EFSA Panel on F ood Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) ; Scientific Opinion on Flavouring Group Evaluation 63, Revision 2 (FGE.63Rev2): Consideration of aliphatic secondary alcohols, ketones and related esters evaluated by JECFA (59 th and 6 9 th meeting s) structurally related to saturated and unsaturated aliphatic secondary alcohols, ketones and esters of secondary alcohols and saturated linear or branched - chain carboxylic acids evaluated by EFSA in FGE.07 Rev4

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 63, Revision 2 (FGE.63Rev2): Consideration of aliphatic secondary alcohols, ketones and related esters evaluated by JECFA (59th and 69th meetings) structurally related to saturated and unsaturated aliphatic secondary alcohols, ketones and esters of secondary alcohols and saturated linear or branched-chain carboxylic acids evaluated by EFSA in FGE.07Rev4[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 20 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 59th and 69th meetings in 2002 and 2008. This revision is made due to inclusion of one additional substance, 4-methylpent-3-en-2-one [FL-no: 07.101], cleared for genotoxicity concern. 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 20 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 considered and for all 20 substances, the information is adequate.

[1] On request from the European Commission, Question No EFSA-Q-2012-00512, adopted on 9 April 2013.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Groups on Flavourings: Ulla Beckman Sundh, Leon Brimer, Wilfried Bursch, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Wim Mennes, Gerard Mulder and Harriet Wallin for the preparatory work on this scientific opinion and the hearing experts: Vibe Beltoft, Pia Lund and Karin Nørby and EFSA staff: Annamaria Rossi and Kim Rygaard Nielsen for the support provided to this scientific opinion.

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KEY WORDS

Food safety flavourings, alcohols, ketones, esters, JECFA 59th meeting, JECFA 69th meeting, FGE.07.

SUMMARY

Following a request from the European Commission the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was asked to deliver a scientific opinion to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to 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.

In Flavouring Group Evaluation 63, Revision 1 (FGE.63Rev1) the EFSA considered 19 flavouring substances from two groups of flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at its 59th meeting and at its 69th meeting. The present revision of FGE.63, FGE.63Rev2, includes the consideration of one additional substance, 4-methylpent-3-en-2-one [FL-no: 07.101]. This substance [FL-no: 07.101] was evaluated by the JECFA at its 59th meeting and the substance is an α,β-unsaturated ketone originally allocated to and evaluated in FGE.204 in which it was considered not to be of concern with respect to genotoxicity. The Panel concluded that the additional substance fits well together with the 19 aliphatic secondary alcohols, ketones and related esters considered in the FGE.63.Rev1. Therefore, the present revision of FGE.63, FGE.63Rev2, considers 20 flavouring substances evaluated by the JECFA.

The Panel concluded that the 20 substances in the JECFA flavouring group of aliphatic secondary alcohols, ketones and related esters are structurally related to the group of 49 saturated and unsaturated aliphatic secondary alcohols, ketones and esters of secondary alcohols and saturated linear or branched-chain carboxylic acids evaluated in FGE.07Rev4.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 20 substances considered in this FGE.

For all 20 substances, the JECFA evaluation is based on MSDI values derived from production figures from the EU.

For three substances [FL-no: 02.252, 07.190 and 09.936], the Industry has submitted normal and maximum use levels. For [FL-no: 02.252 and 09.936], which are expected to be metabolised to innocuous products, the mTAMDI values are below their respective thresholds of concern for structural class I (1800 microgram/person/day) and class II (540 microgram/person/day). For substance [FL-no: 07.190], the mTAMDI value is above the threshold of concern for structural class II of 540 microgram/person/day to which it is allocated. Therefore, for this substance more reliable exposure data are required. On the basis of such additional data, the flavouring substance should be reconsidered along the steps of the Procedure. Following this procedure additional toxicological data might become necessary. For the remaining 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 assessment in order to finalise the evaluation.

In order to determine whether the conclusion for the 20 JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity are available for all 20 JECFA-evaluated substances.

Thus, for all 20 JECFA evaluated aliphatic secondary alcohols, ketones and related esters [FL-no: 02.252, 07.015, 07.069, 07.099, 07.100, 07.101, 07.114, 07.123, 07.151, 07.190, 07.240, 07.247,

07.249, 07.256, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936] 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 AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 2232/96[4] of the European Parliament and the Council 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[5], as last amended by Commission Decision 2009/163/EC[6]. 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[7], which is broadly based on the opinion of the Scientific Committee on Food (SCF, 1999).

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

In the period 2000 - 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 AS PROVIDED BY THE EUROPEAN COMMISSION

The European Food Safety Authority (EFSA) is requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments. The evaluation programme was finalised at the end of 2009.

In addition, the European Commission requests the European Food Safety Authority to carry out a safety assessment on the substance 4-methylpent-3-en-2-one [FL-no: 07.101], in accordance with Commission Regulation (EC) No 1565/2000.

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

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

[6] Commission Decision 2009/163/EC of 26 February 2009 amending Decision 1999/217/EC as regards the Register of flavouring substances used in or on foodstuffs. Official Journal of the European Union 27.2.2009, L 55, 41.

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

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000, hereafter named the "EFSA Procedure". This Procedure is based on the opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996; JECFA, 1997; JECFA, 1999), 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, 2006).

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, 1999).

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

1. History of the Evaluation of the Substances in the present FGE

At its 59st meeting the JECFA evaluated a group of 39 flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters (JECFA, 2003). One of the JECFA evaluated substances is not in the Register [(*E,R*)-3,7-dimethyl-1,5,7-octatrien-3-ol (JECFA No: 1154)], and 25 substances [FL-no: 02.023, 02.099, 02.102, 02.104, 02.136, 02.193, 07.044, 07.048, 07.081, 07.082, 07.099, 07.101, 07.102, 07.104, 07.105, 07.106, 07.107, 07.121, 07.138, 07.139, 07.177, 07.188, 07.244, 07.247 and 07.256] are α,β-unsaturated ketones or precursors for such, which have been considered together with other α,β-unsaturated substances. FGE.63 therefore only dealt with 13 JECFA evaluated substances (EFSA, 2008a).

The Revision 1 of FGE.63, FGE.63Rev1 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012c), included the consideration of six additional substances, three substances [FL-no: 07.099, 07.247 and 07.256] were evaluated by the JECFA at their 59th meeting (JECFA, 2003) and three [FL-no: 02.252, 07.190 and 09.936] were evaluated at the 69th meeting (JECFA, 2009b). Furthermore, the Industry had for six substances [FL-no: 07.069, 07.114, 09.657, 09.658, 09.923 and 09.925] submitted information on the stereoisomeric composition and for three substances [FL-no: 07.069, 07.100 and 09.658] provided EU production volumes (EFFA, 2010).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
63	7 July 2007	http://www.efsa.europa.eu/en/efsajournal/pub/706.htm	13
63Rev1	26 September 2012	http://www.efsa.europa.eu/en/efsajournal/pub/2900.htm	19
63Rev2	9 April 2013		20

The present revision of FGE.63, FGE.63Rev2, includes the consideration of one additional substance, 4-methylpent-3-en-2-one [FL-no: 07.101]. This substance is an α,β-unsaturated ketone and was originally evaluated in FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d) in which it was considered not to be of concern with respect to genotoxicity.

2. Presentation of the Substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA Status

This FGE deals with 20 JECFA evaluated substances, seventeen substances from the 59th meeting, 2002, and three substances from the 69th meeting, 2008:

- Of the 39 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 59th meeting (JECFA, 2003) one is not in the Register [(*E,R*)-3,7-dimethyl-1,5,7-octatrien-3-ol (JECFA No: 1154)], and 25 substances [FL-no: 02.023, 02.099, 02.102, 02.104, 02.136, 02.193, 07.044, 07.048, 07.081, 07.082, 07.099, 07.101, 07.102, 07.104, 07.105, 07.106, 07.107, 07.121, 07.138, 07.139, 07.177, 07.188, 07.244, 07.247 and 07.256] are α,β-unsaturated ketones or precursors for such, which have been considered together with other α,β-unsaturated substances. Of these 25 substances, three substances [FL-no: 07.099, 07.247 and 07.256] were evaluated in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011) in which they were considered not to be of concern with respect to genotoxicity. These three substances were included in revision 1 of FGE.63, FGE.63Rev1. Another one of these 25 substances, 4-methylpent-3-en-2-one [FL-no: 07.101], was evaluated in FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d) in which the substance was considered not to be of concern with respect to genotoxicity. Therefore, from the 59th JECFA meeting, 17 substances are considered in this FGE.63Rev2.

- Of the 17 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 69th meeting (JECFA, 2009b) five are not in the Register [(*E,Z*)-4-octen-3-one (JECFA No: 1843), (*E*)-2-nonen-4-one (JECFA No: 1844), (*E*)-5-nonen-2-one (JECFA No: 1845), 10-undecen-2-one (JECFA No: 1849) and 8-nonen-2-one (JECFA No: 1851)], six have been evaluated in other FGEs to be of no safety concern [FL-no: 02.253, 07.097, 07.239, 09.565, 09.822 and 09.938], and three substances [FL-no: 02.155, 09.281 and 09.282] have been evaluated in FGE.205 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012b) in which they were considered to be of concern with respect to genotoxicity. The remaining three substances [FL-no: 02.252, 07.190 and 09.936] were evaluated in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011) in which they were considered not to be of concern with respect to genotoxicity. These three substances were included in revision 1 of FGE.63, FGE.63Rev1 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012c).

2.1.2. EFSA Considerations

Seven of the α,β-unsaturated ketones [FL-no: 02.252, 07.099, 07.101, 07.190, 07.247, 07.256 and 09.936] evaluated by the JECFA at its 59th and 69th meetings (JECFA, 2003; JECFA, 2009b) were evaluated by EFSA with respect to genotoxicity, six in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011) and one in FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d) and were considered not to be of concern with respect to genotoxicity.

The Panel concluded that these seven substances together with 13 aliphatic secondary alcohols, ketones and related esters considered in FGE.63 are structurally related to the group of 49 saturated and unsaturated aliphatic secondary alcohols, ketones and esters of secondary alcohols and saturated linear or branched-chain carboxylic acids evaluated by EFSA in Flavouring Group Evaluation 07, Revision 4 (FGE.07Rev4) (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a).

2.2. Isomers

2.2.1. Status

Eight substances in the group of JECFA evaluated aliphatic secondary alcohols, ketones and related esters have a chiral centre [FL-no: 02.252, 07.069, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936] and eight substances can exist as geometrical isomers [FL-no: 02.252, 07.099, 07.114, 07.123, 07.190, 07.247, 07.256 and 09.936].

2.2.2. EFSA Considerations

Adequate information on isomeric composition is available for all substances. It is foreseen that no quantitative information on the stereoisomeric composition of [FL-no: 07.114] can be obtained. Therefore, the Panel consider the available information adequate.

For the substance [FL-no: 07.123], the CAS register number (CASrn) specify the stereoisomeric composition.

2.3. Specifications

2.3.1. JECFA Status

The JECFA specifications are available for all 20 substances (JECFA, 2002b; JECFA, 2009a). See Table 3.

2.3.2. EFSA Considerations

No comments.

3. Intake Estimations

3.1. JECFA Status

For all 20 substances evaluated by the JECFA, intake data (MSDI) were available for the EU, see Table 2 and Table 9.

3.2. EFSA Considerations

For all substances the Industry has submitted production figure for EU.

For three substances [FL-no: 02.252, 07.190 and 09.936], the Industry has submitted use levels for normal and maximum use (Flavour Industry, 2004) (see Table 1). Based on these normal use levels, mTAMDI values can be calculated (see Table 2), (EFSA, 2004). For one substance [FL-no: 07.190], the mTAMDI value is above the thresholds of concern for structural class II of 540 microgram/person/day to which it is allocated. The remaining two flavouring substances [FL-no: 02.252 and 09.936] have mTAMDI intake estimates below the threshold of concern for their structural class (class I and class II, respectively).

For 17 substances, use levels are needed in order to calculate the mTAMDIs.

Table 1: Normal and Maximum use levels (mg/kg) available for three JECFA evaluated substances in FGE.63Rev2

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**
02.252	0,0005 0,025	0,0005 0,025	0,005 0,25	0,0005 0,025	0,0005 0,025	0,05 2,5	- -	0,005 0,25	0,0005 0,025	0,0005 0,025	- -	- -	0,0005 0,025	- -	0,05 2,5	0,05 2,5	0,0005 0,025	0,0005 0,025
07.190	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
09.936	0,0005 0,025	0,0005 0,025	0,005 0,25	0,0005 0,025	0,0005 0,025	0,05 2,5	- -	0,005 0,25	0,0005 0,025	0,0005 0,025	- -	- -	0,0005 0,025	- -	0,05 2,5	0,05 2,5	0,0005 0,025	0,0005 0,025

Table 2: Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
02.252	4,8-Dimethyl-3,7-nonadien-2-ol	3	0.1	19	Class I	1800
09.657	1-Methylbutyl acetate	2.9	3		Class I	1800
09.658	1-Methylbutyl butyrate	0.47	1		Class I	1800
09.923	Hept-2-yl butyrate	3.0	3		Class I	1800
09.924	(+/-)-3-Heptyl acetate	3.0	3		Class I	1800
09.925	Nonan-3-yl acetate	3.0	3		Class I	1800
07.015	6-Methylhept-5-en-2-one	100	44		Class II	540
07.069	Tetrahydro-pseudo-ionone	0.012	0.01		Class II	540
07.099	6-Methylhepta-3,5-dien-2-one	13	5		Class II	540
07.100	5-Methylhex-5-en-2-one	0.24	0.3		Class II	540
07.101	4-Methylpent-3-en-2-one	0.34	ND		Class II	540
07.114	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	0.085	ND		Class II	540
07.123	Geranylacetone	41	2		Class II	540
07.151	Decan-3-one	3.0	3		Class II	540
07.190	Octa-1,5-dien-3-one	0.061	ND	1600	Class II	540
07.240	2-Methylheptan-3-one	3.0	3		Class II	540
07.247	(E,E)-3,5-Octadien-2-one	3.0	4		Class II	540
07.249	Undecan-6-one	3.0	3		Class II	540
07.256	(3Z)-4,8-Dimethyl-3,7-nonadiene-2-one	6.1	6.6		Class II	540
09.936	4,8-Dimethyl-3,7-nonadien-2-yl acetate	3	0.2	19	Class II	540

ND – not determined

4. Genotoxicity Data

4.1. Genotoxicity Studies

4.1.1. Genotoxicity Studies - Text taken[8] from the 59th JECFA meeting (JECFA, 2003)

In vitro

Assays for reverse mutation were performed with 6-methyl-5-hepten-2-one [FL-no: 07.015] and 6-methyl-3,5-heptadien-2-one [FL-no: 07.099]. There was no evidence of mutagenicity for 6-methyl-5-hepten-2-one at concentrations up to 380 µg/plate in TA98, TA100, TA1535 or TA1537 strains of *Salmonella typhimurium* (Florin et al., 1980). There was also no evidence of mutagenicity for 6-methyl-3,5-heptadien-2-one at concentrations up to 370 µg/plate in the same strains (Florin et al., 1980).

In vivo

No *in vivo* studies were reported by the JECFA at the 59th meeting.

For a summary of *in vitro / in vivo* genotoxicity data considered by the JECFA, see Table 4.

4.1.2. Genotoxicity Studies - Text taken[9] from the 69th JECFA meeting (JECFA, 2009b)

For the substances evaluated by the JECFA at the 69th meeting, no genotoxicity data were provided (JECFA, 2009b).

4.2. Genotoxicity Studies - Text taken[10] from EFSA FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a)

In vitro / In vivo

In vitro genotoxicity data have been reported for nine candidate substances. Negative results were obtained in bacterial systems (+/- metabolic activation) with six candidate substances: one saturated aliphatic acyclic secondary alcohol [FL-no: 02.183]; two saturated ketones [FL-no: 07.181 and 07.205]; two unsaturated ketones [FL-no: 07.198 and 07.262] and the ester isopropyl hexadecanoate [FL-no: 09.606]. Negative results were also obtained for the candidate substances pseudo-ionone [FL-no: 07.198], pentan-3-ol [FL-no: 02.077] and methyl-3-butan-2-one [FL-no: 07.178], the two first mentioned being tested for chromosomal aberrations in mammalian cells and the latter for induction of aneuploidy in yeast cells, respectively.

Induction of aneuploidy in yeast cells has been demonstrated for pentan-3-one [FL-no: 07.084]. The effect, measured only at high concentrations, approaching cytotoxic levels, can be considered to be a threshold effect, not mediated by direct interaction with DNA. In addition, induction of aneuploidy described in the paper is strongly potentiated by ice treatments included in the experimental protocol, consistently with tubulin dissociation at low temperature *in vitro*; in the absence of this passage the effect is very weak. Therefore, the effect could be considered as an effect occurring only under unrealistic experimental conditions and the extrapolation of this result to the *in vivo* situation in

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

humans is questionable. Furthermore, it is well recognised that the relevance of fungal systems is limited when induction of aneuploidy in mammalian systems has to be evaluated.

Pseudo-ionone [FL-no: 07.198] was considered with respect to genotoxicity in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011) where the Panel concluded that the data available ruled out the concern for genotoxicity. Pseudo-ionone was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the presence or absence of S9 and it is concluded that under the test conditions applied pseudo-ionone is not mutagenic in bacteria. Pseudo-ionone was also evaluated in an *in vitro* micronucleus assay in human peripheral blood lymphocytes for its ability to induce chromosomal damage or aneuploidy in the presence and absence of rat S9 fraction as an *in vitro* metabolising system. Under the conditions of this study, pseudo-ionone was not clastogenic and/or aneugenic in cultured human lymphocytes.

In vitro genotoxicity data are also available for 10 supporting substances.

No evidence of mutagenicity obtained with bacterial and/or mammalian cells systems was reported for: one saturated aliphatic acyclic secondary alcohol [FL-no: 02.079], five saturated [FL-no: 07.002, 07.050, 07.017, 07.053 and 07.122] and two unsaturated [FL-no: 07.015 and 07.099] aliphatic acyclic ketones; two esters of an aliphatic acyclic secondary alcohol with linear aliphatic carboxylic acids [FL-no: 09.003 and 09.105]. 4-Methyl-2-pentanone [FL-no: 07.017] gave negative results also when tested for chromosomal aberration activity.

Beside the negative results in *in vitro* bacterial point mutation tests, acetone [FL-no: 07.050] showed no evidence of increased sister chromatid exchanges in several cytogenetic assays on different mammalian cells, as well as no induction of chromosomal aberrations in Chinese hamster ovary cells up to very high concentrations. Only one test on hamster lung fibroblasts (conducted at an unspecified acetone concentration) and an aneuploidy induction test on *Saccharomyces cerevisiae* (about 7 % acetone) gave positive results. However, these two studies were considered not relevant on the basis of their poor quality and taking into account all the other negative genotoxicity results obtained with acetone, including results *in vivo* (see below).

6-Methylhepta-3,5-dien-2-one [FL-no: 07.099] was considered with respect to genotoxicity in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011) where the Panel concluded that the data available ruled out the concern for genotoxicity. 6-Methylhepta-3,5-dien-2-one was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the presence or absence of S9 and it was concluded that under the test conditions applied 6-methylhepta-3,5-dien-2-one is not mutagenic in bacteria. 6-Methylhepta-3,5-dien-2-one was also evaluated in an *in vitro* micronucleus assay in human peripheral blood lymphocytes for its ability to induce chromosomal damage or aneuploidy in the presence and absence of rat S9 fraction as an *in vitro* metabolising system. Under the conditions of this study, 6-methylhepta-3,5-dien-2-one was not clastogenic and/aneugenic in cultured human lymphocytes.

In vivo data are available for four supporting substances: one saturated aliphatic secondary alcohol [FL-no: 02.079] and three saturated aliphatic ketones [FL-no: 07.017, 07.050 and 07.053], which exhibited no genotoxic potential in the micronucleus cytogenetic assay at doses approaching the LD_{20} and the LD_{50} of the tested substances.

Conclusion on Genotoxicity

On the basis of available data from *in vitro* and *in vivo* tests on candidate and supporting substances, it can be concluded that the 49 candidate substances included in this group exhibit no genotoxic potential.

For a summary of *in vitro / in vivo* genotoxicity data considered by EFSA, see Table 5 and 6.

4.3. Genotoxicity Studies - Text taken[11] from EFSA FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011)

The Industry has submitted data concerning genotoxicity studies for 6-methylhepta-3,5-dien-2-one [FL-no: 07.099], a representative substance for FGE.19, subgroup 1.2.3 (EFSA, 2008b), evaluated in FGE.206 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2011). In this revision of FGE.63, the data below are of importance for the assessment of the genotoxic potential of six candidate substances [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936], which have a structural alert for genotoxicity.

In vitro

6-Methylhepta-3,5-dien-2-one [FL-no: 07.099] was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in the presence or absence of S9. In the first experiment the concentrations tested were 1.6, 8, 40, 200, 1000 and 5000 μg/plate, and the plate incorporation methodology was used. Severe toxicity was observed at 5000 μg/plate in all strains (complete killing of bacteria). No increase in revertant colonies was observed at any of the tested concentrations. In the second experiment the concentrations were 20.5, 51.2, 128, 320, 800, 2000 and 5000 μg/plate of 6-methylhepta-3,5-dien-2-one, and treatments in the presence of S9 were carried out according to the pre-incubation method. In the absence of S9 the standard plate incorporation method was performed. Slight thinning of the bacterial lawn or complete killing of the bacteria was observed in all strains at 2000 and 5000 μg/plate in the absence of S9. In the presence of S9, cytotoxicity was observed at 800 μg/plate and above and severe toxicity (complete killing of bacteria) was observed at 5000 μg/plate in all strains (Williams, 2009a). The study design complied with current recommendations (OECD 471; GLP) and an acceptable top concentration was achieved. There was no evidence of mutagenic effect induced by 6-methylhepta-3,5-dien-2-one in any of the strains, either in the absence or presence of S9. No precipitation was observed at any tested concentrations (Williams, 2009a). It is concluded that under the test conditions applied, 6-methylhepta-3,5-dien-2-one [FL-no: 07.099] is not mutagenic in bacteria.

6-Methylhepta-3,5-dien-2-one [FL-no: 07.099] was evaluated in an *in vitro* micronucleus assay in human peripheral blood lymphocytes for its ability to induce chromosomal damage or aneuploidy in the presence and absence of rat S9 fraction as an *in vitro* metabolising system. The assay was performed in accordance with OECD 487 Guideline and in compliance with GLP. In a preliminary toxicity study, a wide range of concentrations up to 2000 μg/ml of 6-methylhepta-3,5-dien-2-one was tested. The highest concentration used in the main test (450 μg/ml) was limited by toxicity observed in the preliminary study. Cells were stimulated for 48 hours with phytohaemaglutinin to produce exponentially growing cells, and then treated for 3 hours (followed by 21 hours recovery) with 0, 225, 325 or 450 μg/ml of 6-methylhepta-3,5-dien-2-one in the absence of S9 and 0, 225, 300 and 350 μg/ml in the presence of S9, respectively. The levels of toxicity (reduction in replication index) at the top concentrations were 60 % and 51 % without and with S9, respectively. In a parallel assay, cells were treated for 24 hours with 0, 100, 120 or 150 μg/ml of 6-methylhepta-3,5-dien-2-one in the absence of S9 with no recovery period. The top concentration induced 56 % toxicity. There were 2 replicate cultures per treatment, and 1000 binucleate cells per replicate (i.e. 2000 cells per dose) were scored for micronuclei. No evidence of chromosomal damage or aneuploidy was observed by increased levels of micronucleated binucleate cells (MNBN) in the presence or absence of S9 metabolic activation (Whitwell, 2010). Under the conditions of this study, 6-methylhepta-3,5-dien-2-one was not clastogenic and/aneugenic in cultured human lymphocytes.

For a summary of *in vitro* genotoxicity data considered by EFSA, see Table 7.

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

Conclusion on Genotoxicity

The Panel concluded that the *in vitro* genotoxicity data on 6-methylhepta-3,5-dien-2-one [FL-no: 07.099] do not indicate genotoxic potential.

4.4. Genotoxicity Studies - Text taken[12] from EFSA FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d)

The Industry has submitted data concerning genotoxicity studies for 4-methylpent-3-en-2-one [FL-no: 07.101], a substance from FGE.19, subgroup 1.2.1 (EFSA, 2008b), evaluated in FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d). In this revision of FGE.63, the data below are of importance for the assessment of the genotoxic potential of the candidate substance [FL-no: 07.101], which have a structural alert for genotoxicity.

In vitro

Bacterial Reverse Mutation Assay

An Ames assay was conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 to assess the mutagenicity of 4-methylpent-3-en-2-one [FL-no: 07.101], both in the absence and presence of rat liver metabolising system (S9-mix) in two experiments (Williams, 2009b). A preliminary range-finding cytotoxicity experiment using standard plate-incorporation methodology was conducted in strain TA100 only at concentrations of 1.6, 8, 40, 200, 1000 and 5000 µg/plate in the absence and presence of S9-mix, plus negative (solvent) and positive controls. Evidence of toxicity, in terms of a slight thinning of the background bacterial lawn, was observed only at the top concentration in the presence of S9-mix. The data from the range-finding experiment were considered acceptable for mutation assessment, and therefore, to complete the first experiment, the remaining four strains were tested at the same concentrations both in the presence and absence of S9-mix using the same methodology. No evidence of toxicity was observed in these strains, and no increases in reverse mutants relative to the vehicle control were observed.

In a second experiment, 4-methylpent-3-en-2-one was tested in all five *S. typhimurium* strains with and without S9-mix using a narrowed concentration range of 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate. A pre-incubation step was also included when the chemical was tested in the presence of S9-mix. Following these treatments, evidence of toxicity in the form of a slight thinning of the background bacterial lawn was observed at the highest concentrations (2500 and 5000 µg/plate) in all strains in the presence of S9-mix and in strain TA102 in the absence of S9-mix. A small increase (1.5-fold) in TA1535 revertants was seen at the higest concentration in the absence of S9-mix that was significant at $p < 0.05$, but this small increase was not seen in the first experiment at similar concentrations and was considered by the study authors to be due to chance. No increases in revertant numbers were observed for the other strains and treatment conditions.

Based on the above results the Panel concluded that 4-methylpent-3-en-2-one [FL-no: 07.101] did not induce mutations in five strains of *S. typhimurium* when tested up to toxic concentrations in the absence and in the presence of metabolic activation (Williams, 2009b).

In vitro micronucleus assay

4-Methylpent-3-en-2-one [FL-no: 07.101] was tested for the induction of chromosome damage and potential aneugenic effects in mammalian cells *in vitro* by examining the effect on the frequency of

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

micronuclei in cultured human peripheral blood lymphocytes, treated in the absence and presence of rat liver metabolising system (S9-mix) (Stone, 2011).

A preliminary range-finding experiment was conducted with and without S9-mix, in order to determine the effect of the test substance upon Replication Index (RI), which was used as a basis for choosing a range of concentrations to be evaluated in the main study. 4-Methylpent-3-en-2-one was added to cell cultures after 48 hours from culture initiation (stimulation by phytohaemagglutinin PHA), either for 3 hours in the absence or presence of S9-mix, or for 24 hours in the absence of S9-mix. Micronuclei were analysed at multiple concentrations for each treatment group. For the 3-hour treatment (3 + 21 hours recovery) the concentrations were 0, 600, 800 and 981.4 µg/ml (without S9-mix) and 0, 200, 400, 800, 981.4 µg/ml (with S9-mix). The levels of cytotoxicity (reduction in RI) induced at the top concentrations were 22 % and 54 % in the absence and presence of S9-mix, respectively. Although, the recommended range of toxicity (50 - 60 %) was not reached in the absence of S9-mix, the top concentration of 981.4 µg/ml was equivalent to 10 mM, which is the required upper limit for a non-toxic substance. For 24-hour treatment without S9-mix the concentrations were 0, 100, 200, 275 and 300 µg/ml and the level of cytotoxicity (reduction in RI) at the top concentration reached 62 %, which exceeded the target (50 - 60 %) range. One thousand binucleate cells per culture from two replicate cultures per concentration were scored for micronuclei.

Treatment of cells with 4-methylpent-3-en-2-one for 3 hours in the presence of S9-mix resulted in statistically significant ($p \leq 0.05$) increases in MNBN frequency compared to the concurrent vehicle control at the highest concentration analysed (981.4 µg/mL). However, only one replicate culture in the assay resulted in MNBN cell frequencies outside of the normal range and the authors considered this result as equivocal. Therefore a confirmatory experiment was performed with 4-methylpent-3-en-2-one at concentrations of 0, 100, 200, 400 and 500 µg/ml for 3 hours with S9-mix. The lower concentrations chosen in the second experiment were on the basis of an unexplained shift in toxicity, but the concentrations selected for analysis in this experiment gave comparable toxicity to those selected in the prior experiment under this treatment condition, and 58 % cytotoxicity (determined as reduction in RI) was achieved at the top concentration. These treatments resulted in frequencies of MNBN cells that were similar to concurrent controls and there were no significant differences.

Considering that the significant increase in MNBN cell frequencies in the first experiment were not reproduced in the second one, the Panel concluded that 4-methylpent-3-en-2-one [FL-no: 07.101] did not induce micronuclei in cultured human peripheral blood lymphocytes when tested up to toxic concentrations in both the absence and presence of S9-mix metabolism (Stone, 2011).

For a summary of *in vitro* genotoxicity data considered by EFSA, see Table 8.

Discussion of Mutagenicity/Genotoxicity Data

The representative substance 4-methylpent-3-en-2-one [FL-no: 07.101] is considered negative in the Ames test with *S. typhimurium* tester strains consistent with the requirements for current regulatory guidelines. Statistically significant increase in the number of revertant colonies observed in tester strain TA1535 in the absence of S9-mix metabolism in one experiment following treatment with 4-methylpent-3-en-2-one are judged not biologically relevant, since they were not reproduced in the second experiment (Williams, 2009b; Ballantyne, 2011).

Investigations at chromosome and genome levels in mammalian cells *in vitro* showed that 4-methylpent-3-en-2-one induced a small but statistically significant increase in the frequency of micronucleated binucleate cells (MNBN) only in the presence of S9-mix metabolism following a three hour treatment at the highest concentration tested (981.4 µg/ml). However, only one replicate culture fell outside the historical vehicle control range values. Following additional scoring of 2000 erythrocytes, the resulting MNBN frequencies, although still significantly higher than concurrent vehicle control, lied within historical control range values. In a second confirmatory experiment (3-

hour treatment in the presence of S9-mix) performed at concentrations lower than concentrations used in the previous experiment, due to an unexplained shift of toxicity (comparable toxicity to those observed in the first experiment, but at lower concentrations), no significant increase in MNBN frequencies was observed. Based on these results the Panel concluded that 4-methylpent-3-en-2-one did not induce micronuclei in human peripheral blood lymphocytes, both in the absence and presence of rat liver S9-mix metabolism.

Conclusion on Genotoxicity

The Panel noted that for 4-methylpent-3-en-2-one [FL-no: 07.101], the data available showed that it did not induce mutations in bacteria or micronuclei in human peripheral blood lymphocytes, neither in the presence nor in the absence of rat liver S9-mix metabolic activation. Based on these findings, the Panel concluded that 4-methylpent-3-en-2-one does not present a safety concern with respect to genotoxicity and accordingly the flavouring substance can be evaluated using the Procedure.

4.5. EFSA Considerations

The Panel concluded that the data available do not preclude evaluation of the 20 aliphatic secondary alcohols, ketones and related esters through the Procedure.

5. Application of the Procedure

5.1. Application of the Procedure to 20 Aliphatic Secondary Alcohols, Ketones and Related Esters by the JECFA (JECFA, 2003; JECFA, 2009b)

According to the JECFA six of the substances belong to structural class I and 14 to structural class II using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

The JECFA concluded all 20 aliphatic 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 the intakes for all substances are below the thresholds for their structural classes I and II (step A3).

In conclusion, the JECFA evaluated all 20 substances as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 20 aliphatic secondary alcohols, ketones and related esters are summarised in Table 9: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and Related Esters (JECFA, 2003; JECFA, 2009b).

5.2. Application of the Procedure to 49 Saturated and Unsaturated Aliphatic Secondary Alcohols, Ketones and Esters of Secondary Alcohols and Saturated Linear or Branched-chain Carboxylic Acids by EFSA, FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a)

Twenty-eight of the candidate substances [FL-no: 02.077, 02.124, 02.142, 02.148, 02.177, 02.182, 02.183, 02.190, 02.255**,** 07.084, 07.178, 07.239, 09.304, 09.323, 09.325, 09.328, 09.332, 09.386, 09.388, 09.391, 09.604, 09.605, 09.606, 09.608, 09.609, 09.676, 09.880 and 09.926] are classified into structural class I, according to the decision tree approach presented by Cramer et al. (Cramer et al., 1978). The remaining 21 candidate substances [FL-no: 02.145, 02.194, 02.211, 07.072, 07.150, 07.156, 07.157, 07.158, 07.160, 07.162, 07.181, 07.182, 07.185, 07.189, 07.198, 07.199, 07.201,

07.204, 07.205, 07.236 and 07.262], which are unsaturated aliphatic secondary alcohols or acyclic aliphatic saturated or unsaturated ketones, are in structural class II.

Forty-eight substances were concluded at step A3 using the EFSA Procedure – i.e. the substances are expected to be metabolised to innocuous products (step 2) and the estimated daily intakes for 48 substances are below the thresholds of concern for their structural classes (step A3).

One candidate substance, 5-methylheptan-3-one [FL-no: 07.182], cannot be predicted to be metabolised to innocuous products and therefore, proceeds to step B3. The estimated daily intake of this substance of 0.32 microgram/*capita*/day does not exceed the threshold of concern for structural class II (540 microgram/person/day). Accordingly, the candidate substance proceeds to step B4 of the Procedure. On the basis of a study on the neurotoxic effects of orally administered 5-methylheptan-3-one [FL-no: 07.182] to male rats, a NOAEL of 82 mg/kg body weight (bw)/day was established (IBM Corp., 1989). This NOAEL provides a margin of safety of 1.5×10^7 based on the estimated intake of the candidate substance of 0.32 microgram/*capita*/day. Based on results of the safety evaluation sequence this candidate substance does not pose a safety concern when used as flavouring substance at the estimated level of intake, based on the MSDI approach.

The stepwise evaluations of the 49 substances are summarised in Table 10: Summary of Safety Evaluation Applying the Procedure (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a).

5.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 20 substances in the group of aliphatic secondary alcohols, ketones and related esters.

CONCLUSIONS

In Flavouring Group Evaluation 63, Revision 1 (FGE.63Rev1) the EFSA considered 19 flavouring substances (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012c) from two groups of flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at its 59th meeting (JECFA, 2003) and its 69th meeting (JECFA, 2009b). The present revision of FGE.63, FGE.63Rev2, includes the consideration of one additional substance, 4-methylpent-3-en-2-one [FL-no: 07.101]. This substance was evaluated by the JECFA at its 69th meeting (JECFA, 2009b). It was originally allocated to and evaluated in FGE.204 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012d) in which it was considered not to be of concern with respect to genotoxicity.

Therefore, the present revision of FGE.63, FGE.63Rev2, considers 20 flavouring substances evaluated by the JECFA.

The Panel concluded that the additional substance fits well together with the 19 aliphatic secondary alcohols, ketones and related esters considered in the FGE.63Rev1.

The Panel concluded that the 20 substances in the JECFA flavouring group of aliphatic secondary alcohols, ketones and related esters are structurally related to the group of 49 saturated and unsaturated aliphatic secondary alcohols, ketones and esters of secondary alcohols and saturated linear or branched-chain carboxylic acids evaluated in FGE.07Rev4.

The Panel agrees with the application of the Procedure as performed by the JECFA for the 20 substances considered in this FGE.

For all 20 substances, the JECFA evaluation is based on MSDI values derived from production figures from the EU.

For three candidate substances [FL-no: 02.252, 07.190 and 09.936], the Industry has submitted normal and maximum use levels. For [FL-no: 02.252 and 09.936], which are expected to be metabolised to innocuous products, the mTAMDI values are below their respective thresholds of concern for structural class I (1800 microgram/person/day) and class II (540 microgram/person/day). For substance [FL-no: 07.190], the mTAMDI value is above the threshold of concern for structural class II of 540 microgram/person/day to which it is allocated. Therefore, for this substance more reliable exposure data are required. On the basis of such additional data, the flavouring substance should be reconsidered along the steps of the Procedure. Following this procedure, additional toxicological data might become necessary. For the remaining 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 assessment in order to finalise the evaluation.

In order to determine whether the conclusion for the 20 JECFA-evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity are available for all 20 JECFA-evaluated substances.

Thus, for all 20 JECFA evaluated aliphatic secondary alcohols, ketones and related esters [FL-no: 02.252, 07.015, 07.069, 07.099, 07.100, 07.101, 07.114, 07.123, 07.151, 07.190, 07.240, 07.247, 07.249, 07.256, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936] the Panel agrees with the JECFA conclusion “No safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

Table 3: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2002d; JECFA, 2009b)

Table 3: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2002b; JECFA, 2009a)

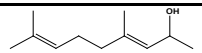
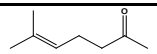
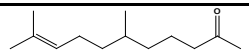
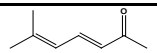
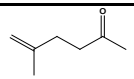
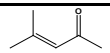
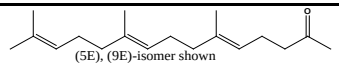
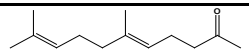
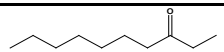
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
02.252 1841	4,8-Dimethyl-3,7-nonadien-2-ol		4102 67845-50-5	Liquid $C_{11}H_{20}O$ 168	Insoluble Soluble	70 (2.6 hPa) IR NMR 95 %	1.465-1.473 0.860-0.870	Racemate. Mixture of E/Z stereoisomers: 50-80 % (E) (EFFA, 2012).
07.015 1120	6-Methylhept-5-en-2-one		2707 149 110-93-0	Liquid $C_8H_{14}O$ 126.19	Insoluble Miscible	173.1 NMR 97 %	1.435-1.445 0.846-0.854	
07.069 1121	Tetrahydro-pseudo-ionone		3059 2053 4433-36-7	Liquid $C_{13}H_{24}O$ 196.33	Insoluble Miscible	234 NMR 95 %	1.449-1.455 0.865-0.875	Racemate (EFFA, 2010).
07.099 1134	6-Methylhepta-3,5-dien-2-one		3363 11143 1604-28-0	Liquid $C_8H_{12}O$ 124.18	Almost insoluble Miscible	190 NMR 96 %	1.528-1.537 0.895-0.899	Mixtureof E/Z stereoisomers: 60-90 % (E) (EFFA, 2012).
07.100 1119	5-Methylhex-5-en-2-one		3365 11150 3240-09-3	Liquid $C_7H_{12}O$ 112.17	Insoluble Miscible	148-149 NMR 97 %	1.428-1.433 0.862-0.868	
07.101 1131	4-Methylpent-3-en-2-one		3368 11853 141-79-7	Liquid $C_6H_{10}O$ 98.14	Slightly soluble Miscible	126.76 NMR 95 %	1.442-1.447 0.862-0.868	
07.114 1123	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	 (5E), (9E)-isomer shown	3442 11206 762-29-8	Liquid $C_{18}H_{30}O$ 262.44	Soluble Miscible	147-148 NMR 96 %	1.478-1.483 0.885-0.895	Mixture of (5E,9E)-, (5Z,9Z)-, (5E,9Z)- and (5Z,9E)-isomers (EFFA, 2010).
07.123 1122	Geranylacetone		3542 11088 3796-70-1	Liquid $C_{13}H_{22}O$ 194.32	Slightly soluble Miscible	247 NMR 95 %	1.463-1.471 0.861-0.867	
07.151 1118	Decan-3-one		3966 11056 928-80-3	Liquid $C_{10}H_{20}O$ 156.27	Insoluble Miscible	204-205 NMR 97 %	1.421-1.427 0.820-0.830	

Table 3: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2002b; JECFA, 2009a)

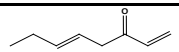
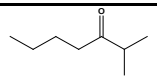
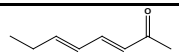
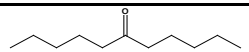
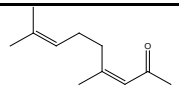
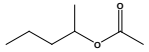
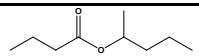
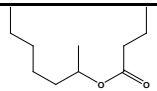
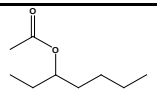
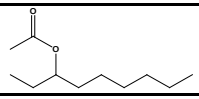
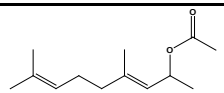
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
07.190 1848	Octa-1,5-dien-3-one		4405 65213-86-7	Liquid $C_8H_{12}O$ 124.18	Practically insoluble or insoluble Freely soluble	169 MS 95 %	1.438-1.444 0.823-0.829	Mixture of E/Z stereoisomers: 60-90 % (E) (EFFA, 2012).
07.240 1156	2-Methylheptan-3-one		4000 13019-20-0	Liquid $C_8H_{16}O$ 128.2	Insoluble Miscible	158-160 NMR 98 %	1.408-1.413 0.811-0.821	
07.247 1139	(E,E)-3,5-Octadien-2-one		4008 30086-02-3	Liquid $C_8H_{12}O$ 124.2	Insoluble Miscible	220 NMR 95 %	1.508-1.516 0.880-0.890	
07.249 1155	Undecan-6-one		4022 927-49-1	Liquid $C_{11}H_{22}O$ 170.3	Insoluble Miscible	228 NMR 97 %	1.424-1.430 0.826-0.836	
07.256 1137	(3Z)-4,8-Dimethyl-3,7-nonadiene-2-one		3969 817-88-9	Liquid $C_{11}H_{18}O$ 166.26	Insoluble Freely soluble	200-201 n.a. IR NMR 94 %	1.473-1.477 0.869-0.875	Mixture of E/Z stereoisomers: 60-90 % (E) (EFFA, 2012). Register name to be changed to 4,8-Dimethyl-3,7-nonadiene-2-one.
09.657 1146	1-Methylbutyl acetate		4012 10761 626-38-0	Liquid $C_7H_{14}O_2$ 130.2	Insoluble Partially Soluble	135 NMR 98 %	1.369-1.400 0.862-0.866	Racemate (EFFA, 2010).
09.658 1142	1-Methylbutyl butyrate		3893 10763 60415-61-4	Liquid $C_9H_{18}O_2$ 158.24	Insoluble 50% Soluble	185-186 IR NMR MS 99 %	1.409-1.415 0.862-0.868	Racemate (EFFA, 2010).
09.923 1144	Hept-2-yl butyrate		3981 39026-94-3	Liquid $C_{11}H_{22}O_2$ 186.3	Insoluble Miscible	210 NMR 98 %	1.413-1.417 0.855-0.860	Racemate (EFFA, 2010).
09.924 1143	(+/-)-3-Heptyl acetate		3980 5921-83-5	Liquid $C_9H_{18}O_2$ 158.2	Insoluble Miscible	185 NMR 98 %	1.406-1.414 0.858-0.867	Racemate. Register name to be changed to 3-Heptyl acetate.
09.925 1145	Nonan-3-yl acetate		4007 60826-15-5	Liquid $C_{11}H_{22}O_2$ 186.3	Insoluble Miscible	225 NMR 98 %	1.416-1.423 0.854-0.864	Racemate (EFFA, 2010).

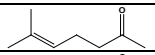
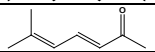
Table 3: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2002b; JECFA, 2009a)

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
09.936 1847	4,8-Dimethyl-3,7-nonadien-2-yl acetate		4103 91418-25-6	Liquid $C_{13}H_{22}O_2$ 210	Insoluble Soluble	75-83 (3 hPa) IR NMR 95 %	1.451-1.459 0.890-0.900	Racemate. Mixture of E/Z stereoisomers: 50-80 % (E) (EFFA, 2012).

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.

Table 4: Summary of Genotoxicity Data of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (JECFA, 2003)

Table 4: Summary of Genotoxicity Data of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (JECFA, 2003)

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
07.015 1120	6-Methylhept-5-en-2-one		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	380 µg/plate	Negative[1]	(Florin et al., 1980)
07.099 1134	6-Methyl-3,5-heptadien-2-one		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	370 µg/plate	Negative[1]	(Florin et al., 1980)

1 With and without metabolic activation.

Table 5: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Table 5: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Chemical Name [Fl.No.]	Test system	Test Object	Concentration	Result	Reference	Comments
(Acetone [07.050])	Rec assay	*B. subtilis*	NR	Negative [1]	(Kawachi et al., 1980)	8
	Rec assay	*B. subtilis*	NR	Negative	(Ishizaki et al., 1979)	8
	Ames test	*S. typhimurium* TA100	0.1 to 1000 µg/plate	Negative	(Rapson et al., 1980)	8
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	174 µg/plate	Negative [1]	(Florin et al., 1980)	8
	Ames test	*S. typhimurium* TA98, TA100	NR	Negative [1]	(Kawachi et al., 1980)	8
	Ames test [2]	*S. typhimurium* TA98, TA100	30 µl/plate	Negative [4]	(Yamaguchi, 1985)	8
	Ames test	*S. typhimurium* TA97, TA98, TA100, TA1535, TA1537	Up to 10000 µg/plate	Negative [1]	(McCann et al., 1975)	8
	Ames test [2]	*S. typhimurium* TA97, TA98, TA100, TA1535, TA1537	Up to 10000 µg/plate	Negative [1]	(Zeiger et al., 1992)	8
	Ames test	*S. typhimurium* TA100	500 µg/plate	Negative [1]	(Yamaguchi, 1982)	8
	Ames test	*S. typhimurium* TA97, TA98, TA100	20 to 40 µg	Negative [1]	(Azizan and Blevins, 1995)	8
	Sister chromatid exchange	Human embryo fibroblasts	NR	Negative [4]	(Kawachi et al., 1980)	8
	Sister chromatid exchange	Hamster lung fibroblasts	NR	Negative [4]	(Kawachi et al., 1980)	8
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 10 µg/ml	Negative	(Sasaki et al., 1980)	8
	Sister chromatid exchange	Chinese hamster ovary cells	Up to 5020 µg/ml	Negative [1]	(Loveday et al., 1990)	8
	Sister chromatid exchange	Diploid human fibroblasts	5 µg/ml	Negative	(Sasaki et al., 1980)	8
	Sister chromatid exchange	Human lymphocytes	395 µg/ml	Negative	(Norppa et al., 1983)	8
	Sister chromatid exchange	Human lymphocytes	0.1 to 1 mM	Negative	(Zarani et al., 1999)	8
	Chromosomal aberrations	Chinese hamster ovary cells	Up to 5020 µg/ml	Negative [1]	(Loveday et al., 1990)	8
	Chromosomal aberrations	Hamster lung fibroblasts	NR	Positive [4]	(Kawachi et al., 1980)	8
	Aneuploidy induction	*S. cerevisiae*	6.98-7.83 %	Positive [4]	(Zimmermann et al., 1985)	10
(Isopropyl alcohol [02.079])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	174 µg/plate	Negative [1]	(Florin et al., 1980)	8
	Ames test [2]	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2uvrA	5 to 5000 µg/plate	Negative [1]	(Shimizu et al., 1985)	8
	Ames test [2]	*S. typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1537	Up to 10 mg/plate [5]	Negative [1]	(Zeiger et al., 1992)	8
	Forward mutation	Chinese hamster ovary cells [6]	0.5 to 5.0 mg/ml	Negative [1]	(CMA, 1990)	8
	Forward mutation	Chinese hamster ovary cells [6]	0.5 to 5.0 mg/ml	Negative [1]	(Kapp et al., 1993)	8
(2-Butanone [07.053])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10000 µg/plate	Negative [1]	(Douglas et al., 1980)	8
	Ames test	*S. typhimurium* TA102, TA104	1 mg/plate	Negative	(Marnett et al., 1985)	8
(2-Butanone [07.053]) continued	Ames test [2]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 to 5000 µg/plate	Negative [1]	(Shimizu et al., 1985)	8
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.04 to 26 µg/plate	Negative [1]	(O'Donoghue et al., 1988)	8

Table 5: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Chemical Name [Fl.No.]	Test system	Test Object	Concentration	Result	Reference	Comments
	Ames test [2]	*S. typhimurium* TA97, TA98, TA100, TA104, TA1535, TA1537	Up to 10000 µg/plate	Negative [1]	(Zeiger et al., 1992)	8
	Ames test	*S. typhimurium* TA102	5000 µg/plate	Negative [4]	(Müller et al., 1993)	8
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, *E. coli* WP2uvrA	4000 µg/plate	Negative	(Brooks et al., 1988)	8
	Gene conversion	*S. cerevisiae*	5 mg/ml	Negative [1]	(Brooks et al., 1988)	8
	Forward Mutation	L5178Y/TL+/- mouse lymphoma cells	0.67 to 12 µg/ml	Negative [1]	(O'Donoghue et al., 1988)	8
	Unscheduled DNA synthesis	Human lymphocytes	0.72 mg/ml	Negative [1]	(Perocco et al., 1983)	8
	Unscheduled DNA synthesis	Rat hepatocytes	7.2 to 360 mg/ml	Negative	(O'Donoghue et al., 1988)	8
	Chromosomal aberrations	Rat hepatocytes	1000 µg/ml	Negative	(Brooks et al., 1988)	8
	Chromosomal aberrations	Chinese hamster ovary cells	1000 µg/ml	Negative [1]	(Brooks et al., 1988)	8
	Cell transformation assay[1]	BALB/3T3 cells (clone A31-1)	6-18 µl/ml	Negative	(O'Donoghue et al., 1988)	
	Aneuploidy induction	*S. cerevisiae*	3.38 %	Positive [4]	(Zimmermann et al., 1985)	11
Pentan-3-one [07.084]	Aneuploidy induction	*S. cerevisiae*	1.48 %	Positive [4]	(Zimmermann et al., 1985)	11
Pentan-3-ol [02.077]	Chromosomal aberrations	Chinese hamster ovary cells	0.5 to 10 %	Negative [1]	(Abbondandolo et al., 1980)	
	Forward mutation	*S. pombe*	0.5 to 10 %	Negative [1]	(Abbondandolo et al., 1980)	
(2-Heptanone [07.002])	Unscheduled DNA synthesis	Rat hepatocytes	1000 ppm	Negative	(Barber et al., 1999)	
Methyl-3-butan-2-one [07.178]	Aneuploidy induction	*S. cerevisiae*	1.23 to 1.36 %	Negative [4]	(Zimmermann et al., 1985)	11
	Aneuploidy induction	*S. cerevisiae*	0.84 to 1.23 %	Negative [4]	(Zimmermann et al., 1985)	11
(4-Methyl-2-pentanone [07.017])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.03 to 3 mg/plate	Negative [1]	(O'Donoghue et al., 1988)	8
	Ames test [2]	*S. typhimurium* TA97, TA98, TA100, TA1535	Up to 6667 µg/plate	Negative [1]	(Zeiger et al., 1992)	8
	Ames test	*E. coli* WP2uvrA	8000 µg/plate	Negative [4]	(Brooks et al., 1988)	8
	Gene conversion	*S. cerevisiae*	5 mg/ml	Negative [1]	(Brooks et al., 1988)	8
	Forward mutation	L5178Y/TL+/- mouse lymphoma cells	0.26 to 3.7 µg/ml	Negative [1]	(O'Donoghue et al., 1988)	8
	Unscheduled DNA synthesis	Rat hepatocytes	8 to 80 µg/ml	Negative	(O'Donoghue et al., 1988)	8
	Chromosomal aberrations	Rat hepatocytes	1000 µg/ml	Negative	(Brooks et al., 1988)	8
	Cell transformation assay[1]	BALB/3T3 cells (clone A31-1)	1-7µl/ml	Negative	(O'Donoghue et al., 1988)	
	Chromosomal aberrations	Chinese hamster ovary cells	1000 µg/ml	Negative [1]	(Brooks et al., 1988)	8
Methyl-4-pentan-2-ol [02.183]	Ames test [2]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, E. coli WP2uvrA	5000 µg	Negative [1]	(Shimizu et al., 1985)	
Methyl-6-heptan-2-one [07.181]	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	5000 µg/plate	Negative [1]	(BASF, 1989a)	
(2,6-Dimethyl-4-heptanone [07.122])	Ames test [2]	*S. typhimurium* TA98, TA100, TA1535, TA1537	1 to 333 µg/plate	Negative [1]	(Mortelmans et al., 1986)	8
Trimethyl-6,10,14-pentadecan-2-one [07.205]	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	5000 µg/plate	Negative [1]	(BASF, 1989b)	

Table 5: Summary of Genotoxicity Data (*in vitro)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Chemical Name [Fl.No.]	Test system	Test Object	Concentration	Result	Reference	Comments
(6-Methyl-5-hepten-2-one [07.015])	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	380 µg/plate	Negative [1]	(Florin et al., 1980)	9
(Isopropyl acetate [09.003])	Ames test [2]	*S. typhimurium* TA97, TA98, TA100, TA1537, TA1538	Up to 10 mg/plate	Negative [1]	(Zeiger et al., 1992)	8
(Isopropyl myristate [09.105])	Ames test [7]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Negative [1]	(Blevins and Taylor, 1982)	8
Isopropyl hexadecanoate [09.606]	Ames test [7]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Negative [1]	(Blevins and Taylor, 1982)	
9-Decen-2-one [07.262]	Ames test[10]	*S. typhimurium* TA98, TA100, TA1535, TA1537	Up to 5 µL/plate	Negative[1]	(Flavour Industry, 2009)	
	Ames test[10]	*E. coli* WP2 (pKM 101)	Up to 5 µL/plate	Negative[1]	(Flavour Industry, 2009)	
(6-Methylhepta-3,5-dien-2-one [07.099])	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	370 µg/plate	Negative[1]	(Florin et al., 1980)	9
	Reverse Mutation	S. typhimurium TA98, TA100, TA1535, TA1537 and TA102	1.6, 8, 40, 200, 1000 and 5000 µg/plate	Negative[1]	(Williams, 2009a)	Toxicity observed in all strains at 2000 µg/plate or greater in the absence of S9 and at 800 µg/plate in the presence of S9. Study design complied with current recommendations. Acceptable top concentration was achieved.
	Micronucleus induction	Human peripheral blood lymphocytes	225, 325 and 450 µg/ml [13] 225, 300 and 350 µg/ml [14]	Negative	(Whitwell, 2010)	Complies with draft OECD Guideline 487. Acceptable levels of cytotoxicity achieved at the top concentrations used in all parts of the study.
Pseudo-ionone [07.198]	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	0.03 to 30 µmol/plate	Negative	(Florin et al., 1980)	
	Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA 102	0.128, 0.64, 3.2, 16, 80, 400 and 2000 µg/plate	Negative[1]	(Beevers, 2009)	Toxicity was observed in all strains at 400 µg/plate and greater in the presence and absence of S9 in this experiment.
			0.12.5, 25, 50, 100, 200 and 400 µg/plate [12]	Negative[1]		Precipitation was observed in the 400 µg/plate concentration in the presence and absence of S9 in this experiment. Study design complies with current recommendations. Acceptable top concentrations were achieved.
	Micronucleus induction	Human peripheral blood lymphocytes	30, 50 and 60 µg/ml[13] 100, 110 and 120 µg/ml[14]	Negative	(Lloyd, 2010)	Complies with draft OECD Guideline 487. Acceptable levels of cytotoxicity achieved at the top concentrations used in all parts of the study.
	Micronucleus induction	Human peripheral blood lymphocytes	10, 15 and 20 µg/ml[15]	Negative	(Lloyd, 2010)	Complies with draft OECD Guideline 487. Acceptable levels of cytotoxicity achieved at the top concentrations used in all parts of the study.

1. Assay performed with and without metabolic activation.
2. Modified Ames (Pre-incubation) protocol.
3. Assay performed with S9 metabolic activation.
4. Assay performed without S9 metabolic activation.
5. Maximum non-toxic dose.
6. HGPRT locus.
7. Spot test.
8. Summarised by JECFA, 51st meeting (JECFA, 1999).
9. Summarised by JECFA 59th meeting (JECFA, 2003).
10. Direct incorporation method.
11. Unusual experimental protocol for detection of aneuploidy, which can be considered a threshold effect not mediated by a direct interaction with DNA. Positive results were obtained at concentrations approaching cytotoxic levels and are very likelydue to the presence of technical artefacts (low temperature treatment inducing tubulin dissociation). Indeed, absence of effect was recorded when the ice treatment was skipped. – The limited relevance of fungal systems together with the uncertainquality of these results make questionable their extrapolation to the *in vivo* situation in humans.

12. Assay modified with pre-incubation in the presence of S9.
13. Without metabolic activation, 3 hours treatment + 21 hours recovery.
14. With metabolic activation, 3 hours treatment + 21 hours recovery.
15. Without metabolic activation, 24 hours + 0 hours recovery.

Table 6: Summary of Genotoxicity Data (*in vivo)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Table 6: Summary of Genotoxicity Data (*in vivo)* EFSA / FGE.07Rev4 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2012a) (substances in brackets are JECFA-evaluated substances)

Chemical Name	Test system	Test Object	Route	Dose	Result	Reference	Comments
(Isopropyl alcohol [02.079])	Micronucleus test	ICR Mouse (15M & 15F)	i.p. injection in 0.9 % NaCl	350-2500 mg/kg	Negative	(Kapp et al., 1993)	1
(Acetone [07.050])	Micronucleus test	Chinese hamster (5M & 5F)	i.p. injection in corn oil	865 mg/kg	Negative	(Basler, 1986)	1
(2-Butanone [07.053])	Micronucleus test	CD-1 mice (5M & 5F)	i.p. injection in corn oil	LD20 (1.96 ml/kg)	Negative	(O'Donoghue et al., 1988)	1
	Micronucleus test	Chinese hamster (5M & 5F)	i.p. injection in corn oil	411mg/kg	Negative	(Basler, 1986)	1
(4-Methyl-2-pentanone [07.017])	Micronucleus test	CD-1 mice (5M & 5F)	i.p. injection in corn oil	LD20 (0.73 ml/kg)	Negative	(Basler, 1986)	1

1. Summarised by JECFA, 51st meeting (JECFA, 1999).

Table 7: Genotoxicity (*in vitro*) Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 1.2.3 (FGE.206)

Table 7: Genotoxicity (*in vitro*) Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 1.2.3

FL-no	Chemical Name	Test System *in vitro*	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
[07.099]	6-Methylhepta-3,5-dien-2-one	Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA 102	1.6, 8, 40, 200, 1000 and 5000 µg/plate [1]	Negative	(Williams, 2009a)	Toxicity observed in all strains at 2000 µg/plate or greater in the absence of S9 and at 800 µg/plate in the presence of S9. Study design complied with current recommendations. Acceptable top concentration was achieved.
				20.48, 51.2, 128, 320, 800, 2000 and 5000 µg/plate [1,2]	Negative		
		Micronucleus induction	Human peripheral blood lymphocytes	225, 325 and 450 µg/ml [3] 225, 300 and 350 µg/ml [4]	Negative	(Whitwell, 2010)	Complies with draft OECD Guideline 487. Acceptable levels of cytotoxicity achieved at the top concentrations used in all parts of the study.
				100, 120 or 150 µg/ml [5]	Negative		

[1] With and without metabolic activation.

[2] Assay modified with pre-incubation in the presence of S9.

[3] Without metabolic activation, 3 hours treatment + 21 hours recovery.

[4] With metabolic activation, 3 hours treatment + 21 hours recovery.

[5] Without metabolic activation, 24 hours + 0 hours recovery.

Table 8: Genotoxicity (*in vitro*) Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 1.2.1 (FGE.204)

Table 8: Genotoxicity (*in vitro*) Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 1.2.1

FL-no	Chemical Name	Test System *in vitro*	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
[07.101]	4-Methylpent- 3-en-2-one	Reverse Mutation	*S.typhimurium* TA98, TA100, TA102, TA1535 and TA1537	1.6 - 5000 µg/plate [1]	Negative	(Williams, 2009b)	Valid. Study design complies with current recommendations.
				156.25 - 5000 µg/plate [1,2]	Negative		
		Micronucleus Assay	Human peripheral blood lymphocytes	600 - 981.4 µg/ml [3]	Negative	(Stone, 2011)	Valid Complies with OECD Guideline 487.
				200 - 981.4 µg/ml [4]	Negative		
				100 - 500 µg/ml [4]	Negative		
				100 - 300 µg/ml [5]	Negative		

Validity of genotoxicity studies:

Valid.

Limited validity (e.g. if certain aspects are not in accordance with OECD Guidelines or current standards and / or limited documentation).

Insufficient validity (e.g. if main aspects are not in accordance with any recognised guidelines (e.g. OECD) or current standards inappropriate / not validated test system).

Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided, text not in a Community language).

[1] With and without S9-mix metabolic activation.
[2] Assay modified with pre-incubation in the presence of S9-mix.
[3] Without metabolic activation, 3 hours treatment + 21 hours recovery.
[4] With metabolic activation, 3 hours treatment + 21 hours recovery.
[5] Without metabolic activation, 24 hours + 0 hours recovery.

Table 9: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA *(JECFA, 2003; JECFA, 2009b)*

Table 9: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA *(JECFA, 2003; JECFA, 2009b)*

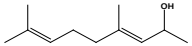
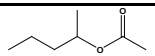
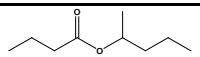
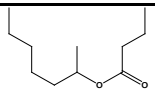
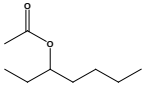
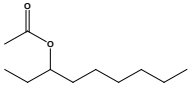
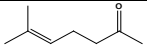
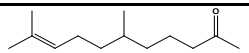
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
02.252 1841	4,8-Dimethyl-3,7-nonadien-2-ol		3 0.1	Class I A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. 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.
09.657 1146	1-Methylbutyl acetate		2.9 3	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.
09.658 1142	1-Methylbutyl butyrate		0.47 1	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.
09.923 1144	Hept-2-yl butyrate		3.0 3	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.
09.924 1143	(+/-)-3-Heptyl acetate		3.0 3	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. Register name to be changed to 3-Heptyl acetate.
09.925 1145	Nonan-3-yl acetate		3.0 3	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.
07.015 1120	6-Methylhept-5-en-2-one		100 44	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.
07.069 1121	Tetrahydro-pseudo-ionone		0.012 0.01	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.

Table 9: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA *(JECFA, 2003; JECFA, 2009b)*

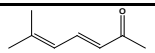
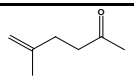
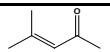
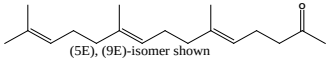
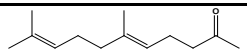
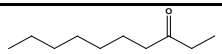
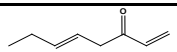
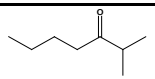
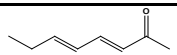
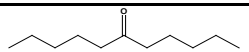
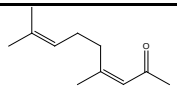
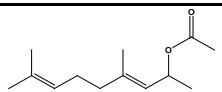
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
07.099 1134	6-Methylhepta-3,5-dien-2-one		13 5	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. 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.
07.100 1119	5-Methylhex-5-en-2-one		0.24 0.3	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.
07.101 1131	4-Methylpent-3-en-2-one		0.34 ND	Class II A3: Intake below threshold	4)	Evaluated in FGE.204, genotoxicity concern could be ruled out. 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.
07.114 1123	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	 (5E), (9E)-isomer shown	0.085 ND	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.
07.123 1122	Geranylacetone		41 2	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 levels of intake based on the MSDI approach. CASrn refers to (E)-isomer.
07.151 1118	Decan-3-one		3.0 3	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 levels of intake based on the MSDI approach.
07.190 1848	Octa-1,5-dien-3-one		0.061 ND	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. 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.
07.240 1156	2-Methylheptan-3-one		3.0 3	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.
07.247 1139	(E,E)-3,5-Octadien-2-one		3.0 4	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. No safety concern at the estimated	No safety concern at the estimated level of intake based on the MSDI approach.

Table 9: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA *(JECFA, 2003; JECFA, 2009b)*

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
						level of intake based on the MSDI approach.	
07.249 1155	Undecan-6-one		3.0 3	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 estimated levels of intake based on the MSDI approach.
07.256 1137	(3Z)-4,8-Dimethyl-3,7-nonadiene-2-one		6.1 6.6	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. 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. Register name to be changed to 4,8-Dimethyl-3,7-nonadiene-2-one.
09.936 1847	4,8-Dimethyl-3,7-nonadien-2-yl acetate		3 0.2	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. 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 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.

ND: not determined

Table 10: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)

Table 10: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)

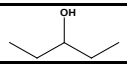
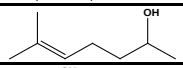
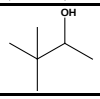
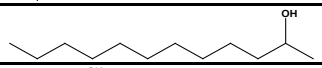
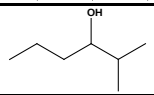
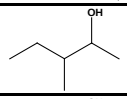
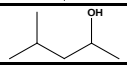
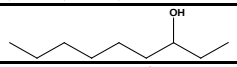
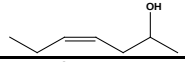
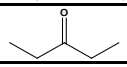
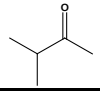
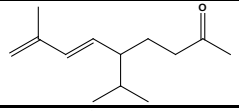
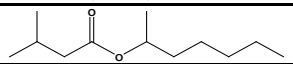
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
02.077	Pentan-3-ol		0.19	Class I A3: Intake below threshold	4)	6)	
02.124	6-Methylhept-5-en-2-ol		0.0061	Class I A3: Intake below threshold	4)	6)	
02.142	3,3-Dimethylbutan-2-ol		0.24	Class I A3: Intake below threshold	4)	6)	
02.148	Dodecan-2-ol		0.35	Class I A3: Intake below threshold	4)	6)	
02.177	2-Methylhexan-3-ol		0.12	Class I A3: Intake below threshold	4)	6)	
02.182	3-Methylpentan-2-ol		0.12	Class I A3: Intake below threshold	4)	6)	
02.183	4-Methylpentan-2-ol		0.0012	Class I A3: Intake below threshold	4)	6)	
02.190	Nonan-3-ol		0.011	Class I A3: Intake below threshold	4)	6)	
02.255	(Z)-4-Hepten-2-ol		0.03	Class I A3: Intake below threshold	4)	6)	
07.084	Pentan-3-one		0.24	Class I A3: Intake below threshold	4)	6)	
07.178	3-Methylbutan-2-one		0.073	Class I A3: Intake below threshold	4)	6)	
07.239 1840	[R-(E)]-5-Isopropyl-8-methylnona-6,8-dien-2-one		0.24	Class I A3: Intake below threshold	4)	6)	
09.304	sec-Heptyl isovalerate		0.0012	Class I A3: Intake below threshold	4)	6)	

Table 10: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)

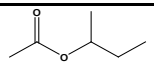
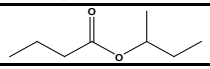
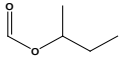
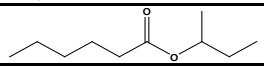
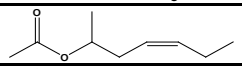
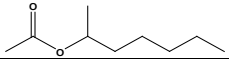
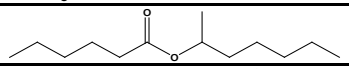
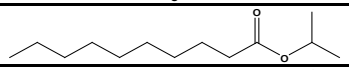
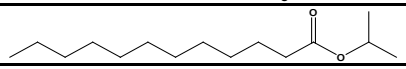
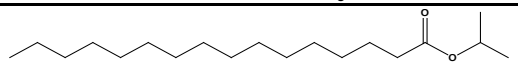
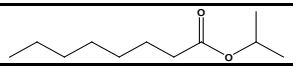
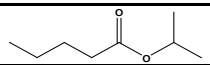
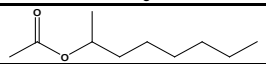
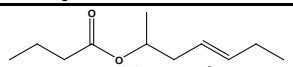
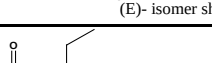
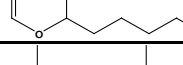
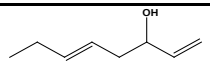
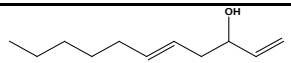
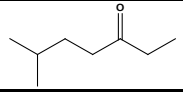
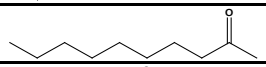
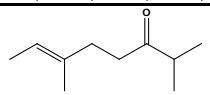
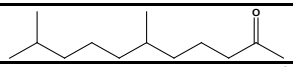
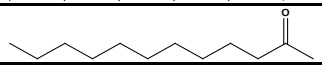
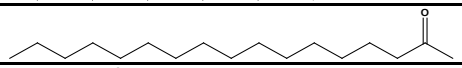
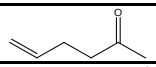
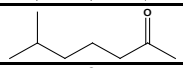
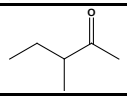
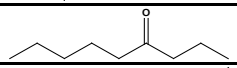
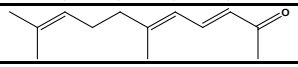
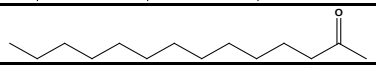
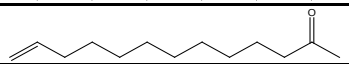
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
09.323	sec-Butyl acetate		0.0012	Class I A3: Intake below threshold	4)	6)	
09.325	sec-Butyl butyrate		1.3	Class I A3: Intake below threshold	4)	6)	
09.328	sec-Butyl formate		0.12	Class I A3: Intake below threshold	4)	6)	
09.332	sec-Butyl hexanoate		0.024	Class I A3: Intake below threshold	4)	6)	
09.386	sec-Hept-4(cis)-enyl acetate		0.024	Class I A3: Intake below threshold	4)	6)	
09.388	sec-Heptyl acetate		0.12	Class I A3: Intake below threshold	4)	6)	
09.391	sec-Heptyl hexanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.604	Isopropyl decanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.605	Isopropyl dodecanoate		0.12	Class I A3: Intake below threshold	4)	6)	
09.606	Isopropyl hexadecanoate		0.012	Class I A3: Intake below threshold	4)	6)	
09.608	Isopropyl octanoate		1.3	Class I A3: Intake below threshold	4)	6)	
09.609	Isopropyl valerate		0.012	Class I A3: Intake below threshold	4)	6)	
09.676	sec-Octyl acetate		0.011	Class I A3: Intake below threshold	4)	6)	
09.880	Hept-4-enyl-2 butyrate	 (E)- isomer shown	0.79	Class I A3: Intake below threshold	4)	6)	
09.926	Octan-3-yl formate		0.24	Class I A3: Intake below threshold	4)	6)	
02.145	2,6-Dimethylocta-1,5,7-trien-3-ol		0.0085	Class II A3: Intake below threshold	4)	6)	a)

Table 10: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)

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
02.194	Octa-1,5-dien-3-ol		0.061	Class II A3: Intake below threshold	4)	6)	a)
02.211	Undeca-1,5-dien-3-ol		0.061	Class II A3: Intake below threshold	4)	6)	a)
07.072	6-Methylheptan-3-one		0.19	Class II A3: Intake below threshold	4)	6)	
07.150	Decan-2-one		0.52	Class II A3: Intake below threshold	4)	6)	
07.156	2,6-Dimethyloct-6-en-3-one	 (E)- isomer shown	0.0012	Class II A3: Intake below threshold	4)	7)	
07.157	6,10-Dimethylundecan-2-one		0.085	Class II A3: Intake below threshold	4)	6)	
07.158	Dodecan-2-one		0.73	Class II A3: Intake below threshold	4)	6)	
07.160	Heptadecan-2-one		0.12	Class II A3: Intake below threshold	4)	6)	
07.162	Hex-5-en-2-one		0.049	Class II A3: Intake below threshold	4)	6)	
07.181	6-Methylheptan-2-one		0.0012	Class II A3: Intake below threshold	4)	6)	
07.185	3-Methylpentan-2-one		1.2	Class II A3: Intake below threshold	4)	6)	
07.189	Nonan-4-one		0.52	Class II A3: Intake below threshold	4)	6)	
07.198	Pseudo-ionone		0.12	Class II A3: Intake below threshold	4)	6)	a)
07.199	Tetradecan-2-one		0.073	Class II A3: Intake below threshold	4)	6)	
07.201	Tridec-12-en-2-one		0.024	Class II A3: Intake below threshold	4)	6)	

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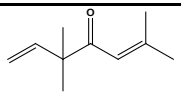
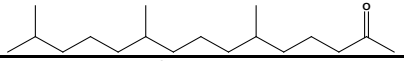
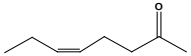
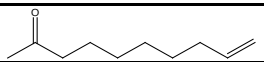
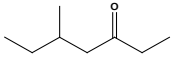
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
07.204	3,3,6-Trimethylhepta-1,5-dien-4-one		0.012	Class II A3: Intake below threshold	4)	6)	a)
07.205	6,10,14-Trimethylpentadecan-2-one		0.0073	Class II A3: Intake below threshold	4)	6)	
07.236	5-Octen-2-one	 (Z)-isomer shown	0.0097	Class II A3: Intake below threshold	4)	6)	
07.262	9-Decen-2-one		73	Class II A3: Intake below threshold	4)	6)	
07.182	5-Methylheptan-3-one		0.32	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	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 3 (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.206, genotoxicity concern could be ruled out.

b) NOAEL for neurotoxicity: 82 mg/kg bw/day; Adequate Margin of Safety.

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ABBREVIATIONS

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)
GLP	Good laboratory practise
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MNBN	Micronucleated binucleate cells
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
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
RI	Replication Index
SCE	Sister chromatic exchange

SCF	Scientific Committee on Food
WHO	World Health Organisation