)	
	Dog; NR 1/5	Diet	500 mg/kg bw /day	37 days	<500	(Miller et al., 1933)	
	Dog; NR 1/3	Diet	1300 mg/kg bw /day	90 days	<1300[4]	(Miller et al., 1933)	
(Isobornyl acetate [09.218])	Rat; M, F 3/30	Gavage	0, 15, 90, 270 mg/kg bw /day	91 days	15 (M) 90 (F)[5]	(Gaunt et al., 1971b)	
(*d*-Fenchone [07.159])	Dog; NR 1/1	Oral	1064 mg/kg bw /day	16 days	<1064	(Rimini, 1901)	
((1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one [07.215])	Rat NR 4/5	Gavage	0, 250, 500, 1000, 1200 mg/kg bw/day[6]	56 days	75	(Skramlik, 1959)	

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

[1] Total number of test groups does not include control animals.

[2] Total number per test group includes both male and female animals.

[3] Study performed with either a single dose or multiple doses that produced no adverse effect.

[4] Animals were gradually introduced to the final dose level of 1,300 mg/kg bw per day over a 2-month period.

[5] Author specified a single NOEL of 15 mg/kg bw per day, without distinguishing between male and female rats.

[6] Study performed using sage oil at doses of 0, 250, 500, 1000 or 1200 mg/kg bw per day. With an estimated camphor content of approximately 30 %, these doses provide approximately 0, 75, 150, 300 or 360 mg/kg bw per day of camphor.

TABLE IV.3: DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental and reproductive toxicity data are available for the candidate substances of the present flavouring group evaluation but for one supporting substance evaluated by JECFA at the 63rd meeting. This supporting substance is listed in brackets.

TABLE IV.3: DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Chemical Name	Study type Duration	Species/Sex No/group	Route	Dose levels (mg/kg/day)	NOAEL (mg/kg/day) Including information on possible maternal toxicity	Reference
((1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one [07.215])	Teratology Gestation days 6-15	Rat; F	Gavage	100, 400 and 800	No adverse effects on fetal growth, viability, or morphological development were reported.	(NTP, 1992i)
	Teratology Gestation days 6-19	Rabbit; F	Gavage	0, 50, 200 and 400	No effect on fetal growth, viability or morphological development was observed.	(NTP, 1992j)
	Teratogenicity Gestation days 6-17	Rat; F	Gavage	216, 464 and 1000	No evidence of teratogenicity.	(Leuschner, 1997)
	Teratogenicity Gestation days 6-18	Rabbit; F	Gavage	147, 316 and 681	No increased incidences in variations, retardations or malformations were observed at any of the treated dose levels.	(Leuschner, 1997)

F: Female.

In vitro mutagenicity/genotoxicity data are available for none of the candidate substances of the present Flavouring Group Evaluation but for three supporting substances evaluated by the JECFA at the 63rd meeting (JECFA, 2006a) as well as one structurally related supporting substance. Supporting substances are listed in brackets.

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

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
(Borneol [02.016])	Reverse mutation	*Salmonella typhimurium* TA97, TA98, TA100	1 mg/ml (1000 µg/ml)	Negative[1]	(Azizan and Blevins, 1995)	
	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Up to 5 mg/plate (5000 µg/plate)	Negative	(Simmon et al., 1977)	
	DNA repair	*Bacillus subtilis* M45 and H17	Up to 10 mg/disk	Positive	(Yoo, 1986)	
	Mutation test	*Escherichia coli* WP2 uvrA (trp-)	0.4-3.2 mg/plate	Negative	(Yoo, 1986)	
(Isobornyl propionate [09.131])	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Up to 3.6 mg/plate (3600 µg/plate)	Negative	(Wild et al., 1983)	
((1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one [07.215])	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1538	4, 20, 100, 500 and 2500 µg/plate	Negative[2]	(Anderson and Styles, 1978)	
	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	≤ 50 µg/plate	Negative[3]	(Marzin, 1998)	
	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	≤ 150 µg/plate	Negative[1]	(Marzin, 1998)	
	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1538	10, 33, 100, 333 and 667 µg/plate	Negative[1]	(NTP, 1992h)	
	Sister chromatid exchange	Chinese hamster ovary cells	250, 500, 750, 1000 and 1500 µg/ml	Negative[1,3]	(NTP, 1992h)	
	Sister chromatid exchange	Chinese hamster ovary cells	500, 525, 550, 575 and 600 µg/ml	Negative[2]	(NTP, 1992h)	
(*d,l*-Camphor)	Reverse mutation	*Salmonella typhimurium* TA97a, TA98, TA100, TA102		Negative[1]	(Gomes-Carneiro et al., 1998)	

[1] Tested with and without metabolic activation.

[2] Tested with metabolic activation.

[3] Tested without metabolic activation.

In vivo mutagenicity/genotoxicity data are available for none of the candidate substances of the present Flavouring Group Evaluation but for one supporting substances evaluated by the JECFA at the 63th meeting (JECFA, 2006a) as well as one structurally related supporting substance. Supporting substance is listed in brackets.

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

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments
(Isobornyl propionate [09.131])	Somatic mutation and recombination	*Drosophila melanogaster*	Oral	10 mM (2103 µg/ml)	Negative	(Wild et al., 1983)	
	Micronucleus formation	Mouse bone marrow cells	IP	841, 1893, and 2944 mg/kg bw	Negative[1]	(Wild et al., 1983)	
(*d*,*l*-Camphor)	Micronucleus induuction	Mouse peripheral blood erythrocytes	Dermal	200, 400, 600, 800 and 1000 mg/kg bw	Negative[2]	(NTP, 1999c)	Daily application, 5days/week; 13 weeks.

[1]Administered via intraperitoneal injection.

[2]Administered topically.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
BW	Body Weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids Chemical Abstract Service
CHO	Chinese Hamster Ovary (cells)
CoE	Council of Europe
DNA	Deoxyribonucleic Acid
EC	European Commission
EFFA	European Flavour and Fragrance Association
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
ID	Identity
IOFI	International Organization of the Flavour Industry
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal Dose, 50 %; Median lethal dose
MS	Mass Spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate, reduced form
No	Number
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Program
SCE	Sister Chromatid Exchange
SCF	Scientific Committee on Food
SMART	Somatic Mutation and Recombination Test
TAMDI	Theoretical Added Maximum Daily Intake
UDP	Uridine Diphosphate

UDPGT	UDP-glucuronosyltransferase
UDS	Unscheduled DNA Synthesis
WHO	World Health Organisation