



**EFSA ; Scientific Opinion on Flavouring Group Evaluation 63, Revision 1 (FGE.63Rev1): 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 (2012)**

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## SCIENTIFIC OPINION

### Scientific Opinion on Flavouring Group Evaluation 63, Revision 1 (FGE.63Rev1):

**Consideration of aliphatic secondary alcohols, ketones and related esters evaluated by JECFA (59<sup>th</sup> and 69<sup>th</sup> 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 (2012)<sup>1</sup>**

**EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)<sup>2,3</sup>**

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 19 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 59<sup>th</sup> and 69<sup>th</sup> meetings in 2002 and 2008. This revision is made due to inclusion of six additional substances, 4,8-dimethyl-3,7-nonadien-2-ol, 6-methylhepta-3,5-dien-2-one, octa-1,5-dien-3-one, (*E,E*)-3,5-octadien-2-one, (3*Z*)-4,8-dimethyl-3,7-nonadiene-2-one and 4,8-dimethyl-3,7-nonadien-2-yl acetate [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936] 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 19 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.

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<sup>1</sup> On request from the Commission, Question No EFSA-Q-2012-00518, EFSA-Q-2012-00517, EFSA-Q-2012-00516, EFSA-Q-2012-00515, EFSA-Q-2012-00514, EFSA-Q-2012-00513, adopted on 27 September 2012.

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**KEY WORDS**

Food safety, flavourings, aliphatic, secondary, alcohols, ketones, esters, JECFA, 59<sup>th</sup> meeting, 69<sup>th</sup> meeting, FGE.07.

## SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to 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 FGE.63 the EFSA evaluated 13 flavouring substances (EFSA, 2008ae) from a group of 39 flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at its 59<sup>th</sup> meeting (JECFA, 2003a). At its 69<sup>th</sup> meeting (JECFA, 2009c), the JECFA evaluated an additional 17 aliphatic secondary alcohols, ketones and related esters. The present revision of FGE.63, FGE.63Rev1, includes the consideration of six additional substances, 4,8-dimethyl-3,7-nonadien-2-ol, 6-methylhepta-3,5-dien-2-one, octa-1,5-dien-3-one, (*E,E*)-3,5-octadien-2-one, (3*Z*)-4,8-dimethyl-3,7-nonadiene-2-one and 4,8-dimethyl-3,7-nonadien-2-yl acetate [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936]. Three of these substances [FL-no: 07.099, 07.247 and 07.256] were evaluated by the JECFA at the 59<sup>th</sup> meeting (JECFA, 2003a) and three substances [FL-no: 02.252, 07.190 and 09.936] were evaluated by the JECFA at its 69<sup>th</sup> meeting (JECFA, 2009c). These six substances are  $\alpha,\beta$ -unsaturated ketones or may be metabolised to  $\alpha,\beta$ -unsaturated ketones and were originally allocated to and evaluated in FGE.206 (EFSA, 2011c) in which they were considered not to be of concern with respect to genotoxicity. Therefore, the present revision of FGE.63, FGE.63Rev1, considers 19 flavouring substances evaluated by the JECFA.

The Panel concluded that the six additional substances fit well together with the 13 aliphatic secondary alcohols, ketones and related esters considered in the FGE.63.

The Panel concluded that the 19 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 the Flavouring Group Evaluation 07, Revision 4 (FGE.07Rev4).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances considered in this FGE.

For all 19 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 16 substances evaluated through the Procedure use levels are needed to calculate the mTAMDI 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 19 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 19 JECFA-evaluated substances.

Thus, for all 19 JECFA evaluated aliphatic secondary alcohols, ketones and related esters [FL-no: 02.252, 07.015, 07.069, 07.099, 07.100, 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

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

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a).

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

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

## TERMS OF REFERENCE AS PROVIDED BY THE 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 (EC, 2000a). These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC (EC, 1999a) and its consecutive amendments. The evaluation programme was finalised at the end of 2009.

The Commission requested EFSA, based on additional submitted data on genotoxicity, to carry out re-evaluation of the six flavouring substances [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936] and depending on the outcome to proceed to the evaluation of these flavouring substances through the Procedure, also according to Commission Regulation (EC) No 1565/2000 (EC, 2000a).

## ASSESSMENT

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

The following issues are of special importance.

### *Intake*

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

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

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

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

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

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

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

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

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

#### *Genotoxicity*

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



provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

### Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of 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.

## HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

At its 59<sup>th</sup> meeting the JECFA evaluated a group of 39 flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters (JECFA, 2003a). 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  $\alpha,\beta$ -unsaturated ketones or precursors for such, which have been considered together with other  $\alpha,\beta$ -unsaturated substances. FGE.63 therefore only dealt with 13 JECFA evaluated substances (EFSA, 2008ae).

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
63	7 July 2007	<a href="http://www.efsa.europa.eu/en/efsajournal/pub/706.htm">http://www.efsa.europa.eu/en/efsajournal/pub/706.htm</a>	13
63Rev1	26 Sep. 2012		19

The present revision of FGE.63, FGE.63Rev1, includes the consideration of six additional substances [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936]. These six substances are  $\alpha,\beta$ -unsaturated ketones or may be metabolised to  $\alpha,\beta$ -unsaturated ketones and were originally allocated to and evaluated in FGE.206 (EFSA, 2011c) in which they were considered not to be of concern with respect to genotoxicity. Three of these substances [FL-no: 07.099, 07.247 and 07.256] were evaluated by the JECFA at the 59<sup>th</sup> meeting (JECFA, 2003a) and three substances [FL-no: 02.252, 07.190 and 09.936] were evaluated at the 69<sup>th</sup> meeting (JECFA, 2009c).

Since the evaluation of FGE.63 in 2007, EU production volumes have been provided for three substances [FL-no: 07.069, 07.100 and 09.658] (EFFA, 2010a), for which the evaluation could not be finalised, due to lack of these data. Based on the newly submitted EU production volumes the substances have already been evaluated in FGE.96<sup>4</sup> (EFSA, 2011a), but for the sake of completion, the information has also been included here as well.

Finally, information on the stereoisomeric composition has been provided (EFFA, 2010a) for six substances [FL-no: 07.069, 07.114, 09.657, 09.658, 09.923 and 09.925] since the previous evaluation of FGE.63 (EFSA, 2008ae).

<sup>4</sup> Consideration of 88 flavouring substances considered by EFSA for which EU production volumes / anticipated production volumes have been submitted on request by DG SANCO.

## 1. Presentation of the Substances in the JECFA Flavouring Group

### 1.1. Description

#### 1.1.1. JECFA Status

This FGE deals with 19 JECFA evaluated substances. Sixteen substances from the 59<sup>th</sup> meeting, 2002 and three substances from the 69<sup>th</sup> meeting, 2008:

- Of the 39 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 59<sup>th</sup> meeting (JECFA, 2003a) 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  $\alpha,\beta$ -unsaturated ketones or precursors for such, which have been considered together with other  $\alpha,\beta$ -unsaturated substances. Of these 25 substances, three substances [FL-no: 07.099, 07.247 and 07.256] were evaluated in FGE.206 (EFSA, 2011c) in which they were considered not to be of concern with respect to genotoxicity. These three substances are included in this revision of FGE.63. Therefore, from the 59<sup>th</sup> JECFA meeting 16 substances are considered in this FGE.63Rev1.
- Of the 17 aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at the 69<sup>th</sup> meeting (JECFA, 2009c) 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, 2012n) 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, 2011c) in which they were considered not to be of concern with respect to genotoxicity. These three substances are included in this revision of FGE.63. Therefore, from the 69<sup>th</sup> JECFA meeting, three substances are considered in this FGE.63Rev1.

#### 1.1.2. EFSA Considerations

Six of the  $\alpha,\beta$ -unsaturated ketones [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936] evaluated by the JECFA (JECFA, 2003a; JECFA, 2009c) were evaluated by the EFSA in FGE.206 (EFSA, 2011c) and were considered not to be of concern with respect to genotoxicity.

The Panel concluded that these six 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, 2012d).

### 1.2. Isomers

#### 1.2.1. 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].

### 1.2.2. 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) is considered to specify the stereoisomeric composition.

## 1.3. Specifications

### 1.3.1. JECFA Status

The JECFA specifications are available for all 19 substances (JECFA, 2002d; JECFA, 2009b). See Table 1.

### 1.3.2. EFSA Considerations

No comments.

## 2. Intake Estimations

### 2.1. JECFA Status

For all 19 substances evaluated by the JECFA intake data were available for the EU, see Table 2.2.2 and Table 3.1.

### 2.2. EFSA Considerations

For all substances, the Industry has submitted production figure for EU. Since the evaluation of FGE.63 in 2007, EU production volumes have been provided for three substances [FL-no: 07.069, 07.100 and 09.658] (EFFA, 2010a), for which the evaluation could not be finalised, due to lack of these data. These data have been used in this consideration (see Table 2.2.2 and Table 3.1).

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, 2004n) (see Table 2.2.1). Based on these normal use levels, mTAMDI values can be calculated (see Table 2.2.2), (EFSA, 2004d). 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 16 substances use levels are needed to calculate the mTAMDI.

**Table 2.2.1 Normal and Maximum use levels (mg/kg) available for three JECFA evaluated substances in FGE.63Rev1**

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

**Table 2.2.2 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		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
07.114	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one	0.085			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		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		19	Class II	540

### 3. Genotoxicity Data

#### 3.1. Genotoxicity Studies

##### 3.1.1. Genotoxicity Studies - Text Taken<sup>5</sup> from the 59<sup>th</sup> JECFA meeting (JECFA, 2003a)

###### *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 59<sup>th</sup> meeting.

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

##### 3.1.2. Genotoxicity Studies - From the 69<sup>th</sup> JECFA meeting (JECFA, 2009c)

For the substances evaluated by the JECFA at the 69<sup>th</sup> meeting no genotoxicity data were provided (JECFA, 2009c).

#### 3.2. Genotoxicity Studies - Text Taken<sup>6</sup> from EFSA FGE.07Rev4 (EFSA, 2012d)

###### *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

<sup>5</sup> The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

<sup>6</sup> The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

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 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, 2011c) 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 either bacterial 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, 2011c) 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 LD20 and the LD50 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 2.2 and 2.3.

### **3.3. Genotoxicity Studies - Text Taken<sup>7</sup> from EFSA FGE.206 (EFSA, 2011c)**

The Industry has submitted data concerning genotoxicity studies for 6-methylhepta-3,5-dien-2-one [FL-no: 07.099] a representative substance for subgroup 1.2.3 in FGE.19 (EFSA, 2011c). The data below are of importance for the assessment, in this revision of FGE.63, 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 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 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 phytohaemagglutinin 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

<sup>7</sup> 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. 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, 2010a). 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 2.4.

#### *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.

### **3.4. EFSA Considerations**

The Panel concluded that the data available do not preclude evaluation of the 19 aliphatic secondary alcohols, ketones and related esters through the Procedure.

## **4. Application of the Procedure**

### **4.1. Application of the Procedure to 19 Aliphatic Secondary Alcohols, Ketones and Related Esters by JECFA (JECFA, 2003a; JECFA, 2009c)**

According to the JECFA six of the substances belong to structural class I and 13 to structural class II using the decision tree approach presented by Cramer *et al.* (Cramer *et al.*, 1978).

The JECFA concluded all 19 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 19 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 19 aliphatic secondary alcohols, ketones and related esters are summarised in Table 3.1: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and Related Esters (JECFA, 2003a; JECFA, 2009c).

### **4.2. 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, 2012d)**

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 in 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.

48 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  $1.5 \times 10^7$  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 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA, 2012d).

### 4.3. EFSA Considerations

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances in the group of aliphatic secondary alcohols, ketones and related esters.

## 5. Conclusion

In FGE.63 the EFSA evaluated 13 flavouring substances (EFSA, 2008ae) from a group of 39 flavouring substances consisting of aliphatic secondary alcohols, ketones and related esters evaluated by the JECFA at its 59<sup>th</sup> meeting (JECFA, 2003a). At its 69<sup>th</sup> meeting the JECFA evaluated an additional 17 aliphatic secondary alcohols, ketones and related esters. The present revision of FGE.63, FGE.63Rev1, includes the consideration of six additional substances, 4,8-dimethyl-3,7-nonadien-2-ol, 6-methylhepta-3,5-dien-2-one, octa-1,5-dien-3-one, (*E,E*)-3,5-octadien-2-one, (3*Z*)-4,8-dimethyl-3,7-nonadiene-2-one and 4,8-dimethyl-3,7-nonadien-2-yl acetate [FL-no: 02.252, 07.099, 07.190, 07.247, 07.256 and 09.936]. Three of these substances [FL-no: 07.099, 07.247 and 07.256] were evaluated by the JECFA at the 59<sup>th</sup> meeting (JECFA, 2003a) and three substances [FL-no: 02.252, 07.190 and 09.936] were evaluated by the JECFA at its 69<sup>th</sup> meeting (JECFA, 2009c). These six substances are  $\alpha,\beta$ -unsaturated ketones or may be metabolised to  $\alpha,\beta$ -unsaturated ketones and were originally allocated to and evaluated in FGE.206 (EFSA, 2011c) in which they were considered not to be of concern with respect to genotoxicity. Therefore, the present revision of FGE.63, FGE.63Rev1 considers 19 flavouring substances evaluated by the JECFA.

The Panel concluded that the six additional substances fit well together with the 13 aliphatic secondary alcohols, ketones and related esters considered in the FGE.63.

The Panel concluded that the 19 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 the Flavouring Group Evaluation 07, Revision 4 (FGE.07Rev4).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 19 substances considered in this FGE.

For all 19 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 16 substances evaluated through the Procedure use levels



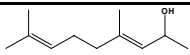
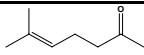
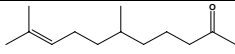
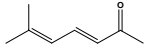
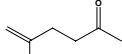
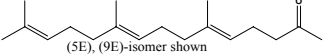
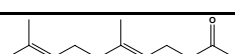
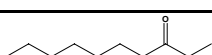
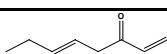
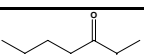
are needed to calculate the mTAMDI in order to identify those flavouring substances that need more refined exposure assessment in order to finalise the evaluation

In order to determine whether the conclusion for the 19 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 19 JECFA-evaluated substances.

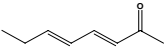
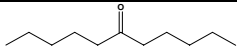
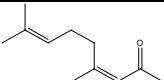
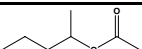
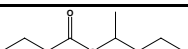
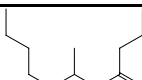
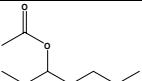

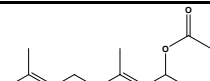
Thus, for all 19 JECFA evaluated aliphatic secondary alcohols, ketones and related esters [FL-no: 02.252, 07.015, 07.069, 07.099, 07.100, 07.114, 07.123, 07.151, 07.190, 07.240, 07.247, 07.249, 07.256, 09.657, 09.658, 09.923, 09.924, 09.925 and 09.936] the Panel agrees with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

**TABLE 1: SPECIFICATION SUMMARY**

**Table 1: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2003a; JECFA, 2009c)**

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 <sub>11</sub> H <sub>20</sub> 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, 2012c).
07.015 1120	6-Methylhept-5-en-2-one		2707 149 110-93-0	Liquid C <sub>8</sub> H <sub>14</sub> 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 <sub>13</sub> H <sub>24</sub> O 196.33	Insoluble Miscible	234 NMR 95 %	1.449-1.455 0.865-0.875	Racemate (EFFA, 2010a).
07.099 1134	6-Methylhepta-3,5-dien-2-one		3363 11143 1604-28-0	Liquid C <sub>8</sub> H <sub>12</sub> O 124.18	Almost insoluble Miscible	190 NMR 96 %	1.528-1.537 0.895-0.899	Mixture of E/Z stereoisomers: 60-90 % (E) (EFFA, 2012c).
07.100 1119	5-Methylhex-5-en-2-one		3365 11150 3240-09-3	Liquid C <sub>7</sub> H <sub>12</sub> O 112.17	Insoluble Miscible	148-149 NMR 97 %	1.428-1.433 0.862-0.868	
07.114 1123	6,10,14-Trimethylpentadeca-5,9,13-trien-2-one		3442 11206 762-29-8	Liquid C <sub>18</sub> H <sub>30</sub> 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, 2010a).
07.123 1122	Geranylacetone		3542 11088 3796-70-1	Liquid C <sub>13</sub> H <sub>22</sub> O 194.32	Slightly soluble Miscible	247 NMR 95 %	1.463-1.471 0.861-0.867	CASrn refers to (E)-isomer. Register name to be changed to (E)-Geranylacetone.
07.151 1118	Decan-3-one		3966 11056 928-80-3	Liquid C <sub>10</sub> H <sub>20</sub> O 156.27	Insoluble Miscible	204-205 NMR 97 %	1.421-1.427 0.820-0.830	
07.190 1848	Octa-1,5-dien-3-one		4405 65213-86-7	Liquid C <sub>8</sub> H <sub>12</sub> 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, 2012c).
07.240 1156	2-Methylheptan-3-one		4000 13019-20-0	Liquid C <sub>8</sub> H <sub>16</sub> O 128.2	Insoluble Miscible	158-160 NMR 98 %	1.408-1.413 0.811-0.821	

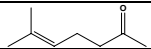
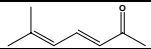
**Table 1: Specification Summary of the Substances in the JECFA Flavouring Groups of Aliphatic Secondary Alcohols, Ketones and related Esters (JECFA, 2003a; JECFA, 2009c)**

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
07.247 1139	(E,E)-3,5-Octadien-2-one		4008 30086-02-3	Liquid C <sub>8</sub> H <sub>12</sub> 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 <sub>11</sub> H <sub>22</sub> 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 <sub>11</sub> H <sub>18</sub> 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, 2012c). 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 <sub>7</sub> H <sub>14</sub> O <sub>2</sub> 130.2	Insoluble Partially Soluble	135 NMR 98 %	1.369-1.400 0.862-0.866	Racemate (EFFA, 2010a).
09.658 1142	1-Methylbutyl butyrate		3893 10763 60415-61-4	Liquid C <sub>9</sub> H <sub>18</sub> O <sub>2</sub> 158.24	Insoluble 50% Soluble	185-186 IR NMR MS 99 %	1.409-1.415 0.862-0.868	Racemate (EFFA, 2010a).
09.923 1144	Hept-2-yl butyrate		3981 39026-94-3	Liquid C <sub>11</sub> H <sub>22</sub> O <sub>2</sub> 186.3	Insoluble Miscible	210 NMR 98 %	1.413-1.417 0.855-0.860	Racemate (EFFA, 2010a).
09.924 1143	(+/-)-3-Heptyl acetate		3980 5921-83-5	Liquid C <sub>9</sub> H <sub>18</sub> O <sub>2</sub> 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 <sub>11</sub> H <sub>22</sub> O <sub>2</sub> 186.3	Insoluble Miscible	225 NMR 98 %	1.416-1.423 0.854-0.864	Racemate (EFFA, 2010a).
09.936 1847	4,8-Dimethyl-3,7-nonadien-2-yl acetate		4103 91418-25-6	Liquid C <sub>13</sub> H <sub>22</sub> O <sub>2</sub> 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, 2012c).

- 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 2: GENOTOXICITY DATA

**Table 2.1: Summary of Genotoxicity Data of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (JECFA, 2003a)**

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

<sup>1</sup> With and without metabolic activation.

**Table 2.2: Summary of Genotoxicity Data (*in vitro*) EFSA / FGE.07 (EFSA, 2012d) (substances in brackets are JECFA-evaluated substances)**

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

		TA1535, TA1537, TA1538			
	Ames test <sup>2</sup>	<i>S. typhimurium</i> TA97, TA98, TA100, TA104, TA1535, TA1537	Up to 10000 µg/plate	Negative <sup>1</sup>	(Zeiger et al., 1992) 8
	Ames test	<i>S. typhimurium</i> TA102	5000 µg/plate	Negative <sup>4</sup>	(Müller et al., 1993) 8
	Ames test	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538, <i>E. coli</i> WP2uvrA	4000 µg/plate	Negative	(Brooks et al., 1988) 8
	Gene conversion	<i>S. cerevisiae</i>	5 mg/ml	Negative <sup>1</sup>	(Brooks et al., 1988) 8
	Forward Mutation	L5178Y/TL+/- mouse lymphoma cells	0.67 to 12 µg/ml	Negative <sup>1</sup>	(O'Donoghue et al., 1988) 8
	Unscheduled DNA synthesis	Human lymphocytes	0.72 mg/ml	Negative <sup>1</sup>	(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 <sup>1</sup>	(Brooks et al., 1988) 8
	Cell transformation assay <sup>1</sup>	BALB/3T3 cells (clone A31-1)	6-18 µl/ml	Negative	(O'Donoghue et al., 1988) 8
	Aneuploidy induction	<i>S. cerevisiae</i>	3.38 %	Positive <sup>4</sup>	(Zimmermann et al., 1985a) 11
Pentan-3-one [07.084]	Aneuploidy induction	<i>S. cerevisiae</i>	1.48 %	Positive <sup>4</sup>	(Zimmermann et al., 1985a) 11
Pentan-3-ol [02.077]	Chromosomal aberrations	Chinese hamster ovary cells	0.5 to 10 %	Negative <sup>1</sup>	(Abbondandolo et al., 1980) 8
	Forward mutation	<i>S. pombe</i>	0.5 to 10 %	Negative <sup>1</sup>	(Abbondandolo et al., 1980) 8
(2-Heptanone [07.002])	Unscheduled DNA synthesis	Rat hepatocytes	1000 ppm	Negative	(Barber et al., 1999) 8
Methyl-3-butan-2-one [07.178]	Aneuploidy induction	<i>S. cerevisiae</i>	1.23 to 1.36 %	Negative <sup>4</sup>	(Zimmermann et al., 1985a) 11
	Aneuploidy induction	<i>S. cerevisiae</i>	0.84 to 1.23 %	Negative <sup>4</sup>	(Zimmermann et al., 1985a) 11
(4-Methyl-2-pentanone [07.017])	Ames test	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	0.03 to 3 mg/plate	Negative <sup>1</sup>	(O'Donoghue et al., 1988) 8
	Ames test <sup>2</sup>	<i>S. typhimurium</i> TA97, TA98, TA100, TA1535	Up to 6667 µg/plate	Negative <sup>1</sup>	(Zeiger et al., 1992) 8
	Ames test	<i>E. coli</i> WP2uvrA	8000 µg/plate	Negative <sup>4</sup>	(Brooks et al., 1988) 8
	Gene conversion	<i>S. cerevisiae</i>	5 mg/ml	Negative <sup>1</sup>	(Brooks et al., 1988) 8
	Forward mutation	L5178Y/TL+/- mouse lymphoma cells	0.26 to 3.7 µg/ml	Negative <sup>1</sup>	(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 <sup>1</sup>	BALB/3T3 cells (clone A31-1)	1-7µl/ml	Negative	(O'Donoghue et al., 1988) 8
	Chromosomal aberrations	Chinese hamster ovary cells	1000 µg/ml	Negative <sup>1</sup>	(Brooks et al., 1988) 8
Methyl-4-pentan-2-ol [02.183]	Ames test <sup>2</sup>	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538, <i>E. coli</i> WP2uvrA	5000 µg	Negative <sup>1</sup>	(Shimizu et al., 1985) 8
Methyl-6-heptan-2-one [07.181]	Ames test	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	5000 µg/plate	Negative <sup>1</sup>	(BASF, 1989a) 8
(2,6-Dimethyl-4-heptanone [07.122])	Ames test <sup>2</sup>	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	1 to 333 µg/plate	Negative <sup>1</sup>	(Mortelmans et al., 1986) 8
Trimethyl-6,10,14-pentadecan-2-one [07.205]	Ames test	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	5000 µg/plate	Negative <sup>1</sup>	(BASF, 1989b) 8
(6-Methyl-5-hepten-2-one [07.015])	Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	380 µg/plate	Negative <sup>1</sup>	(Florin et al., 1980) 9
(Isopropyl acetate [09.003])	Ames test <sup>2</sup>	<i>S. typhimurium</i> TA97, TA98, TA100, TA1537, TA1538	Up to 10 mg/plate	Negative <sup>1</sup>	(Zeiger et al., 1992) 8
(Isopropyl myristate [09.105])	Ames test <sup>7</sup>	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Negative <sup>1</sup>	(Blevins and Taylor, 1982) 8

Isopropyl hexadecanoate [09.606]	Ames test <sup>7</sup>	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Negative <sup>1</sup>	(Blevins and Taylor, 1982)	
9-Decen-2-one [07.262]	Ames test <sup>10</sup>	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Up to 5 µL/plate	Negative <sup>1</sup>	(Flavour Industry, 2009m)	
	Ames test <sup>10</sup>	<i>E. coli</i> WP2 (pKM 101)	Up to 5 µL/plate	Negative <sup>1</sup>	(Flavour Industry, 2009m)	
(6-Methylhepta-3,5-dien-2-one [07.099])	Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	370 µg/plate	Negative <sup>1</sup>	(Florin et al., 1980)	9
	Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and TA102	1.6, 8, 40, 200, 1000 and 5000 µg/plate	Negative <sup>1</sup>	(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 <sup>13</sup> 225, 300 and 350 µg/ml <sup>14</sup>	Negative	(Whitwell, 2010a)	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	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	0.03 to 30 µmol/plate	Negative	(Florin et al., 1980)	
	Reverse Mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 and TA102	0.128, 0.64, 3.2, 16, 80, 400 and 2000 µg/plate	Negative <sup>1</sup>	(Beevers, 2009a)	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 <sup>12</sup>	Negative <sup>1</sup>		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 <sup>13</sup> 100, 110 and 120 µg/ml <sup>14</sup>	Negative	(Lloyd, 2010a)	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 <sup>15</sup>	Negative	(Lloyd, 2010a)	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, 51<sup>st</sup> meeting (JECFA, 1999a).

9. Summarised by JECFA 59<sup>th</sup> meeting (JECFA, 2003a).

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 likely due 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 uncertain quality 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 2.3: Summary of Genotoxicity Data (*in vivo*) EFSA / FGE.07Rev4 (EFSA, 2012d) (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., 1993a)	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	LD <sub>20</sub> (1.96 ml/kg)	Negative	(O'Donoghue et al., 1988)	1
	Micronucleus test	Chinese hamster (5M & 5F)	i.p. injection in corn oil	411 mg/kg	Negative	(Basler, 1986)	1
(4-Methyl-2-pentanone [07.017])	Micronucleus test	CD-1 mice (5M & 5F)	i.p. injection in corn oil	LD <sub>20</sub> (0.73 ml/kg)	Negative	(Basler, 1986)	1

1. Summarised by JECFA, 51<sup>st</sup> meeting (JECFA, 1999a).

**Table 2.4: GENOTOXICITY (*in vitro*) Summary of Additionally submitted genotoxicity data on the representative substance of subgroup 1.2.3**

FL-no	Chemical Name	Test System <i>in vitro</i>	Test Object	Concentrations of Substance and Test Conditions	Result	Reference	Comments
[07.099]	6-Methylhepta-3,5-dien-2-one	Reverse Mutation	<i>S. typhimurium</i> 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] 100, 120 or 150 µg/ml [5]	Negative Negative	(Whitwell, 2010a)	

[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.

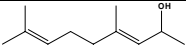
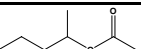
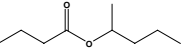



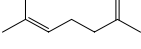
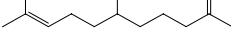
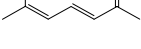
[4] With metabolic activation, 3 hours treatment + 21 hours recovery.

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

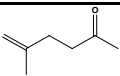
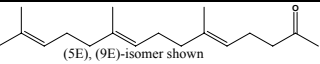
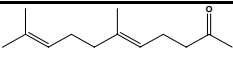
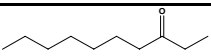
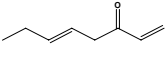
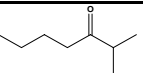
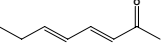
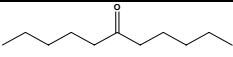
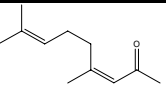


**TABLE 3: SUMMARY OF SAFETY EVALUATIONS**

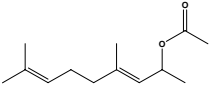
**Table 3.1: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (*JECFA, 2003a; JECFA, 2009c*)**

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI ( $\mu\text{g/capita/day}$ )	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	Class I A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. No safety concern at estimated levels of intake based on the MSDI approach.	No safety concern at estimated levels 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 estimated levels of intake based on the MSDI approach.	No safety concern at estimated levels 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 estimated levels 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 estimated levels of intake based on the MSDI approach. EU 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 estimated levels 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 estimated levels of intake based on the MSDI approach.	No safety concern at estimated levels 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.
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 estimated levels	No safety concern at estimated levels of intake based on the MSDI approach.

**Table 3.1: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (JECFA, 2003a; JECFA, 2009c)**

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI ( $\mu\text{g}/\text{capita}/\text{day}$ )	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
07.100 1119	5-Methylhex-5-en-2-one		0.24 0.3	Class II A3: Intake below threshold	4)	of intake based on the MSDI approach. 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		0.085	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. Register name to be changed to (E)- Geranylacetone.
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 estimated levels of intake based on the MSDI approach.
07.190 1848	Octa-1,5-dien-3-one		0.061	Class II A3: Intake below threshold	4)	Evaluated in FGE.206, genotoxicity concern could be ruled out. No safety concern at estimated levels of intake based on the MSDI approach.	No safety concern at estimated levels 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 estimated levels 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 estimated levels of intake based on the MSDI approach.	No safety concern at estimated levels 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 estimated levels	No safety concern at estimated levels of intake based on the MSDI approach.

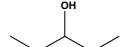
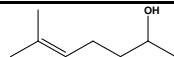
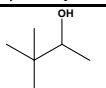
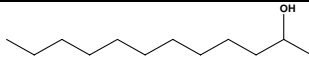
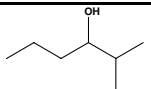
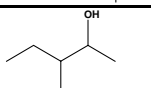
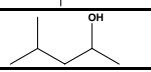
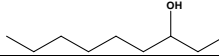
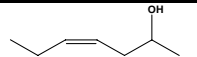
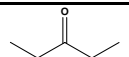
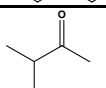
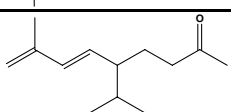
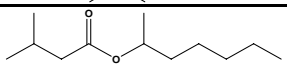
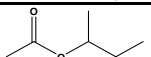
**Table 3.1: Summary of Safety Evaluation of Aliphatic Secondary Alcohols, Ketones and related Esters Evaluated by the JECFA (*JECFA, 2003a; JECFA, 2009c*)**

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI ( $\mu\text{g}/\text{capita}/\text{day}$ )	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOEL, genotoxicity)	EFSA conclusion on the material of commerce
09.936 1847	4,8-Dimethyl-3,7-nonadien-2-yl acetate		3.0	Class II A3: Intake below threshold	4)	of intake based on the MSDI approach.  Evaluated in FGE.206, genotoxicity concern could be ruled out. No safety concern at estimated levels of intake based on the MSDI approach.	Register name to be changed to 4,8- Dimethyl-3,7- nonadiene-2-one.

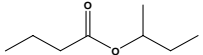
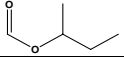
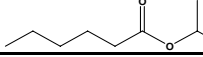
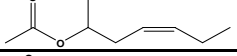
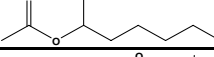
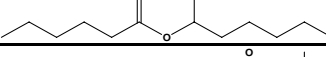
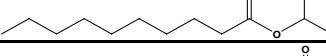
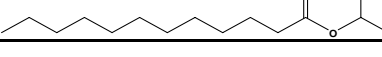
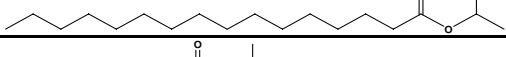
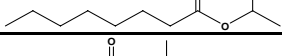
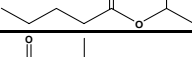
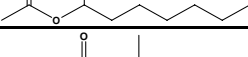
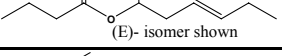
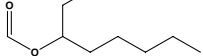
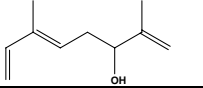
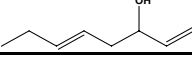
- 1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) =  $\mu\text{g}/\text{capita}/\text{day}$ .
- 2) Thresholds of concern: Class I = 1800  $\mu\text{g}/\text{person}/\text{day}$ , Class II = 540  $\mu\text{g}/\text{person}/\text{day}$ , Class III = 90  $\mu\text{g}/\text{person}/\text{day}$ .
- 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

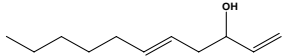
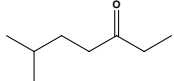
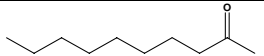
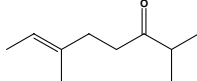
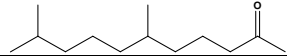
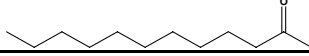
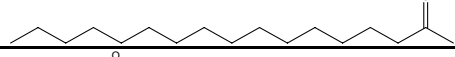
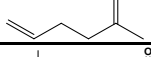
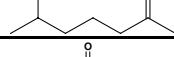
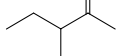
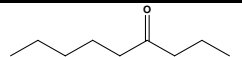
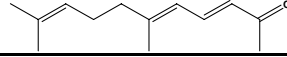
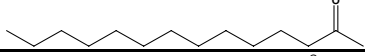
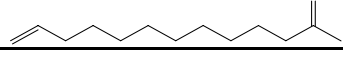
**Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)**

FL-no	EU Register name	Structural formula	MSDI 1) ( $\mu\text{g}/\text{capita}/\text{day}$ )	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)	
09.323	sec-Butyl acetate		0.0012	Class I A3: Intake below threshold	4)	6)	

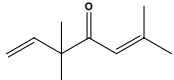
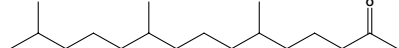
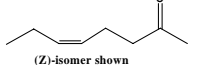
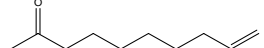
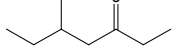
**Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach) (EFSA / FGE.07Rev4)**

FL-no	EU Register name	Structural formula	MSDI 1) ( $\mu\text{g}/\text{capita}/\text{day}$ )	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
09.325	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		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)
02.194	Octa-1,5-dien-3-ol		0.061	Class II A3: Intake below threshold	4)	6)	a)

**Table 3.2: 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) ( $\mu\text{g}/\text{capita}/\text{day}$ )	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
02.211	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)	

**Table 3.2: 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) ( $\mu\text{g}/\text{capita}/\text{day}$ )	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) =  $\mu\text{g}/\text{capita}/\text{day}$ .
  - 2) Thresholds of concern: Class I = 1800  $\mu\text{g}/\text{person}/\text{day}$ , Class II = 540  $\mu\text{g}/\text{person}/\text{day}$ , Class III = 90  $\mu\text{g}/\text{person}/\text{day}$ .
  - 3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
  - 4) No safety concern based on intake calculated by the MSDI approach of the named compound.
  - 5) Data must be available on the substance or closely related substances to perform a safety evaluation.
  - 6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).
  - 7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
  - 8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.
- a) Evaluated in FGE.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
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
PCE	Polychromatic erythrocyte
SCE	Sister chromatic exchange
SCF	Scientific Committee on Food

WHO World Health Organisation