EFSA Scientific Opinion on Flavouring Group Evaluation 87 Revision 1 (FGE.87Rev1): Consideration of bicyclic secondary alcohols, ketones and related esters evaluated by JECFA (63rd meeting) structurally related to bicyclic secondary alcohols, ketones and related esters evaluated by EFSA in FGE.47 (2008)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 87 Revision 1 (FGE.87Rev1):

Consideration of bicyclic secondary alcohols, ketones and related esters evaluated by JECFA (63rd meeting) structurally related to bicyclic secondary alcohols, ketones and related esters evaluated by EFSA in FGE.47 (2008)[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. The present consideration concerns a group of 17 bicyclic secondary alcohols, ketones and related esters evaluated by the JECFA at the 63rd meeting in 2004. This revision of FGE.87 is made due to consideration of two additional substances [FL-no: 02.100 and 02.101] compared to previous version. Additionally, new information on EU production volume on two substances and information on stereoisomeric composition for 13 substances are also included. The substances were evaluated through a stepwise approach that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. The Panel agrees with the application of the Procedure as performed by the JECFA for all 17 substances considered in this FGE and agrees with the JECFA conclusion, "No safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been

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considered for the substances evaluated through the Procedure and for two substances, [FL-no: 02.100 and 02.101], information on the stereoisomeric composition is lacking.

KEY WORDS

Flavouring, food safety, Bicyclic secondary alcohols, ketones and related esters, JECFA, secondary alicyclic saturated alcohols, secondary alicyclic unsaturated alcohols, FGE.47, FGE.87.

SUMMARY

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

This consideration deals with 17 bicyclic secondary alcohols, ketones and related esters, which are in the Register and which were evaluated by the JECFA at its 63rd meeting.

The revision is made due to consideration of two additional substances [FL-no: 02.100 and 02.101] compared to the previous version. These two substances are alpha,beta-unsaturated substances which have been considered with respect to genotoxicity in FGE.211 and FGE.212Rev1, and the Panel concluded that the data available ruled out the concern for genotoxicity and thus concluded that the two substances can be evaluated through the Procedure in this FGE.87Rev1. EU production volume on two substances [FL-no: 09.153 and 09.319] and new information on stereoisomerism for 13 substances [FL-no: 02.016, 02.038, 02.059, 07.159, 09.017, 09.082, 09.131, 09.153, 09.176, 09.218, 09.319, 09.456 and 09.457] are also included.

The Panel concluded that all 17 substances are structurally related to the group of four bicyclic secondary alcohols, ketones and related evaluated by EFSA in the Flavouring Group Evaluation 47 (FGE.47).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 17 bicyclic secondary alcohols, ketones and related esters. It was concluded at step A3 of the Procedure that the 17 substances do not pose a safety concern when used as flavouring substances at estimated levels of intake, based on the MSDI approach.

For all 17 substances evaluated through the Procedure use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessments and to finalise the evaluation.

In order to determine whether the conclusion for the JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications are available for all the materials of commerce. For two of the candidate substances [FL-no: 02.100 and 02.101] the stereoisomeric composition has not been specified. Thus, for these two JECFA-evaluated substances [FL-no: 02.100 and 02.101] the Panel has reservations (information on the stereoisomeric composition is lacking).

For the remaining 15 JECFA-evaluated substances [FL-no: 02.016, 02.038, 02.059, 07.153, 07.159 , 09.017, 09.082, 09.131, 09.153, 09.176, 09.218, 09.269, 09.319, 09.456 and 09.457] the Panel agrees with the JECFA conclusion: “No safety concern at estimated levels of intake as flavouring substances” based on 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).

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

In the period 2000 – 2008, during its 55th, 57th, 59th, 61st, 63rd, 65th, 68th and 69th meetings, the JECFA evaluated about 1000 substances, which are in the EU Register.

TERMS OF REFERENCE

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

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999a), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the "JECFA Procedure". The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be put through the EFSA Procedure.

The following issues are of special importance.

Intake

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

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available,

meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

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

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

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

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

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

"The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 microgram per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the condition of use result in an intake greater than 1.5 microgram per day?")" (JECFA, 1999b).

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

At its 63rd meeting the JECFA evaluated a group of 32 flavouring substances consisting of monocyclic and bicyclic secondary alcohols, ketones and related esters. Three substances were not in the Register, and six are alpha,beta-unsaturated ketones or precursors for such and these will be or have been considered together with other alpha,beta-unsaturated aldehydes and ketones (EFSA, 2008b) in FGE.213, FGE.211 and FGE.212 and revision hereof. One is an ether [FL-no: 16.088] considered in a revision of FGE.59 (FGE.59Rev1). Six are monocyclic secondary alcohols, ketones and related esters considered in FGE.56. Finally, the JECFA evaluated substance, (1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (camphor [FL-no: 07.215]), which the Panel has evaluated in a separate Opinion (EFSA, 2008l). The remaining 15 flavouring substances were considered by EFSA in FGE.87 (EFSA, 2008az).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.87	22 May 2008	http://www.efsa.europa.eu/en/efsajournal/pub/746.htm	15
FGE.87Rev1	1 February 2012		17

The present revision of FGE.87, FGE.87Rev1 includes the consideration of an additional two substances [FL-no: 02.100 and 02.101]. These two substances are precursors for alpha,beta-unsaturated ketones and were allocated to FGE.211 and FGE.212Rev1, respectively.

Since the publication of FGE.87, the EU production volume has been provided for two substances, [FL-no: 09.153 and 09.319] for which the evaluation could not be finalised in the previous version of this FGE, due to lack of these data. Based on the newly submitted EU production volume the substances have already been evaluated in FGE.96 (EFSA, 2010al), but for the sake of completion, the information has also been included here as well.

Finally, new information on the stereoisomeric composition has been provided for 13 substances [FL-no: 02.016, 02.038, 02.059, 07.159, 09.017, 09.082, 09.131, 09.153, 09.176, 09.218, 09.319, 09.456 and 09.457] since the publication of FGE.87 (EFFA, 2010a; EFFA, 2011m).

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has at the 63rd meeting evaluated a group of 32 flavouring substances consisting of monocyclic and bicyclic secondary alcohols, ketones and related esters (JECFA, 2006a).

1.1.2. EFSA Considerations

Three of the 32 JECFA evaluated substances are not included in the Register, alpha-isomethylionyl acetate (JECFA-no: 1410), d,l-menthol-(±)-propylene glycol carbonate (JECFA-no: 1413) and l-monomenthyl glutarate (JECFA-no: 1414).

Six of the 32 JECFA evaluated substances are alpha,beta-unsaturated [FL-no: 02.100, 02.101, 07.089, 07.136, 07.140 and 09.305] and will be or have been evaluated together with other alpha,beta-unsaturated aldehydes and ketones (EFSA, 2008b). Two of these alpha,beta-unsaturated substances [FL-no: 02.100 and 02.101] have been considered with respect to genotoxicity in FGE.211 (EFSA, 2011e) and FGE.212Rev1 (EFSA, 2011f). The Panel concluded that the data available ruled out the concern for genotoxicity and thus concluded that the two substances can be evaluated through the Procedure.

One of the JECFA evaluated substances is an ether [FL-no: 16.088] which is considered together with other ethers in a revision of FGE.59 (FGE.59Rev1). Six of the JECFA evaluated substances are monocyclic secondary alcohols, ketones and related esters and are considered in FGE.56. Finally, the JECFA evaluated substance, (1R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (camphor [FL-no: 07.215]), the Panel evaluated in a separate Opinion (EFSA, 2008l).

This consideration will therefore only deal with 17 bicyclic secondary alcohols, ketones and related esters. The Panel concluded that all substances in the JECFA flavouring group of bicyclic secondary alcohols, ketones and related esters are structurally related to the group of four bicyclic secondary alcohols, ketones and related esters evaluated by EFSA in FGE.47.

1.2. Isomers

1.2.1. JECFA Status

All 17 Register substances have one or more chiral centres **(**see Table 1).

1.2.2. EFSA Considerations

For two of the substances [FL-no: 02.100 and 02.101] the composition of the mixture of stereoisomers has not been specified.

For the two stereoisomeric substances [FL-no: 07.153 and 09.269] with one chiral centre, the CAS register number (CASrn) is considered to cover the stereoisomeric composition.

1.3. Specifications

1.3.1. JECFA Status

JECFA specifications are available for all substances (JECFA, 2005b).

1.3.2. EFSA Considerations

The composition of the mixture has not been specified for two substances [FL-no: 02.100 and 02.101] (see Section 1.2.2). For two substances [FL-no: 02.059 and 07.153] the minimum assay is below 95 %, but information on secondary components is available in the specifications (see Table 1).

2. Intake Estimations

2.1. JECFA Status

For all substances evaluated through the JECFA Procedure production figures are available for the EU.

2.2. EFSA Considerations

No comment.

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text taken[4] from the JECFA (JECFA, 2006a)

Tests for genotoxicity *in vitro* and *in vivo* using standardized protocols have been used to study two representative members [FL-no: 02.016 and 09.131] of the bicyclic secondary alcohols, ketones and related esters group used as flavouring agents.

In vitro

Two members of this group (borneol, [FL-no: 02.016] and isobornyl propionate, [FL-no: 09.131]) consistently gave negative results in the Ames assay when incubated at a concentration of up to 5000 µg/plate with a variety of *Salmonella typhimurium* strains including TA97, TA98, TA100, TA1535, TA1537 and TA1538 with or without metabolic activation (Simmon et al., 1977; Wild et al., 1983; Azizan and Blevins, 1995).

Borneol [FL-no: 02.016] showed no mutagenic activity when tested in *Escherichia coli* WP2 *uvrA* at concentrations of up to 3200 µg/plate (Yoo, 1986).

In the Rec-assay, borneol [FL-no: 02.016] was reported to induce growth inhibition in *Bacillus subtilis* strain M45$^-$ when tested at concentrations of up to 10 mg/disc (Yoo, 1986). This test has very limited relevance for the genotoxicity evaluation.

In vivo

The potential of isobornyl propionate [FL-no: 09.131] to induce sex-linked recessive lethal mutations in adult *Drosophila melanogaster* was studied in a Basc test. No increased frequency of mutation was observed in flies fed with isobornyl propionate [FL-no: 09.131] in a 10 mmol/l solution for 3 days (Wild et al., 1983).

In the test for micronucleus formation, groups of NMRI mice given isobornyl propionate (FL-no: 09.131) at a dose of 841, 1893 or 2944 mg/kg body weight (bw) by intraperitoneal administration showed no increase in micronucleated erythrocytes in samples of bone marrow, 30 hours after administration (Wild et al., 1983).

Conclusion on genotoxicity

The testing of these representative bicyclic secondary alcohols, ketones and related esters in bacterial (Ames assay) and mammalian (micronucleus formation) *in vivo* systems showed no evidence of genotoxic potential, and these results are further supported by the lack of positive findings in the *Drosophila* Basc test.

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

3.2. Genotoxicity Studies - Text taken from FGE.47 (EFSA, 2008at)

No *in vitro / in vivo* genotoxicity data are available for the candidate substances in FGE.47.

[4] *The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed*.

3.3. Genotoxicity Studies - Text taken from FGE.211 (EFSA, 2011e)

The following text is taken from FGE.211 and is relevant for the evaluation of pinocarveol [FL no: 02.100], which was one of the four substances in subgroup 2.5 of FGE.19 (FGE.211) for which a conclusion of no concern for genotoxicity was reached.

The Industry has submitted data concerning genotoxicity studies for a representative substance for this subgroup 2.5 of FGE.19, 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930] (structurally related to 1(7),8-p-menthadien-2-one).

In Vitro Data

The newly available data comprise a bacterial reverse mutation assay and an *in vitro* micronucleus assay with human peripheral blood lymphocytes. The genotoxicity assays have been performed on a commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate and a positional isomer, carvyl acetate. Carvyl acetate can be hydrolysed, followed by oxidation, to carvone, which has been evaluated by EFSA in FGE.212 (EFSA, 2009ai) and NTP (NTP, 1990b) as non-genotoxic. The highest concentration of d-carvone that could be tested without cytotoxicity was 333 µg/plate (Mortelmans et al., 1986), i.e. the cytotoxicity was in the same range as observed for the mixture of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate. The Panel concluded that testing the commercial mixture of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate for genotoxicity allows the evaluation of the genotoxic potential of 1(7),8-p-menthadien-2-yl acetate. The concentrations reported in Table 3 (in FGE.211) are for the mixture of substances.

Bacterial Reverse Mutation Assay

1(7),8-p-menthadien-2-yl acetate/carvyl acetate was tested for mutagenic activity according to OECD guideline 471 and in compliance with GLP (Beevers, 2010a). The test material exhibited a marked toxicity as indicated by thinning of the background lawn, reduced revertant counts and complete killing of test bacteria. However, the Panel considered the remaining number of concentrations without signs of toxicity sufficient to draw a conclusion on mutagenicity in this system (for details see FGE.211, Table 3).

Overall, the Panel concluded that there was no evidence of mutagenic activity of 1(7),8-p-menthadien-2-yl acetate/carvyl acetate at concentrations up to those causing bactericidal effects.

In vitro Micronucleus Test

1(7),8-p-menthadien-2-yl acetate/carvyl acetate was tested for induction of micronulei in human peripheral blood lymphocytes according to OECD guideline 487 and in compliance with GLP (Whitwell, 2010b). The Panel considered that acceptable levels of cytotoxicity as judged upon the replication index were achieved at the top concentrations (for details see FGE.211 Table 3).

Overall, the Panel concluded that there was no evidence of chromosomal damage or aneuploidy, as evidenced by no increase in levels of micronucleated binucleate cells (MNBN) in the presence or absence of S9 metabolic activation.

Discussion of Mutagenicity/Genotoxicity Data

The commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate and a positional isomer, carvyl acetate was tested for all three genetic endpoints: gene mutations, structural and numerical chromosomal aberrations. The test material did not induce gene mutations in bacteria and was not clastogenic and/or aneugenic in mammalian cells *in vitro*. Although this commercial mixture was cytotoxic at high concentrations, the remaining concentrations without signs of toxicity provide a valid data set.

Conclusion

The *in vitro* genotoxicity data on the commercial mixture of the representative substance 1(7),8-p-menthadien-2-yl acetate [FL-no: 09.930] and a positional isomer, carvyl acetate do not indicate genotoxic potential. Accordingly the four substances in this subgroup 2.5 of FGE.19 (FGE.211) would be of no safety concern with respect to genotoxicity, and will then be evaluated through the Procedure.

3.4. Genotoxicity Studies - Text taken from FGE.212Rev1 (EFSA, 2011f)

The following text is taken from FGE.212Rev1 and is relevant for the evaluation of pin-2-en-4-ol [FL no: 02.101], which was one of the isophorone-related substances in subgroup 2.6 of FGE.19 (FGE.212Rev1) for which a conclusion of no concern for genotoxicity was reached.

There are studies available for four substances in this FGE (FGE.212Rev1). For tetramethyl ethylcyclohexenone (mixture of isomers) [FL-no: 07.035] one *in vitro* and one *in vivo* study have been evaluated.

Seven *in vitro* and three *in vivo* studies are available for 3,5,5 trimethylcyclohex-2-en-1-one [FL-no: 07.126] (isophorone).

Three *in vitro* studies are available concerning d-carvone [FL-no: 07.146] and two *in vitro* studies concerning l-carvone [FL-no: 07.147].

Study validation and results are presented in Tables 5 and 6 of FGE.212Rev1.

3,5,5-Trimethylcyclohex-2-en-1-one [FL-no: 07.126] (isophorone) did not induce gene mutations in bacteria but it induced mutations in mammalian cells in a mouse lymphoma TK assay in the absence of metabolic activation (it was not tested in the presence of metabolic activation) (NTP, 1986d). No mutations in the MLTK assay were observed in a study of O'Donoghue et al. (O'Donoghue et al., 1988) at comparable concentrations. Isophorone induced chromosomal aberrations in Chinese hamster lung fibroblasts with and without metabolic activation (Matsuoka et al., 1996) and sister chromatid exchanges (SCE) in CHO cells without metabolic activation (Gulati et al., 1989). Chromosomal aberrations have not been observed in two other studies (Gulati et al., 1989; NTP, 1986d); however, the validity of the results was limited because the types of aberrations were not reported. Isophorone did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro*. *In vivo*, isophorone was tested negative in a sex-linked recessive lethal mutation assay in *Drosophila* (Foureman et al., 1994) and in two micronucleus assays in mice (McKee et al., 1987; O'Donoghue et al., 1988). However, the *Drosophila* assay has only limited relevance and the micronucleus assays were of limited validity.

Negative results were also observed with tetramethyl ethylcyclohexenone [FL-no: 07.035] in bacteria, in a sex-linked recessive lethal mutation assay in *Drosophila* (Wild et al., 1983) and in a mouse micronucleus assay (Wild et al., 1983); however, there was a mixture of isomers tested and the studies were only of limited validity.

d-Carvone [FL-no: 07.146] was not mutagenic in bacteria but induced SCE and chromosomal aberrations in CHO cells in the presence and absence of metabolic activation, respectively (NTP, 1990b).

Conclusion on Genotoxicity and Carcinogenicity (cited from FGE.212)

The Panel concluded that 3,5,5 trimethylcyclohex-2-en-1-one [FL-no: 07.126] (isophorone) is genotoxic *in vitro* while a final conclusion on the genotoxicity *in vivo* could not be drawn based on the data available. It is carcinogenic in male rats and male mice. It was also predicted to be genotoxic in one of the four MultiCASE models (while it was out of domain in the ISS model).

d-Carvone [FL-no: 07.146] is genotoxic *in vitro* while no *in vivo* data were available. d-Carvone, was not carcinogenic in mice and was predicted to be non-genotoxic in the four MultiCASE models (while it was out of domain in the ISS model). No data are available on l-carvone. However, *in vivo* studies in humans show that the metabolism of ingestion-correlated amounts of d- or l-carvone occurs via a major oxidative pathway of the isopropylene side chain yielding diol and two carboxylic acids, irrespective of the stereochemical difference between the two parent isomers of carvone (Engel, 2001). Accordingly, the results for d-carvone can be used for l-carvone as well.

The negative results reported from *in vivo* studies on the genotoxicity of tetramethyl ethylcyclohexenone [FL-no: 07.035] were only of limited validity.

Data submitted from Industry in reply to Genotoxicity Data requested in FGE.212 (cited from the FGE.212Rev1)

Honma *et al.* (Honma et al., 1999a; Honma et al., 1999b) found that isophorone did not clearly induce mutations in the mouse lymphoma assay (MLA) following 3 hour treatments, but observed that it was mutagenic after 24 hour treatments in the absence of S9. Although only graphs are plotted, it seems that increases in mutation frequency (MF) that exceeded the Global Evaluation Factor (GEF) occurred at around 1250-1500 µg/ml where toxicity (by relative survival) reached 70 - 90 %.

The NTP conducted a mouse bone marrow chromosomal aberration (CA) study on isophorone. Groups of 8 male B6C3F1 mice (larger group sizes than required by OECD) were dosed i.p. with isophorone at 125, 250 and 500 mg/kg bw. The standard protocol for *in vivo* CA is not given on the NTP website. However, based on Shelby and Witt (Shelby and Witt, 1995), animals should have been sampled at 17 hours and, if negative, also at 36 hours. The data on the NTP website are only for bone marrow sampled at 36 hours It is therefore possible that a 17 hours sample was also taken, and found to be negative, but the data have not been posted. Fifty cells per animal were scored for CA and no increases in CA were seen. No measures of toxicity were recorded, but i.p. dosing should have guaranteed systemic exposure. The control CA frequency was normal (2.75 %) and the positive control (dimethylbenzanthracene) produced a significant response in CA frequency.

A DNA binding study was conducted in which F344-rats and B6C3F1-mice (the strains used in the NTP carcinogenicity study) were exposed to isophorone (Thier et al., 1990). Animals of both sexes were dosed once or five times by gavage with 500 mg/kg bw of unlabelled isophorone spiked with [1,3,5-^{14}C]-isophorone (specific activity: 52 mCi per mmol, 1.92 GBq per mmol). An additional group of acute dosed male rats received undiluted ^{14}C-isophorone for increased sensitivity. Rats and mice were maintained for 24 hours in closed metabolic cages. Twenty four hours after exposure, livers and kidneys (the tumour target tissues) were removed from the animals. DNA was isolated through hydroxyapatite chromatography and radioactivity was measured by liquid scintillation counting. No positive controls were included. Also no untreated controls were included, but, except for the liver sample of one mouse in the five times dose group, radioactivity values were within 2σ of background (6 dpm). Radioactivity values therefore did not indicate significant attachment of radioactivity to DNA. From these results it can be concluded that neither isophorone nor its metabolites bind covalently to DNA.

A study (Morishita et al., 1997b) was designed to investigate whether isophorone and/or α2µ-globulin[5] might be involved in the induction of preputial gland tumours in F-344 rats (10/sex/dose group). A series of experiments was performed in order to study several parameters including:

[5] Since interaction with α2µ-glubulin is not of direct relevance for the evaluation of genotoxic potential, this information is omitted from this study summary.

- Binding of isophorone to DNA of kidney and preputial gland. Groups of 10 male rats were dosed by gavage with 500 mg/kg of [^{14}C]-isophorone (specific activity 14.65 mCi/mmol; 100 µCi/animal). Positive control animals were dosed with ^{3}H-labeled methyl nitrosourea.

- DNA adduct detection by ^{32}P-postlabeling in young adult male and female rats (7 per group) dosed by gavage with 0, 250 or 500 mg/kg isophorone for five days.

Extraction of preputial gland and kidney DNA from rats treated with single 500 mg/kg labeled doses yielded no evidence of isophorone binding to DNA, whereas the positive control showed significant binding to DNA of preputial gland and kidney. These negative results with isophorone were confirmed in the ^{32}P -postlabeling assays.

In addition Industry has also asked whether the information submitted for isophorone (cyclohexenyl derivative) could also be applied to evaluate the genotoxic potential of the five-carbon membered ring substances (i.e. cyclopentenyl derivatives) in subgroup 2.6 (letter of EFFA to EFSA, dated 14/4-2010) (EFFA, 2010f). This request was supported by the argumentation that there is structural resemblance with respect to steric hindrance around the alpha,beta-unsaturated double bond. In addition, Industry argued that the π-conjugation systems in these molecules is very nearly planar and that therefore the reactivity and genotoxic potentials of the five- and six-membered ring systems would be similar. No further data were provided to substantiate this argumentation.

Discussion of the Additional Data (cited from the FGE.212Rev1)

Conflicting results were reported in two valid studies with the mouse lymphoma assay (MLA): one negative (O'Donoghue et al., 1988) and one positive (NTP, 1986d) at comparable concentrations. Mixed results were also reported in two studies of limited validity: one negative (Honma et al., 1999a) and one positive (Honma et al., 1999b). Another negative result was reported in a study (McKee et al., 1987), the validity of which cannot be evaluated. In the light of the clearly negative results in two valid bacterial gene mutation tests (Ames test) and in a valid Sex Linked Recessive Lethal Mutations test (SLRL) in *Drosophila*, and taking into account the lack of specificity and high sensitivity of the MLA, overall the results presently available are considered of questionable relevance. The Panel agrees that isophorone demonstrates some genotoxic activity *in vitro* but that the new data demonstrate lack of clastogenicity *in vivo*. In addition, the new DNA-binding data from two separate studies provide convincing evidence that isophorone does not induce tumours via a genotoxic mechanism. On the basis of these data it may be argued that there is no need to perform further *in vivo* genotoxicity studies such as the Comet assay or bone marrow micronucleus test. Thus, based on the data available the Panel concluded that there is no concern with respect to genotoxicity of isophorone.

Since based on the additional information the concern for the genotoxic potential for isophorone has been alleviated, The Panel concluded in FGE212Rev1 that a genotoxic potential could also be ruled out for the other isophorone-related six-carbon members of this subgroup of FGE.19.

3.5. EFSA Consideration

For two of the candidate substances [FL-no: 02.100 and 02.101] 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 supporting substances. Thus, the Panel concluded that the two substances [FL-no: 02.100 and 02.101] can be evaluated through the Procedure in this FGE.87Rev1. For the remaining 15 candidate substances in FGE.87Rev1 [FL-no: 02.016, 02.038, 02.059, 07.153, 07.159, 09.017, 09.082, 09.131, 09.153, 09.176, 09.218, 09.269, 09.319, 09.456 and 09.457], genotoxicity data are available on two substances [FL-no: 02.016 and 09.131]. The genotoxicity of these two substances could not be adequately assessed. However, the data available do not preclude the evaluation of these 15 candidate substances using the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to 17 Bicyclic Secondary Alcohols, Ketones and related Esters by the JECFA (JECFA, 2006a)

According to the JECFA, 15 of the 17 substances belong to structural class I and two to structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).
The JECFA concluded the 17 bicyclic secondary alcohols, ketones and related esters at step A3 in the

JECFA Procedure, i.e. the substances are expected to be metabolised to innocuous products (step 2) and concluded that the intakes for all substances are below the thresholds for their structural classes I and II (step A3).

In conclusion, the JECFA considered that the bicyclic secondary alcohols, ketones and related esters evaluated through the Procedure, were of no safety concern at the estimated levels of intakes based on the MSDI approach.

The evaluations of the bicyclic secondary alcohols, ketones and related esters are summarised in Table 3.1: Summary of Safety Evaluation of Bicyclic Secondary Alcohols, Ketones and Related Esters (JECFA, 2006a).

4.2. Application of the Procedure to Four Bicyclic Secondary Alcohols, Ketones and Related Esters by EFSA in FGE.47 (EFSA, 2008at)

Step 1

Three of the four candidate substances are classified into structural class I and one into structural class II according to the decision tree approach as presented by Cramer et al. (Cramer et al., 1978).

Step 2

All four 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 evaluation scheme.

Step A3

The estimated *per capita* daily intakes for all four candidate substances classified in structural classes I and II are below the human intake threshold of concern (i.e. 1800 μg/person per day for class I and 540 μg/person per day for class II).

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

4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the bicyclic secondary alcohols, ketones and related esters. It was concluded at step A3 of the Procedure that the 17 substances do not pose a safety concern when used as flavouring substances at estimated levels of intake, based on the MSDI approach.

5. Conclusion

The Panel concluded that all the 17 substances in the JECFA flavouring group of bicyclic secondary alcohols, ketones and related esters are structurally related to the group of four bicyclic secondary alcohols, ketones and related evaluated by EFSA in the Flavouring Group Evaluation 47 (FGE.47).

The Panel agrees with the application of the Procedure as performed by the JECFA for the bicyclic secondary alcohols, ketones and related esters. It was concluded at step A3 of the Procedure that the 17 substances do not pose a safety concern when used as flavouring substances at estimated levels of intake, based on the MSDI approach.

For all 17 substances use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessments and to finalise the evaluation.

In order to determine whether the conclusion for the JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications are available for all the materials of commerce. For two of the candidate substances [FL-no: 02.100 and 02.101] the stereoisomeric composition has not been specified. Thus, for two JECFA-evaluated bicyclic secondary alcohols, ketones and related esters [FL-no: 02.100 and 02.101] the Panel has reservations (information on the stereoisomeric composition of is lacking).

For the remaining 15 JECFA-evaluated bicyclic secondary alcohols, ketones and related esters [FL-no: 02.016, 02.038, 02.059, 07.153, 07.159, 09.017, 09.082, 09.131, 09.153, 09.176, 09.218, 09.269, 09.319, 09.456 and 09.457] the Panel agrees with the JECFA conclusion: “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY

Table 1: Specifications Summary for the JECFA Evaluated Substances in the Present Group (JECFA, 2005b)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Bicyclic Secondary Alcohols, Ketones and Related Esters (JECFA, 2005b)

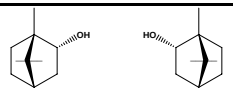
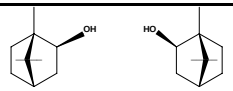
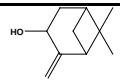
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.016 1385	Borneol		2157 64 507-70-0	Solid $C_{10}H_{18}O$ 154.25	Very slightly soluble Soluble	n.a. 202 IR 97 %	n.a. n.a.	Racemate (±) = DL-Borneol (EFFA, 2010a). CASrn refers to (1R,2S,4R)-rel. Register name to be changed to DL-Borneol (EFFA, 2011m). According to JECFA "Min. Assay value may incl. Isoborneol, other isomers of borneol, trace amounts of fenchyl alcohol & other $C_{10}H_{18}O$ compounds".
02.038 1397	Fenchyl alcohol		2480 87 1632-73-1	Solid $C_{10}H_{18}O$ 154.25	Very slightly soluble Soluble	n.a. 35-40 IR 97 %	n.a. n.a.	Racemate (EFFA, 2010a). According to JECFA "Min. Assay value is (97 %) of $C_{10}H_{18}O$ which may include small amounts of borneol and isoborneol".
02.059 1386	Isoborneol		2158 2020 124-76-5	Solid $C_{10}H_{18}O$ 154.25	Very slightly soluble Soluble	n.a. 212-214 IR 92 %	n.a. n.a.	Racemate (±) = DL-isoborneol (EFFA, 2011m). CASrn in Register refers to (1R,2R,4R)-rel. Register name to be changed to DL-Isoborneol (EFFA, 2011m). According to JECFA: Min. assay value is "92 %" and secondary components "3-5 % borneol".
02.100 1403	Pinocarveol 6)		3587 10303 5947-36-4	Liquid $C_{10}H_{16}O$ 152.24	Insoluble Soluble	210 NMR 95 %	1.445-1.451 0.977-0.983	Composition of stereoisomeric mixture to be specified.

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Bicyclic Secondary Alcohols, Ketones and Related Esters (JECFA, 2005b)

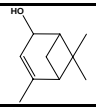
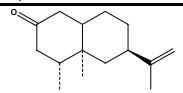
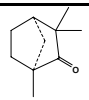
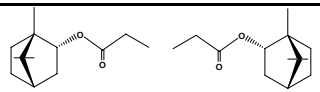
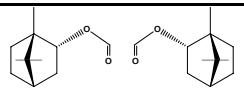
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.101 1404	Pin-2-en-4-ol 6)		3594 10304 473-67-6	Solid $C_{10}H_{16}O$ 152.24	Very slightly soluble Soluble	n.a. 63-67 NMR 95 %	n.a. n.a.	Composition of stereoisomeric mixture to be specified.
07.153 1407	1,10-Dihydronootkatone		3776 20489-53-6	Liquid $C_{15}H_{24}O$ 220.36	Very slightly soluble Soluble	100-104(0.09hPa NMR 90 %	1.502-1.508 0.975-0.988	CASrn in Register refers to (4R,4aS,6R,8aS)-stereoisomer. Register name to be changed accordingly. According to JECFA "Min. assay value is (90 %) and secondary components (5-6% nootkatone)".
07.159 1396	d-Fenchone		2479 551 4695-62-9	Liquid $C_{10}H_{16}O$ 152.24	Insoluble Soluble	192 IR 97 %	1.460-1.467 0.940-0.948	D-(+)-Fenchone (EFFA, 2010a). CASrn in Register refers to (1S,4R)-isomer. According to JECFA "Min. Assay value is "97 % of $C_{10}H_{16}O$" which may include small amounts of d-camphor".
09.017 1387	Bornyl acetate		2159 207 76-49-3	Liquid $C_{12}H_{20}O_2$ 196.29	Slightly soluble Soluble	226 25 IR 98 %	1.462-1.466 0.981-0.985	Racemate (±) = DL-Bornyl acetate (EFFA, 2010a). CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl acetate (EFFA, 2011m). According to JECFA "Min. Assay value is 98 % and may include isobornyl acetate and other bornyl acetate isomers".
09.082 1389	Bornyl formate		2161 349 7492-41-3	Liquid $C_{11}H_{18}O_2$ 182.26	Slightly soluble Soluble	106-108 (27hPa) NMR 95 %	1.466-1.472 1.007-1.013 (20°)	Racemate (±) = DL-Bornyl formate (EFFA, 2011m) CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl formate (EFFA, 2011m).

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Bicyclic Secondary Alcohols, Ketones and Related Esters (JECFA, 2005b)

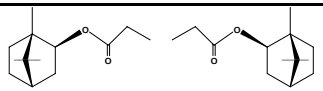
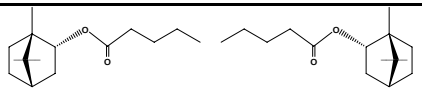
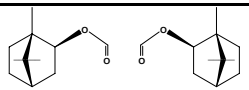
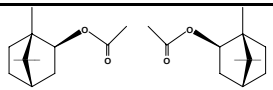
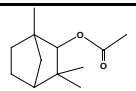
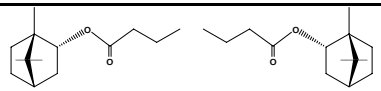
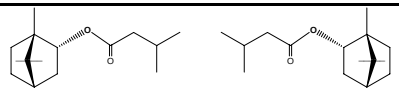
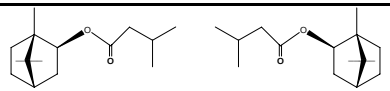
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
09.131 1391	Isobornyl propionate		2163 412 2756-56-1	Liquid $C_{13}H_{22}O_2$ 210.32	Soluble Soluble	245 NMR 97 %	1.461-1.465 0.968-0.971	Racemate (±) = DL-Isobornyl propionate (EFFA, 2010a). CASrn in Register refers to (1R,2R,4R)-rel. Register name to be changed to DL-Isobornyl propionate (EFFA, 2011m). According to JECFA "Min. Assay value may include small amounts of bornyl propionate".
09.153 1392	Bornyl valerate		2164 471 7549-41-9	Liquid $C_{15}H_{26}O_2$ 238.37	Insoluble Soluble	136-137 (16hPa) NMR 96 %	1.459-1.465 0.957-0.963	Racemate (±) = DL-Bornyl valerate (EFFA, 2010a). CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl valerate (EFFA, 2011m). According to JECFA: Min. assay value "may include small amounts of isobornyl valerate".
09.176 1390	Isobornyl formate		2162 565 1200-67-5	Liquid $C_{11}H_{18}O_2$ 182.26	Slightly soluble Soluble	94-95 (20 hPa) NMR 96 %	1.469-1.473 1.011-1.017	Racemate (±) = DL-Isobornyl formate (EFFA, 2010a). CASrn in Register refers to (1R,2R,4R)-rel. Register name to be changed to DL-Isobornyl formate (EFFA, 2011m). According to JECFA: Min. Assay value "may include small amounts of bornyl formate".
09.218 1388	Isobornyl acetate		2160 2066 125-12-2	Liquid $C_{12}H_{20}O_2$ 196.29	Insoluble Soluble	227 IR 97 %	1.462-1.465 0.979-0.984	Racemate (±) = DL-Isobornyl acetate (EFFA, 2010a). CASrn in Register refers to (1R,2R,4R)-rel. Register name to be changed to DL-Isobornyl acetate (EFFA, 2011m).

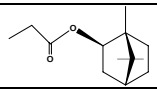
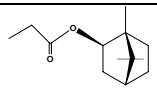
Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Bicyclic Secondary Alcohols, Ketones and Related Esters (JECFA, 2005b)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
								According to JECFA "Min. Assay value may include small amounts of bornyl acetate".
09.269 1399	Fenchyl acetate		3390 11769 13851-11-1	Liquid $C_{12}H_{20}O_2$ 196.29	Slightly soluble Soluble	220 NMR 98 %	1.456-1.462 0.973-0.979	Racemate. (CASrn in Register refers to the racemate).
09.319 1412	Bornyl butyrate		3907 13109-70-1	Liquid $C_{14}H_{24}O_2$ 224.34	Slightly soluble Soluble	247 MS 97 %	1.462-1.469 0.981-0.991	Racemate (±) = DL-Bornyl butyrate. CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl butyrate (EFFA, 2011m).
09.456 1393	Bornyl isovalerate		2165 451 76-50-6	Liquid $C_{15}H_{26}O_2$ 238.37	Insoluble Soluble	260 NMR 97 %	1.458-1.461 0.944-0.947	Racemate (±) = DL-Bornyl isovalerate. CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl isovalerate (EFFA, 2011m).
09.457 1394	Isobornyl isovalerate		2166 452 7779-73-9	Liquid $C_{15}H_{26}O_2$ 238.37	Insoluble Soluble	266-269 NMR 96 %	1.463-1.469 0.900-0.906	Racemate (±) = DL-Isobornyl isovalerate. CASrn in Register refers to (1R,2R,4R)-rel. Register name to be changed to DL-Isobornyl isovalerate (EFFA, 2011m).

1) Solubility in water, if not otherwise stated.
2) Solubility in 95 % ethanol, if not otherwise stated.
3) At 1013.25 hPa, if not otherwise stated.
4) At 20°C, if not otherwise stated.
5) At 25°C, if not otherwise stated.
6) Stereoisomeric composition not specified.

TABLE 2: GENOTOXICITY DATA

Table 2.1: Summary of Genotoxicity Data of Bicyclic Secondary Alcohols, Ketones and Related Esters Evaluated by the JECFA (JECFA, 2006a)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
02.016 1385	Borneol		Reverse mutation	*S. typhimurium* TA97, TA98, TA100	1 mg/ml (1000 µg/ml)	Negative[1]	(Azizan and Blevins, 1995)
			Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	≤ 5 mg/plate (5000µg/plate)	Negative[1]	(Simmon et al., 1977)
			DNA repair	*B. subtilis* M45$^-$ and H17$^+$	≤ 10mg/disc	Positive	(Yoo, 1986)
			Mutation test	*E. coli* WP2 *uvr*A (trp-)	0.4-3.2 mg/plate	Negative	(Yoo, 1986)
09.131 1391	Isobornyl propionate		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	≤ 3.6 mg/plate (3600 µg/plate)	Negative[1]	(Wild et al., 1983)
In vivo							
09.131 1391	Isobornyl propionate		Somatic mutation and recombination	*D. melanogaster*	10 mmol/l (2103 µg/ml)	Negative[2]	(Wild et al., 1983)
			Micronucleus formation	Mouse bone marrow cells	841, 1893 and 2944 mg/kg bw	Negative[3]	(Wild et al., 1983)

[1] Tested with and without metabolic activation.
[2] Dose calculated based on the relative molecular mass of substance = 210.32.
[3] Administered via intraperitoneal injection.

No *in vitro / in vivo* genotoxicity data are available for the candidate substances in FGE.47 (EFSA, 2008at).

Table 3: Summary of Safety Evaluations

Table 3.1: Summary of Safety Evaluation of Bicyclic Secondary Alcohols, Ketones and Related Esters *(JECFA, 2006a)*

Table 3.1: Summary of Safety Evaluation of Bicyclic Secondary Alcohols, Ketones and Related Esters *(JECFA, 2006a)*

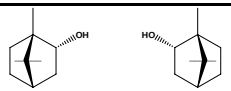
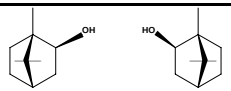
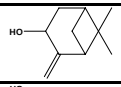
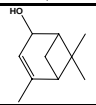
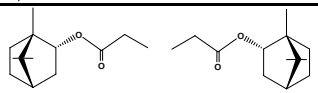
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.016 1385	Borneol		130 23	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Borneol. No safety concern at the estimated level of intake based on the MSDI approach.
02.038 1397	Fenchyl alcohol		55 17	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
02.059 1386	Isoborneol		21 0.07	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Isoborneol. No safety concern at the estimated level of intake based on the MSDI approach.
02.100 1403	Pinocarveol		0.012 0.01	Class I A3: Intake below threshold	4)	Evaluated in FGE.211, genotoxicity concern could be ruled out.	Composition of stereoisomeric mixture to be specified.
02.101 1404	Pin-2-en-4-ol		0.012 0.2	Class I A3: Intake below threshold	4)	Evaluated in FGE.212Rev1, genotoxic concern could be ruled out.	Composition of stereoisomeric mixture to be specified.
09.017 1387	Bornyl acetate		18 3	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Bornyl acetate. No safety concern at the estimated level of intake based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Bicyclic Secondary Alcohols, Ketones and Related Esters *(JECFA, 2006a)*

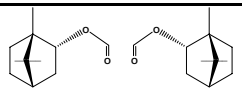
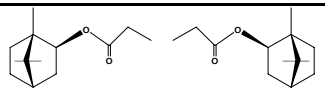
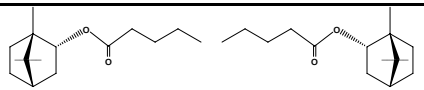
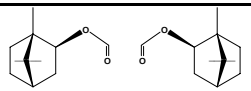
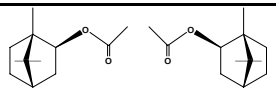
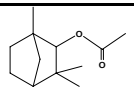
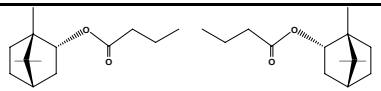
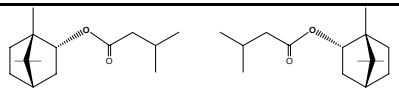
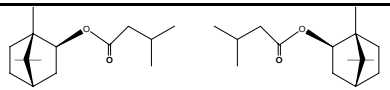
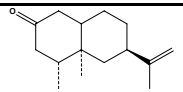
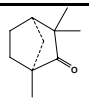
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.082 1389	Bornyl formate		1.2 0.09	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Bornyl formate. No safety concern at the estimated level of intake based on the MSDI approach.
09.131 1391	Isobornyl propionate		2.6 0.007	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Isobornyl propionate. No safety concern at the estimated level of intake based on the MSDI approach.
09.153 1392	Bornyl valerate		3.7 5	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Bornyl valerate. No safety concern at the estimated level of intake based on the MSDI approach.
09.176 1390	Isobornyl formate		0.61 0.4	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Isobornyl formate. No safety concern at the estimated level of intake based on the MSDI approach.
09.218 1388	Isobornyl acetate		890 236	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Isobornyl acetate. No safety concern at the estimated level of intake based on the MSDI approach.
09.269 1399	Fenchyl acetate		2.9 0.07	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

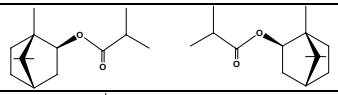
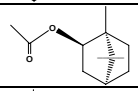
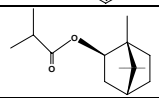
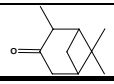
Table 3.1: Summary of Safety Evaluation of Bicyclic Secondary Alcohols, Ketones and Related Esters *(JECFA, 2006a)*

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
09.319 1412	Bornyl butyrate		6.1 9	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	CASrn in Register refers to (1R,2S,4R)-rel. Register name to be changed to DL-Bornyl butyrate. No safety concern at the estimated level of intake based on the MSDI approach.
09.456 1393	Bornyl isovalerate		0.12 0.5	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Bornyl isovalerate. No safety concern at the estimated level of intake based on the MSDI approach.
09.457 1394	Isobornyl isovalerate		0.012 0.08	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	Register name to be changed to DL-Isobornyl isovalerate. No safety concern at the estimated level of intake based on the MSDI approach.
07.153 1407	1,10-Dihydronootkatone		0.24 0.9	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	CASrn refers to (4R,4aS,6R,8aS)-stereoisomer. Register name to be changed accordingly. No safety concern at the estimated level of intake based on the MSDI approach.
07.159 1396	d-Fenchone		6 5	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

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.

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.47)

Table3.2: 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
09.584	Isobornyl isobutyrate		0.085	Class I A3: Intake below threshold	4)	7)	
09.848	(1S-endo)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate		0.011	Class I A3: Intake below threshold	4)	7)	
09.888	Isobornyl 2-methylbutyrate		0.061	Class I A3: Intake below threshold	4)	7)	
07.171	Isopinocamphone		0.024	Class II A3: Intake below threshold	4)	7)	

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.
6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

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ABBREVIATIONS

BW	Body weight
CA	Chromosomal Aberration
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DNA	Deoxyribonucleic acid
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GEF	Global Evaluation Factor
GLP	Good laboratory practise
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MLA	Mouse Lymphoma Assay
MNBN	Micronucleated Binucleate Cells
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
MF	Mutation Frequency (MF)
NCE	Normochromatic Erythrocyte
No	Number
NOAEL	No observed adverse effect level

NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PCE	Polychromatic erythrocyte
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food
SLRL	Sex Linked Recessive Lethal Mutations test
UDS	Unscheduled DNA Synthesis (UDS)
WHO	World Health Organisation