European Food Safety Authority

The EFSA Journal (2009) ON-879, 1-27

SCIENTIFIC OPINION

Flavouring Group Evaluation 213: alpha,beta-Unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19[1]

Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

(Question No EFSA-Q-2008-768)

Adopted on 27 november 2008

PANEL MEMBERS

Arturo Anadon, David Bell, Mona-Lise Binderup, Wilfried Bursch, Laurence Castle, Riccardo Crebelli, Karl-Heinz Engel, Roland Franz, Nathalie Gontard, Thomas Haertle, Trine Husøy, Klaus-Dieter Jany, Catherine Leclercq, Jean Claude Lhuguenot, Wim Mennes, Maria Rosaria Milana, Karla Pfaff, Kettil Svensson, Fidel Toldra, Rosemary Waring, Detlef Wölfle.

SUMMARY

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) was asked to provide scientific advise for 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 asked to evaluate flavouring substances using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000.

The present Flavouring Group Evaluation 213 (FGE.213) concerns 26 substances. The 26 substances correspond to subgroup 2.7 of FGE.19. Twenty-three of the substances are alpha,beta-unsaturated alicyclic ketones [FL-no: 07.008, 07.010, 07.014, 07.041, 07.047, 07.056, 07.057, 07.075, 07.076, 07.080, 07.083, 07.089, 07.108, 07.109, 07.117, 07.118, 07.119, 07.120, 07.127, 07.136, 07.168, 07.200 and 16.044] and three are precursors for such ketones [FL-no: 02.106, 09.305 and 09.525].

[1] For citation purposes: Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids on a request from the Comission on Flavouring Group Evaluation 213: alpha,beta-Unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19. The EFSA Journal (2009) ON-879, 1-27.

The Panel concluded that ethyl maltol [FL-no: 07.047], 3-ethylcyclopentan-1,2-dione [FL-no: 07.057] and the nine structurally related substances [FL-no: 07.117, 07.118, 07.119, 07.120, 07.056, 07.168, 07.075, 07.076 and 07.080] can be evaluated through the Procedure.

For maltol [FL-no: 07.014], a micronucleus assay after oral application is required in addition to an *in vivo* Comet assay in order to clarify the genotoxic potential. A combination of the micronucleus assay and the Comet assay in a single study would also be acceptable.The outcome would also be applicable to maltyl isobutyrate [FL-no: 09.525].

Due to the structural similarities and to the lack of data, the remaining substances (including two precursors of a ketone) [FL-no: 02.106, 07.008, 07.010, 07.041, 07.083, 07.089, 07.108, 07.109, 07.127, 07.136, 07.200, 09.305 and 16.044] cannot be evaluated through the Procedure. Additional data on genotoxicity are required for representatives of these 13 substances according to the Genotoxicity Test Strategy for Substances Belonging to Subgroups of FGE.19.

Key words: Alicyclic alpha,beta-unsaturated ketones, flavouring substances, safety evaluation.

TABLE OF CONTENTS

BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other flavouring 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 2008/478/EC (EC, 2008a). 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, 1999). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

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

Flavouring Group Evaluation 19 (FGE.19) contains 360 flavouring substances from the EU Register being alpha,beta-unsaturated aldehydes or ketones and precursors which could give rise to such carbonyl substances via hydrolysis and/or oxidation (EFSA, 2008b).

The alpha,beta-unsaturated aldehyde and ketone structures were considered by the Panel to be structural alerts for genotoxicity. The Panel noted that there were limited genotoxicity data on these flavouring substances but that positive genotoxicity studies were identified for some substances in the group.

The alpha,beta-unsaturated carbonyls were subdivided into 28 subgroups on the basis of structural similarity (EFSA, 2008b). In an attempt to decide which of the substances could go through the Procedure, a (quantitative) structure-activity relationship (Q)SAR prediction of the genotoxicity of these substances was undertaken considering a number of models (DEREKfW, TOPKAT, DTU-NFI MultiCASE Models and ISS Local Models (Gry et al., 2007)).

The Panel noted that for most of these models internal and external validation has been performed, but considered that the outcome of these validations was not always extensive enough to appreciate the validity of the predictions of these models for these alpha,beta-unsaturated carbonyls. Therefore, the Panel considered it inappropriate to totally rely on (Q)SAR predictions at this point in time and decided not to take substances through the Procedure based on negative (Q)SAR predictions only.

The Panel took note of the (Q)SAR predictions by using two ISS Local Models (Benigni & Netzeva, 2007a; Benigni & Netzeva, 2007b) and four DTU-NFI MultiCASE Models (Gry et al., 2007; Nikolov et al., 2007) and the fact that there are available data on genotoxicity, *in vitro* and *in vivo*, as well as data on carcinogenicity for several substances. The Panel decided that 11 subgroups (1.1.2, 1.1.3, 1.1.4, 2.4, 2.6, 2.7, 3.1, 3.3, 4.1, 4.2 and 4.4) (EFSA, 2008b) should be further examined to determine whether evaluation through the Procedure is feasible. Corresponding to these 11 subgroups 11 Flavouring Group Evaluations (FGEs) were established (FGE.201, 202, 203,

210, 212, 213, 214, 216, 217, 218 and 220). If the Panel concludes for any substances in these 11 FGEs that they cannot be evaluated using the Procedure then it has to be decided if there is a safety concern for certain substances or if additional data are required in order to finalise the evaluation. If the Panel concludes that a genotoxic potential can be ruled out for the substances they will be merged with structurally related substances in other FGEs and evaluated using the Procedure.

TERMS OF REFERENCE

European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances prior to their authorisation and inclusion in a community list according to Commission Regulation (EC) No 1565/2000 (EC, 2000a).

ACKNOWLEDGEMENTS

European Food Safety Authority wishes to thank the members of the Working Groups on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Wilfried Bursch, Angelo Carere, Riccardo Crebelli, Karl-Heinz Engel, Henrik Frandsen, Jørn Gry, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Catherine Leclercq, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Gerard Pascal, Iona Pratt, Gerrit Speijers, Harriet Wallin.

ASSESSMENT

1. Presentation of the Substances in the Flavouring Group Evaluation 213

1.1. Description

The present Flavouring Group Evaluation 213 (FGE.213) concerns 26 substances, which are listed in Table 1.). The 26 substances correspond to subgroup 2.7 of FGE.19 (EFSA, 2008b). Twenty-three of the substances are alpha,beta-unsaturated alicyclic ketones [FL-no: 07.008, 07.010, 07.014, 07.041, 07.047, 07.056, 07.057, 07.075, 07.076, 07.080, 07.083, 07.089, 07.108, 07.109, 07.117, 07.118, 07.119, 07.120, 07.127, 07.136, 07.168, 07.200 and 16.044] and three are precursors for such ketones [FL-no: 02.106, 09.305 and 09.525]. Two of these substances [FL-no: 02.106 and 09.305] are precursors of the ketone beta-ionone [FL-no: 07.008] and one [FL-no: 09.525] is a precursor of the ketone maltol [FL-no: 07.014]. Ten of the ketones have the possibility for keto-enol tautomerism [FL-no: 07.056, 07.057, 07.075, 07.076, 07.080, 07.117, 07.118, 07.119, 07.120 and 07.168]. Based on experimental evidence for other diketones it is anticipated that the enol is the predominant form.

A summary of their current evaluation status by the JECFA is given in Table 2 (JECFA, 1999a; JECFA, 2001b; JECFA, 2006a; JECFA, 2007a).

The alpha,beta-unsaturated aldehyde and ketone structures are considered by the Panel to be structural alerts for genotoxicity (EFSA, 2008b). Accordingly, the available data on genotoxic or carcinogenic activity for the 23 alpha,beta-unsaturated ketones [FL-no: 07.008, 07.010, 07.014, 07.041, 07.047, 07.056, 07.057, 07.075, 07.076, 07.080, 07.083, 07.089, 07.108, 07.109, 07.117, 07.118, 07.119, 07.120, 07.127, 07.136, 07.168, 07.200 and 16.044], corresponding to 26 substances in FGE.213, will be considered in this FGE.

The Panel has also taken into consideration the outcome of the predictions from five selected (Q)SAR models (Benigni & Netzeva, 2007a; Gry et al., 2007; Nikolov et al., 2007) on the 23 ketones [FL-no: 07.008, 07.010, 07.014, 07.041, 07.047, 07.056, 07.057, 07.075, 07.076, 07.080, 07.083, 07.089, 07.108, 07.109, 07.117, 07.118, 07.119, 07.120, 07.127, 07.136, 07.168, 07.200 and 16.044]. The 23 ketones and their (Q)SAR predictions are shown in Table 3.

2. Toxicity

2.1. (Q)SAR Predictions

In Table 3 the outcomes of the (Q)SAR predictions for possible genotoxic activity in five *in vitro* (Q)SAR models (ISS Local Model-Ames test, DTU-NFI MultiCASE-Ames test, -Chromosomal aberration test in Chinese hamster ovary cells (CHO), -Chromosomal aberration test in Chinese hamster lung cells (CHL), and -Mouse lymphoma test) are presented.

Maltol [FL-no: 07.014], ethyl maltol [FL-no: 07.047] and nootkatone [FL-no: 07.089] were predicted positive with the MultiCASE model on chromosomal aberrations in CHL cells. All other predictions were negative or the substances were out of domain (See Table 3).

2.2. Carcinogenicity Studies

In a combined study of developmental toxicity and carcinogenicity, three successive generations of male and female Charles River CD-COBS rats received 3-ethyl-2-hydroxy-2-cyclopenten-1-one (due to keto-enol tautomerism this substance can exist as two isomers; the keto-isomer is 3-ethylcyclopentan-1,2-dione [FL-no: 07.057], a synonym for the keto-isomer is ethylcyclopentenolone) in the basal diet at doses of 0 (untreated control), 0 (propylene glycol control), 30, 80 or 200 mg/kg body weight (bw) per day. The F_1 generation was initially exposed *in utero,* subsequently via the dams' milk until weaning, and then treated for two years and bred twice (at days 99 and 155). In the F_1 generation, there were 100 animals of each sex in the untreated control group and 50 of each sex in the propylene glycol control and 3-ethyl-2-hydroxy-2-cyclopenten-1-one-treated groups. Survival, clinical symptoms, food consumption, reproductive performance, and haematological and clinical chemical parameters were not adversely affected. Gross pathological and histopathological examination revealed no significant treatment-related effects. The incidence of benign or malignant tumours in treated animals was similar to that in controls. The no observed effect level (NOEL) was 200 mg/kg bw per day (King et al., 1979).

The Panel concluded that 3-ethyl-2-hydroxy-2-cyclopenten-1-one (3-ethylcyclopentan-1,2-dione [FL-no: 07.057]) was not carcinogenic in rats under the study conditions.

Groups of 25 male and female rats were fed for two years on diets containing ethyl maltol [FL-no: 07.047] calculated to deliver 0, 50, 100 and 200 mg ethyl maltol/kg bw/day. No abnormalities were seen as regards survival, clinical appearance, growth rate or food consumption, clinical chemistry, haematology and urinalysis. No histopathological changes and no increases in neoplasms were seen after the treatment with ethyl maltol (Gralla et al., 1969).

Study validation and results are presented in Table 4.

The Panel noted that this study was performed before OECD test guidelines 451/453 (1981) have been established and it does not meet the criteria of these OECD test guidelines with respect to the number of animals. However, the Panel concluded that ethyl maltol was not carcinogenic in rats in this study.

2.3. Genotoxicity Studies

In subgroup 2.7, there are studies available for four substances. For maltol [FL-no: 07.014] eight *in vitro* and three *in vivo* studies have been evaluated. For ethyl maltol [FL-no:07.047] two *in vitro* and one *in vivo* study were evaluated. Numbers of evaluated *in vitro* studies concerning beta-ionone [FL-no: 07.008] and 3-methylcyclopentan-1,2-dione [FL-no: 07.056] were two and one, respectively.

Study validation and results are presented in Table 5 and 6.

In studies which were considered valid, the following results were obtained:

Maltol induced gene mutations in bacteria (Bjeldanes & Chew, 1979) and sister chromatid exchanges (SCE) in human lymphocytes (Jansson et al., 1986). *In vivo*, maltol induced micronuclei in mouse bone marrow after intraperitoneal application (Hayashi et al., 1988). Negative results were obtained in a sex-linked recessive lethal mutation assay in *Drosophila* (Mason et al., 1992). However, the micronucleus assay is considered more relevant than the *Drosophila* assay.

Ethyl maltol induced gene mutations in bacteria (Bjeldanes & Chew, 1979).

A negative result was obtained with beta-ionone in a gene mutation assay in bacteria (Mortelmans et al., 1986).

The validity of other studies was limited or could not be evaluated.

2.4. Conclusion on Genotoxicity and Carcinogenicity

For the substances of this group, the applicabiltity of the (Q)SAR models is very limited since many substances were out of domain in the ISS model and the MultiCASE models.

Two substances [FL-no: 02.106 and 09.305] are precursors of beta-ionone [FL-no: 07.008] and therefore, the conclusions for these two precursors could be based on the conclusions drawn for the corresponding ketone [FL-no: 07.008]. Maltyl isobutyrate [FL-no: 09.525] is a precursor of maltol [FL-no: 07.014], and accordingly, the conclusion for maltyl isobutyrate could be based on the conclusion drawn for maltol.

Maltol and ethyl maltol were considered separately because in contrast to the other substances in this subgroup they contain a ring-oxygen atom.

There is a carcinogenicity study on ethyl maltol [FL-no: 07.047] in rats. Although the number of animals per group were lower than suggested in OECD guidelines they were in accordance with the standards at the time the study was performed and the Panel concluded that the result could overrule the mutagenicity observed with ethyl maltol in bacteria but not the mutagenicity observed with maltol [FL-no: 07.014] *in vitro* and *in vivo*. Since the micronuclei induced by maltol in mice were analysed after intraperitoneal application, a micronucleus assay after oral application is required in addition to an *in vivo* Comet assay in order to clarify the genotoxic potential of maltol. A combination of the micronucleus assay and the Comet assay in a single study would also be acceptable. The result of these assays would also be applicable to maltyl isobutyrate [FL-no: 09.525], which is a precursor of maltol.

No carcinogenicity was observed with 3-ethyl-2-hydroxy-2-cyclopenten-1-one [FL-no: 07.057] in rats. This substance was considered representative for nine substances [FL-no: 07.117, 07.118, 07.119, 07.120, 07.056, 07.168, 07.075, 07.076 and 07.080]. Therefore, the Panel concluded that the structural alert for genotoxicity is overruled for 3-ethyl-2-hydroxy-2-cyclopenten-1-one [FL-no: 07.057] as well as for the nine structurally related substances.

For the 13 remaining substances (including two precursors of a ketone) [FL-no: 02.106, 07.008, 07.010, 07.041, 07.083, 07.089, 07.108, 07.109, 07.127, 07.136, 07.200, 09.305 and 16.044] a genotoxic potential could not be ruled out since only one valid negative bacterial genotoxicity study on [FL-no: 07.008] is available for these substances.

3. Conclusions

The Panel concluded that ethyl maltol [FL-no: 07.047], 3-ethylcyclopentan-1,2-dione [FL-no: 07.057] and the nine structurally related substances [FL-no: 07.117, 07.118, 07.119, 07.120, 07.056, 07.168, 07.075, 07.076 and 07.080] can be evaluated through the Procedure.

For maltol [FL-no: 07.014], a micronucleus assay after oral application is required in addition to an *in vivo* Comet assay in order to clarify the genotoxic potential. A combination of the micronucleus

assay and the Comet assay in a single study would also be acceptable. The outcome would also be applicable to maltyl isobutyrate [FL-no: 09.525].

The remaining 13 substances (including two precursors of a ketone) [FL-no: 02.106, 07.008, 07.010, 07.041, 07.083, 07.089, 07.108, 07.109, 07.127, 07.136, 07.200, 09.305 and 16.044] cannot presently be evaluated through the Procedure. Additional data on genotoxicity are required for representatives of these 13 substances, according to the Genotoxicity Test Strategy for Substances Belonging to Subgroups of FGE.19 (EFSA, 2008bb).

TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 213

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 213

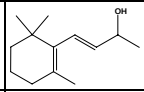
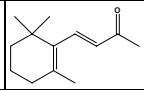
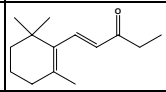
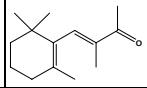
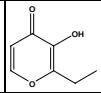
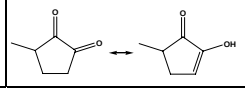
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)
02.106 392	4-(2,2,6-Trimethyl-1-cyclohexenyl)but-3-en-2-ol		3625 22029-76-1	Liquid $C_{13}H_{22}O$ 194.32		107 (4 hPa) IR 92 %	1.499 0.927-0.933
07.008 389	beta-Ionone		2595 142 14901-07-6	Liquid $C_{13}H_{20}O$ 192.30	Insoluble 1 ml in 3 ml 70% alcohol	239 IR 95 %	1.517-1.522 0.940-0.947
07.010 399	Methyl-beta- ionone		2712 144 127-43-5	Liquid $C_{14}H_{22}O$ 206.33		238-242 IR 88 %	1.503-1.508 0.930-0.935
07.014 1480	Maltol		2656 148 118-71-8	Solid $C_6H_6O_3$ 126.11	Very slightly soluble Soluble	159-162 NMR 98 %	n.a. n.a.
07.041	beta-Isomethylionone		650 79-89-0	Solid $C_{14}H_{22}O$ 206.32	1 ml in 1 ml	334 62 95 %	n.a. n.a.
07.047 1481	Ethyl maltol		3487 692 4940-11-8	Solid $C_7H_8O_3$ 140.14	Soluble Soluble	89-93 NMR 99 %	n.a. n.a.
07.056 418	3-Methylcyclopentan-1,2-dione		2700 758 80-71-7	Solid $C_6H_8O_2$ 112.13	1 g in 72 ml water 1 g in 5 ml 90% alcohol	104-108 IR 95 %	

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 213

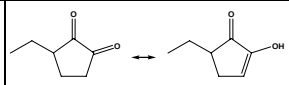
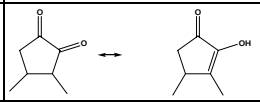
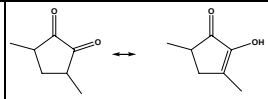
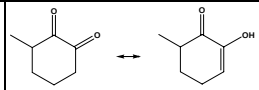
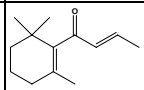
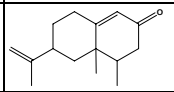
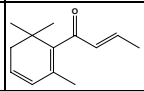
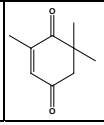
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)
07.057 419	3-Ethylcyclopentan-1,2-dione		3152 759 21835-01-8	Solid $C_7H_{10}O_2$ 126.16	Miscible	78-80 (5 hPa) 36-43 IR 90 %	1.47-1.48 (25°) 1.060-1.066
07.075 420	3,4-Dimethylcyclopentan-1,2-dione		3268 2234 13494-06-9	Solid $C_7H_{10}O_2$ 126.16		66 (1 hPa) 68-72 IR 98 %	
07.076 421	3,5-Dimethylcyclopentan-1,2-dione		3269 2235 13494-07-0	Solid $C_7H_{10}O_2$ 126.16	Insoluble	 87-93 MS 98 %	
07.080 425	3-Methylcyclohexan-1,2-dione		3305 2311 3008-43-3	Solid $C_7H_{10}O_2$ 126.16	Insoluble	69-72 (1 hPa) 57-63 IR 98 %	
07.083 384	beta-Damascone		3243 2340 23726-92-3	Liquid $C_{13}H_{20}O$ 192.30	1 ml in 10 ml 95%	67-70 IR 90 %	1.496-1.501 0.934-0.942 (20°)
07.089 1398	Nootkatone		3166 11164 4674-50-4	Liquid $C_{15}H_{22}O$ 218.35	Slightly soluble Soluble	73-103 (1 hPa) NMR 93 %	1.510-1.523 1.003-1.032
07.108 387	beta-Damascenone		3420 11197 23696-85-7	Liquid $C_{13}H_{18}O$ 190.28	1 ml in 10 ml 95% alcohol	60 IR 98 %	1.508-1.514 0.945-0.952 (20°)
07.109 1857	2,6,6-Trimethylcyclohex-2-en-1,4-dione		3421 11200 1125-21-9	Solid $C_9H_{12}O_2$ 152.2	Slightly soluble Soluble	222 23-28 IR NMR 98 %	n.a. n.a.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 213

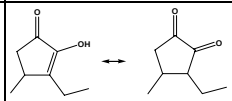
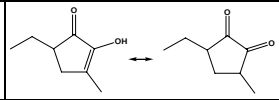
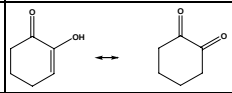
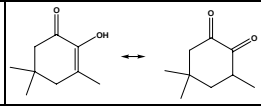
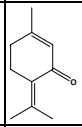
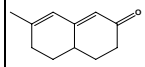
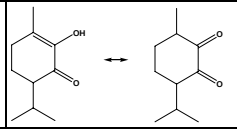
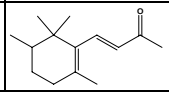
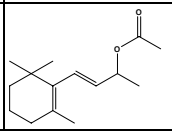
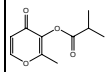
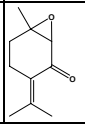
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)
07.117 422	3-Ethyl-2-hydroxy-4-methylcyclopent-2-en-1-one		3453 11077 42348-12-9	Liquid $C_8H_{12}O_2$ 140.18	Slightly insoluble Miscible	 NMR 99 %	1.481-1.487 1.055-1.061
07.118 423	5-Ethyl-2-hydroxy-3-methylcyclopent-2-en-1-one		3454 11078 53263-58-4	Liquid $C_8H_{12}O_2$ 140.18	Slightly soluble Soluble	 NMR 99 %	1.478-1.484 1.053-1.060
07.119 424	2-Hydroxycyclohex-2-en-1-one		3458 11046 10316-66-2	Solid $C_6H_8O_2$ 112.13	Soluble Soluble	53 (3 hPa) 35-38 IR 99.3 %	
07.120 426	2-Hydroxy-3,5,5-trimethylcyclohex-2-en-1-one		3459 11198 4883-60-7	Solid $C_9H_{14}O_2$ 154.21	Slightly soluble Soluble	90-100 (20 hPa) 88 99 %	
07.127 757	p-Mentha-1,4(8)-dien-3-one		3560 11189 491-09-8	Liquid $C_{10}H_{14}O$ 150.22	Insoluble Miscible	233 MS 95 %	1.472-1.478 0.976-0.983
07.136 1405	4,4a,5,6-Tetrahydro-7-methylnapthalen-2(3H)-one		3715 34545-88-5	Solid $C_{11}H_{14}O$ 162.23	Insoluble Soluble	n.a. 36-37 IR 99 %	n.a. n.a.
07.168	2-Hydroxypiperitone 6)		4143 490-03-9	Solid $C_{10}H_{16}O_2$ 168.24	Slightly soluble 1 ml in 1 ml	233 82 NMR MS 98 %	n.a. n.a.

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 213

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)
07.200	4-(2,5,6,6-Tetramethyl-1-cyclohexenyl)but-3-en-2-one 6)		79-70-9	Liquid $C_{14}H_{22}O$ 206.33	Practically insoluble or insoluble 1 ml in 1 ml	108 (2 hPa) MS 95 %	1.515-1.521 0.943-0.949
09.305 1409	beta-Ionyl acetate 6)		3844 10702 22030-19-9	Liquid $C_{15}H_{24}O_2$ 236.35	Insoluble Soluble	120 (3 hPa) NMR 92 %	1.474-1.484 0.934-0.944
09.525 1482	Maltyl isobutyrate		3462 10739 65416-14-0	Liquid $C_{10}H_{12}O_4$ 196.20	Insoluble Soluble	100 (0.01 hPa) IR 96 %	1.493-1.501 1.140-1.153
16.044 1574	Piperitenone oxide 6)		4199 10508 35178-55-3	Solid $C_{10}H_{14}O_2$ 166.22	Soluble Soluble	 25 NMR MS 95 %	n.a. n.a.

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.

n.a.: not applicable.

TABLE 2: SUMMARY OF SAFETY EVALUATION APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH) (JECFA, 1999A; JECFA, 2001B; JECFA, 2006A; JECFA, 2007A)

Table 2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

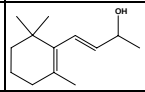
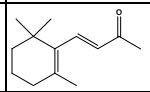
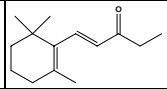
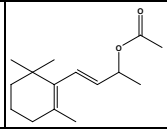
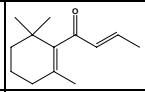
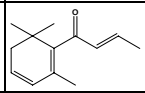
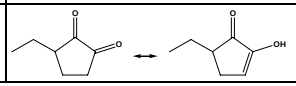
FL-no JECFA-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day) EU USA	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]
02.106 392	4-(2,2,6-Trimethyl-1-cyclohexenyl)but-3-en-2-ol		0.73 0.1	Class I A3: Intake below threshold	4)
07.008 389	beta-Ionone		130 100	Class I A3: Intake below threshold	4)
07.010 399	Methyl-beta- ionone		5.4 0.2	Class I A3: Intake below threshold	4)
09.305 1409	beta-Ionyl acetate		ND 9	Class I A3: Intake below threshold	4)
07.083 384	beta-Damascone		37 10	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)
07.108 387	beta-Damascenone		73 5	Class I B3: Intake below threshold, B4: Adequate NOAEL exists	4)
07.057 419	3-Ethylcyclopentan-1,2-dione		32 23	Class II A3: Intake below threshold	4)

Table 2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

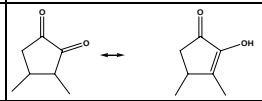
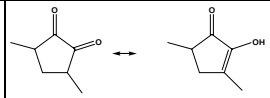
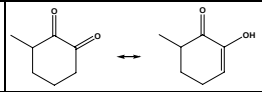
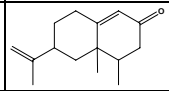
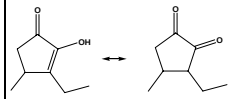
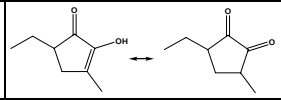
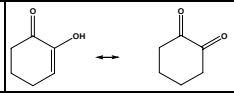
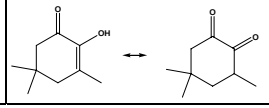
FL-no JECFA-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day) EU USA	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]
07.075 420	3,4-Dimethylcyclopentan-1,2-dione		30 2	Class II A3: Intake below threshold	4)
07.076 421	3,5-Dimethylcyclopentan-1,2-dione		35 29	Class II A3: Intake below threshold	4)
07.080 425	3-Methylcyclohexan-1,2-dione		1.3 8	Class II A3: Intake below threshold	4)
07.089 1398	Nootkatone		130 20	Class II A3: Intake below threshold	4)
07.117 422	3-Ethyl-2-hydroxy-4-methylcyclopent-2-en-1-one		ND 0.17	Class II A3: Intake below threshold	4)
07.118 423	5-Ethyl-2-hydroxy-3-methylcyclopent-2-en-1-one		ND 0.38	Class II A3: Intake below threshold	4)
07.119 424	2-Hydroxycyclohex-2-en-1-one		0.049 0.76	Class II A3: Intake below threshold	4)
07.120 426	2-Hydroxy-3,5,5-trimethylcyclohex-2-en-1-one		1.2 2	Class II A3: Intake below threshold	4)

Table 2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

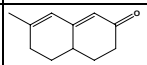
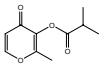
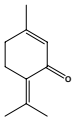
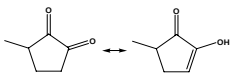
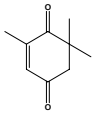
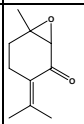
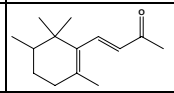
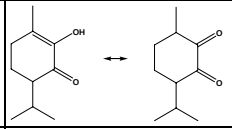
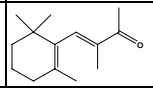
FL-no JECFA-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day) EU USA	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]
07.136 1405	4,4a,5,6-Tetrahydro-7-methylnapthalen-2(3H)-one		ND 0.04	Class II A3: Intake below threshold	4)
09.525 1482	Maltyl isobutyrate		20 38	Class II A3: Intake below threshold	4)
07.127 757	p-Mentha-1,4(8)-dien-3-one		0.012 0.01	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	4)
07.014 1480	Maltol		3060 2898	Class II A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)
07.047 1481	Ethyl maltol		1580 6692	Class II A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)
07.056 418	3-Methylcyclopentan-1,2-dione		570 710	Class II A3: Intake above threshold, A4: Not endogenous, A5: Adequate NOAEL exists	4)
07.109 1857	2,6,6-Trimethylcyclohex-2-en-1,4-dione		50	Class II No evaluation	
16.044 1574	Piperitenone oxide		0.012 0.2	Class III A3: Intake below threshold	4)

Table 2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

FL-no JECFA-no	EU Register name	Structural formula	MSDI 1) (µg/*capita*/day) EU USA	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]
07.200	4-(2,5,6,6-Tetramethyl-1-cyclohexenyl)but-3-en-2-one		0.012		Not evaluated by the JECFA.
07.168	2-Hydroxypiperitone		0.0012		Not evaluated by the JECFA.
07.041	beta-Isomethylionone		0.011		Not evaluated by the JECFA.

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

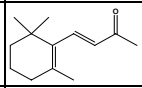
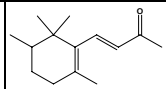
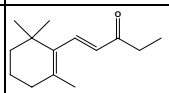
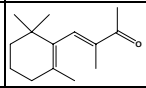
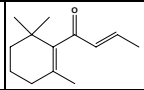
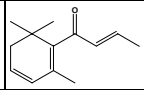
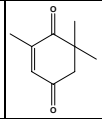
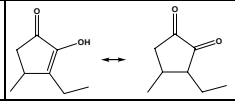
2) *Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day.*

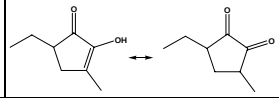
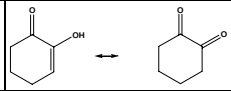
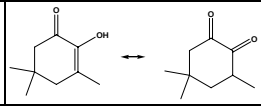
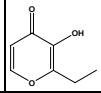
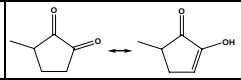
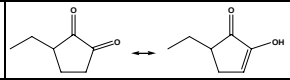
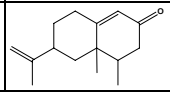
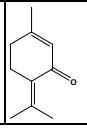
3) *Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.*

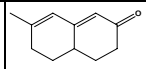
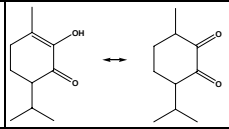
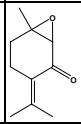
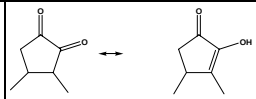
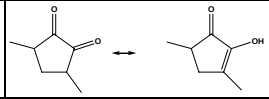
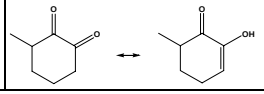
4) *No safety concern based on intake calculated by the MSDI approach of the named compound.*

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

TABLE 3: (Q)SAR PREDICTIONS ON MUTAGENICITY IN FIVE MODELS FOR 23 KETONES FROM SUBGROUP 2.7

FL-no JECFA-no	Sub- group	EU Register name	Structural formula	FEMA no CoE no CAS no	ISS Local Model Ames Test TA100	MultiCASE Ames test	MultiCASE Mouse lymphoma test	MultiCASE Chromosomal aberration test in CHO	MultiCASE Chromosomal aberration test in CHL
07.008 389	2.7	beta-Ionone		2595 142 14901-07-6	NEG	NEG	NEG	NEG	EQU
07.200	2.7	4-(2,5,6,6-Tetramethyl-1-cyclohexenyl)but-3-en-2-one		- - 79-70-9	NEG	NEG	NEG	NEG	EQU
07.010 399	2.7	Methyl-beta- ionone		2712 144 127-43-5	NEG	NEG	OD	OD	EQU
07.041	2.7	beta-Isomethylionone		- 650 79-89-0	NEG	EQU	NEG	NEG	NEG
07.083 384	2.7	beta-Damascone		3243 2340 23726-92-3	OD	NEG	OD	OD	EQU
07.108 387	2.7	beta-Damascenone		3420 11197 23696-85-7	OD	NEG	OD	OD	EQU
07.109	2.7	2,6,6-Trimethylcyclohex-2-en-1,4-dione		3421 11200 1125-21-9	OD	NEG	OD	NEG	EQU
07.117 422	2.7	3-Ethyl-2-hydroxy-4-methylcyclopent-2-en-1-one		3453 11077 42348-12-9	OD	NEG	NEG	OD	NEG

FL-no JECFA-no	Sub- group	EU Register name	Structural formula	FEMA no CoE no CAS no	ISS Local Model Ames Test TA100	MultiCASE Ames test	MultiCASE Mouse lymphoma test	MultiCASE Chromosomal aberration test in CHO	MultiCASE Chromosomal aberration test in CHL
07.118 423	2.7	5-Ethyl-2-hydroxy-3-methylcyclopent-2-en-1-one		3454 11078 53263-58-4	OD	NEG	NEG	NEG	NEG
07.119 424	2.7	2-Hydroxycyclohex-2-en-1-one		3458 11046 10316-66-2	OD	OD	NEG	OD	NEG
07.120 426	2.7	2-Hydroxy-3,5,5-trimethylcyclohex-2-en-1-one		3459 11198 4883-60-7	OD	NEG	NEG	OD	NEG
07.014 1480	2.7	Maltol		2656 148 118-71-8	OD	OD	NEG	OD	POS
07.047 1481	2.7	Ethyl maltol		3487 692 4940-11-8	OD	OD	NEG	OD	POS
07.056 418	2.7	3-Methylcyclopentan-1,2-dione		2700 758 80-71-7	OD	NEG	NEG	OD	NEG
07.057 419	2.7	3-Ethylcyclopentan-1,2-dione		3152 759 21835-01-8	OD	NEG	NEG	OD	NEG
07.089 1398	2.7	Nootkatone		3166 11164 4674-50-4	OD	NEG	NEG	NEG	POS
07.127 757	2.7	p-Mentha-1,4(8)-dien-3-one		3560 11189 491-09-8	OD	NEG	OD	NEG	NEG

FL-no JECFA-no	Sub- group	EU Register name	Structural formula	FEMA no CoE no CAS no	ISS Local Model Ames Test TA100	MultiCASE Ames test	MultiCASE Mouse lymphoma test	MultiCASE Chromosomal aberration test in CHO	MultiCASE Chromosomal aberration test in CHL
07.136 1405	2.7	4,4a,5,6-Tetrahydro-7-methylnapthalen-2(3H)-one		3715 34545-88-5	OD	NEG	NEG	NEG	OD
07.168	2.7	2-Hydroxypiperitone		4143 490-03-9	OD	NEG	NEG	NEG	NEG
16.044 1574	2.7	Piperitenone oxide		4199 10508 35178-55-3	OD	NEG	OD	OD	OD
07.075 420	2.7	3,4-Dimethylcyclopentan-1,2-dione		3268 2234 13494-06-9	OD	NEG	NEG	OD	NEG
07.076 421	2.7	3,5-Dimethylcyclopentan-1,2-dione		3269 2235 13494-07-0	OD	NEG	NEG	NEG	NEG
07.080 425	2.7	3-Methylcyclohexan-1,2-dione		3305 2311 3008-43-3	OD	NEG	NEG	OD	NEG

Column 2: Structure group 2.7: alpha,beta-unsaturated alicyclic ketones.

Column 6: Local model on aldehydes and ketones, Ames TA100 (NEG: Negative; POS: Positive; OD: Out of domain).

Column 7: MultiCASE Ames test (OD: Out of domain; POS: Positive; NEG: Negative; EQU: Equivocal).

Column 8: MultiCASE Mouse lymphoma test (OD: Out of domain; POS: Positive; NEG: Negative; EQU: Equivocal).

Column 9 MultiCASE Chromosomal aberration in CHO (OD: Out of domain; POS: Positive; NEG: Negative; EQU: Equivocal).

Column 10: MultiCASE Chromosomal aberration in CHL (OD: Out of domain; POS: Positive; NEG: Negative; EQU: Equivocal).

OD, out of applicability domain: not matching the range of conditions where a reliable prediction can be obtained in this model. These conditions may be physicochemical, structural, biological, etc.

TABLE 4: CARCINOGENICITY STUDIES

Table 4: Carcinogenicity Studies

Chemical Name [FL-no]	Species; Sex No./Group	Route	Dose levels	Duration	Results	Reference	Comments[a]
Ethyl maltol [07.047]	Rats; Male , Female 25/sex/group	Diet	0, 50, 100 and 200 mg/kg bw/day	2 years	Males: No increase in tumour incidences. Females: No increase in tumour incidences.	(Gralla et al., 1969)	Valid. The study was performed before the introduction of OECD guidelines but is however considered valid.The NOAEL was 200 mg/kg bw/day, the highest dose tested.
3-Ethylcyclopentan-1,2-dione [07.057]	Rats; Male , Female 50/sex/group	Diet	0, 30, 80 and 200 mg/kg bw/day	2 years	Males: No increase in tumour incidences. Females: No increase in tumour incidences.	(King et al., 1979)	Valid. The study was performed before the introduction of OECD guidelines but is however considered valid.The NOAEL was 200 mg/kg bw/day, the highest dose tested.

a: Validity of carcinogenicity studies:

Valid.

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

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

Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).

TABLE 5: GENOTOXICITY (*IN VITRO*)

Table 5: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments [d]
beta-Ionone [07.008]	Gene mutation (preincubation)	*S. typhimurium* TA98, TA100, TA1535, TA1537	1-180 µg/plate	Negative[a]	(Mortelmans et al., 1986)	Valid.
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 mmol/plate	Negative[a]	(Florin et al., 1980)	Insufficient validity (spot test, not according to OECD guideline, methods and results insufficiently reported).
3-Methylcyclopentan-1,2-dione [07.056]	Reverse mutation	*S. typhimurium* TA1535	10 000 µg/plate	Negative[b]	(Heck et al., 1989)	Validity cannot be evaluated (result not reported in detail)
	Unscheduled DNA synthesis	Rat hepatocytes	500 µg/plate	Negative[b]	(Heck et al., 1989)	Validity cannot be evaluated (result not reported in detail).
Maltol [07.014]	Reverse Mutation	*S. typhimurium* TA100	4.44 µmol/plate (560 µg/plate)	Negative[c]	(Kim et al., 1987b)	Insufficient validity (only one concentration was tested with only one bacterial strain without metabolic activation). The main purpose of the study was to investigate antimutagenic effects.
	Reverse Mutation	*S. typhimurium* TA98 and TA100	Up to 3 mg/plate (3,000 µg/plate)	Positive[a]	(Bjeldanes & Chew, 1979)	Valid.
	Reverse Mutation	*S. typhimurium* TA92, TA98, TA100 and TA104	1.5 to 11 µmol/plate (189 to 1,387 µg/plate)	Negative	(Gava et al., 1989)	Limited validity (data not reported in detail).
	Reverse Mutation	*S. typhimurium* TA1535, TA98, TA100 and TA1537	33 to 10,000 µg/plate	Positive[b]	(Mortelmans et al., 1986)	Valid.
	Reverse Mutation	*S. typhimurium* TA97 and TA102	0.1, 0.5, 1, 5, or 10 mg/plate (100, 500, 1,000, 5,000, or 10,000 µg/plate)	Weak Positive[a]	(Fujita et al., 1992)	Result is considered equivocal. Limited validity (the use of only two strains is not according to OECD guideline).
	DNA Damage (SOS Chromotest)	*Escherichia coli PQ*37	5mM (631 µg/ml)	Negative	(Ohshima et al., 1989)	The test system used is considered inappropriate, due to insufficient validity.
	Sister Chromatid Exchange	Chinese hamster ovary cells	Up to 1.5 µmol/ml (12.6 to 189 µg/ml)	Positive[c]	(Gava et al., 1989)	Validity cannot be evaluated (insufficiently reported: number of cells analysed not reported. Statistical test used not reported). SCEs were reported as SCE per chromosome. Effect was less than two-fold compared to control.
	Sister Chromatid Exchange	Human lymphocytes	Up to 1.0 mM (126.11 µg/ml)	Positive	(Jansson et al., 1986)	Validity cannot be evaluated. Relevance of test system for the evaluation of genotoxicity uncertain.
Ethyl maltol [07.047]	Reverse Mutation	*S. typhimurium* TA 1535, TA1537, TA1538, TA98 and TA100	5 concentrations up to cytotoxicity, or max. 3600 µg/plate	Negative[a]	(Wild et al., 1983)	Limited validity (result not reported in detail, no TA102 or *E. Coli*).
	Reverse Mutation	*S. typhimurium* TA98 and TA100	Up to 2 mg/plate (2,000 µg/plate)	Positive[a]	(Bjeldanes & Chew,	Valid.

Table 5: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Reported Result	Reference	Comments [d]
					1979)	

a: With and without metabolic activation.

b: With metabolic activation.

c: Without metabolic activation.

d: Validity of genotoxicity studies:

Valid.

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

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

Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).

TABLE 6: GENOTOXICITY (*IN VIVO*)

Table 6: GENOTOXICITY (*in vivo*)

Chemical Name [FL-no]	Test System	Test Object	Route	Dose	Result	Reference	Comments [a]
Maltol [07.014]	Micronucleus formation	ddY Mouse bone marrow cells	Intraperitoneal	125, 250, or 500 mg/kg	Positive	(Hayashi et al., 1988)	Valid. The induction of micronuclei was up to about 10-fold compared to control.
	Sex-linked Recessive Lethal Mutation	*D. melanogaster*	Feeding	6,000 ppm (6,000 µg/ml)	Equivocal	(Zimmering et al., 1989)	Limited validity (only one exposure level tested). Test system considered of limited relevance.
	Sex-linked Recessive Lethal Mutation	*D. melanogaster*	Feed	10,000 ppm (10,000 µg/ml)	Negative	(Mason et al., 1992)	Valid, however, test system considered of limited relevance.
	Sex-linked Recessive Lethal Mutation	*D. melanogaster*	Injection	0.2 – 0.3 µl, 10,000 ppm (10,000 µg/ml)	Negative	(Mason et al., 1992)	Valid, however, test system considered of limited relevance.
Ethyl maltol [07.047]	Micronucleus formation	NMRI Mouse bone marrow cells	Intraperitoneal	420, 700, or 980 mg/kg	Negative	(Wild et al., 1983)	Limited validity (injected twice; only analysis at one time point; no PCE/NCE ratio reported).
	Micronucleus formation	NMRI Mouse bone marrow cells	Intraperitoneal	980 mg/kg	Negative	(Wild et al., 1983)	Limited validity (single injection, analysis at three time points, no PCE/NCE ratio reported).
	Sex-linked Recessive Lethal Mutation (Basc test)	*D. melanogaster*	Feed	14, 25 or 50 mM	Negative	(Wild et al., 1983)	Limited validity (limited reporting, test system considered of limited relevance).

a: Validity of genotoxicity studies:

Valid.

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

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

Validity cannot be evaluated (e.g. insufficient documentation, short abstract only, too little experimental details provided).

REFERENCES

Benigni, R., Netzeva, T., 2007a. Report on a QSAR model for prediction of genotoxicity of alpha,beta-unsaturated aldehydes in *S. typhimurium* TA 100 and its application for predictions on alpha,beta-unsaturated aldehydes in Flavouring Group Evaluation 19 (FGE.19). Unpublished report submitted by FLAVIS Secretariat to EFSA.

Benigni, R., Netzeva, T., 2007b. Report on a QSAR model for prediction of genotoxicity of alpha,beta-unsaturated ketones in *S. typhimurium* TA 100 and its application for predictions on alpha,beta-unsaturated aldehydes in Flavouring Group Evaluation 19 (FGE.19). Unpublished report submitted by FLAVIS Secretariat to EFSA.

Bjeldanes, L.F., Chew, H., 1979. Mutagenicity of 1,2-dicarbonyl compounds: maltol, kojic acid, diacetyl and related substances. Mutat. Res. 67, 367-371.

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

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

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

EC, 2002b. Commission Regulation No 622/2002 of 11 April 2002 establishing deadlines for the submission of information for the evaluation of chemically defined flavouring substances used in or on foodstuffs. Official Journal of the European Communities 12.4.2002, L 95, 10-11.

EC, 2008a. Commission Decision 2008/478/EC of 17 June 2008 amending Decision 1999/217/EC as regards the register of flavouring substances used in or on foodstuffs. Official Journal of the European Union 24.6.2008, L 163, 42.

EFSA, 2008b. Minutes of the 26th Plenary meeting of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food, Held in Parma on 27 - 29 November 2007. Parma, 7 January 2008. [Online]. Available: http://www.efsa.europa.eu/EFSA/Event_Meeting/afc_minutes_26thplen_en.pdf

EFSA, 2008bb. Genotoxicity Test Strategy for Substances belonging to Subgroups of FGE.19 - Statement of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal (2008) 854, 1-5. [online]. Available: http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902211354.htm

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18, 219-232.

Fujita, H., Sumi, C., Sasaki, M., 1992. [Mutagenicity test of food additives with *Salmonella typhimurium* TA97 and TA102]. Ann. Rep. Tokyo Metrop. Res. Lab. Public Health 43, 219-227. (In Japanese)

Gava, C., Perazzolo, M., Zentilin, L., Levis, A.G., Corain, B., Bombi, G.G., Palumbo, M., Zatta, P., 1989. Genotoxic potentiality and DNA-binding properties of acetylacetone, maltol, and their aluminum(III) and chromium(III) neutral complexes. Toxicol. Environ. Chem. 22(1-4), 149-157.

Gralla, E.J., Stebbins, R.B., Coleman, G.L., Delahunt, C.S., 1969. Toxicity studies with ethyl maltol. Toxicol. App. Pharmacol. 15, 604-613.

Gry, J., Beltoft, V., Benigni, R., Binderup, M.-L., Carere, A., Engel, K.-H., Gürtler, R., Jensen, G.E., Hulzebos, E., Larsen, J.C., Mennes, W., Netzeva, T., Niemelä, J., Nikolov, N., Nørby, K.K., Wedebye, E.B., 2007. Description and validation of QSAR genotoxicity models for use in evaluation of flavouring substances in Flavouring Group Evaluation 19 (FGE.19) on 360 alpha,beta-unsaturated aldehydes and ketones and precursors for these. Unpublished report submitted by FLAVIS Secretariat to EFSA.

Hayashi, M., Kishi, M., Sofuni, T., Ishidate Jr., M., 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem. Toxicol. 26(6), 487-500.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9(1), 257-272.

Jansson, T., Curvall, M., Hedin, A., Enzell, C., 1986. *In vitro* studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid in human lymphocytes by weakly acidic, semivolatile constituents. Mutat. Res. 169, 129-139.

JECFA, 1999a. Safety evaluation of certain food additives. The fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series: 42. IPCS, WHO, Geneva.

JECFA, 2001b. Safety evaluation of certain food additives and contaminants. Fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 46. IPCS, WHO, Geneva.

JECFA, 2006a. Safety evaluation of certain food additives and contaminants. Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 54. IPCS, WHO, Geneva.

JECFA, 2007a. Safety evaluation of certain food additives and contaminants. Sixty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series: 56. IPCS, WHO, Geneva.

Kim, S.B., Hayase, F., Kato, H., 1987b. Desmutagenic effect of alpha-dicarbonyl and alpha-hydroxycarbonyl compounds against mutagenic heterocyclic amines. Mutat. Res. 177, 9-15.

King, T., Faccini, J.M., Nachbaur, J., Perraud, J., Monro, A. M., 1979. 3-Generation and chronic toxicity study in rats. Pfizer Central Research. March 7, 1979. Unpublished report submitted by EFFA to SCF.

Mason, J.M., Valencia, R., Zimmering, S., 1992. Chemical mutagenesis testing in *Drosophila*: VIII. Reexamination of equivocal results. Environ. Mol. Mutag. 19, 227-234.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. *Salmonella* mutagenicity tests II. Results from the testing of 270 chemicals. Environ. Mol. Mutag. 8(Suppl. 7), 1-119.

Nikolov, N., Jensen, G.E., Wedebye, E.B., Niemelä, J., 2007. Report on QSAR predictions of 222 alpha,beta-unsaturated aldehydes and ketones from Flavouring Group Evaluation 19 (FGE.19) on 360 alpha,beta-unsaturated aldehydes and ketones and precursors for these. Unpublished report submitted by FLAVIS Secretariat to EFSA.

Ohshima, H., Friesen, M., Malaveille, C., Brouet, I., Hautefeuille, A., Bartsch, H., 1989. Formation of direct-acting genotoxic substances in nitrosated smoked fish and meat products: Identification of simple phenolic precursors and phenyldiazonium ions as reactive products. Food Chem. Toxicol. 27(3), 193-203.

SCF, 1999. Opinion on a programme for the evaluation of flavouring substances (expressed on 2 December 1999). Scientific Committee on Food. SCF/CS/FLAV/TASK/11 Final 6/12/1999. Annex I the minutes of the 119th Plenary meeting. European Commission, Health & Consumer Protection Directorate-General.

Wild, D., King, M.T., Gocke, E., Eckhard, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, BASC and micronucleus tests. Food Chem. Toxicol. 21(6), 707-719.

Zimmering, S., Mason, J.M., Valencia, R., 1989. Chemical mutagenesis testing in *Drosophila*. VII. Results of 22 coded compounds tested in larval feeding experiments. Environ. Mol. Mutag. 14, 245-251.

ABBREVIATIONS

CAS	Chemical Abstract Service
CHL	Chinese hamster lung cell(s)
CHO	Chinese hamster ovary cell(s)
CoE	Council of Europe
DNA	Deoxyribonucleic acid
DTU-NFI	Danish Technical University – National Food Institute
EC	European Commission
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS	Flavour Information System database
ID	Identity
IR	Infrared spectroscopy
ISS	Istituto Superiore di Sanita
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MS	Mass spectrometry
MSDI	Maximum Survey-derived Daily Intake
NMR	Nuclear magnetic resonance
No	number
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for Economic Co-operation and Development
(Q)SAR	(Quantitative) structure-activity relationship
SCF	Scientific Committee on Food
WHO	World Health Organisation