EFSA ; Scientific Opinion on Flavouring Group Evaluation 98 (FGE.98): Consideration of three ring-unsaturated delta-lactones)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 98 (FGE.98):

Consideration of three ring-unsaturated delta-lactones)[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. The present consideration concerns a group of three unsaturated delta-lactones [FL-no: 10.031, 10.037 and 10.044] previously evaluated by the JECFA at their 49th meeting in 1997. The JECFA considered that further information on the metabolism of these three substances was required and that they should be evaluated together with other substances containing alpha,beta-unsaturation and that, therefore, their evaluation should be deferred. However, the EFSA Panel has considered that these three JECFA evaluated aliphatic lactones can be hydrolysed and metabolised to innocuous products in line with the aliphatic lactones evaluated by EFSA in FGE.10Rev2. 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 concluded that all three substances do not give rise to safety concern at their levels of dietary intake, estimated on the basis of the MSDI approach.

1 On request from the Commission, Question No EFSA-Q-2011-00131, EFSA-Q-2011-00812 and EFSA-2011-008111 adopted on 19 May 2011.

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SUMMARY

The European Food Safety Authority (EFSA) asked the Scientific 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.

The present flavouring group evaluation concerns the EFSA consideration of three of four unsaturated delta-lactones previously evaluated by JECFA at its 49th meeting in 1997. At this meeting the Committee considered that "For the four lactones in class III that contain alpha,beta-unsaturation metabolism may occur either via hydrolysis followed by *beta*-oxidation or via conjugation with glutathione. There was insufficient information from consideration of these four substances alone to predict the route of metabolism with confidence. The Committee considered that further information on the metabolism of these four substances was required and that they should be evaluated together with other substances containing alpha,beta-unsaturation and that, therefore, their evaluation should be deferred."

Three of the four JECFA evaluated substances are Register substances ([FL-no: 10.031], JECFA-no: 245; [FL-no: 10.037], JECFA-no: 246 and [FL-no: 10.044], JECFA-no: 438) The mixture is not a Register substance and will not be considered in this Flavouring Group Evaluation 10, Revision 2 (FGE.10Rev2).

The Panel has considered that these three JECFA evaluated aliphatic lactones can be hydrolysed and metabolised to innocuous products in line with the aliphatic lactones evaluated by EFSA in FGE.10Rev2. The Panel concluded that these three lactones are structurally related to the group of 14 aliphatic lactones evaluated by EFSA in FGE.10Rev2.

The genotoxicity data available for the candidate and supporting lactones do not preclude their evaluation using the Procedure.

European production volumes are available for all three substances from which a MSDI can be derived.

No use levels are available for the three lactones evaluated through the Procedure. Use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the three JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including purity criteria and identity are available for all three JECFA evaluated substances. However, data on solubility in ethanol are lacking for [FL-no: 10.031 and 10.037] and data on solubility in water is lacking for [FL-no: 10.044].

For all three substances [FL-no: 10.031, 10.037 and 10.044] the Panel concluded that their is "no safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

KEY WORDS

Flavourings, food safety, alpha,beta-unsaturated lactone, JECFA, FGE.10Rev2

TABLE OF CONTENTS

BACKGROUND

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

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

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

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

TERMS OF REFERENCE

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

ASSESSMENT

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

The following issues are of special importance.

Intake

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

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

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

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

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

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

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

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

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

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

The present flavouring group evaluation concerns the EFSA consideration of three of four unsaturated delta-lactones previously evaluated by the JECFA at their 49th meeting in 1997. At this meeting the Committee considered that "For the four lactones in class III that contain alpha,beta-unsaturation, metabolism may occur either via hydrolysis followed by beta-oxidation or via conjugation with glutathione. There was insufficient information from consideration of these four substances alone to predict the route of metabolism with confidence. The JECFA Committee considered that further information on the metabolism of these four substances was required and that they should be evaluated together with other substances containing alpha,beta-unsaturation and that, therefore, their evaluation should be deferred."

The alpha,beta-unsaturated aldehyde and ketone structures are structural alert for genotoxicity (EFSA, 2008b). Accordingly the three JECFA evaluated alpha,beta-unsaturated Register substances, which are alpha,beta-unsaturated ketones and lactones, were allocated to FGE.19 (EFSA, 2008b). On the other hand, it is a common anticipation that esters of carboxylic acids and alcohols are readily hydrolysed to the corresponding acids and alcohols. This also accounts for aliphatic lactones (EFSA, 2011p). In this case the structural alert for genotoxicity is lifted and the three substances can be evaluated using the Procedure.

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

At its 49th meeting the JECFA evaluated a group of thirty five aliphatic lactones. Four of these lactones contain alpha,beta-unsaturation (JECFA-no: 245, 246, 438 and a mixture of three alpha,beta-unsaturated lactones). For the four alpha,beta-unsaturated substances the JECFA concluded that the evaluation should be "deferred pending the general consideration of substances containing alpha,beta-unsaturation" (JECFA, 1998a).

1.1.2. EFSA Considerations

Three of the four JECFA-evaluated substances are Register substances ([FL-no: 10.031], JECFA-no: 245; [FL-no: 10.037], JECFA-no: 246 and [FL-no: 10.044], JECFA-no: 438), the mixture is not a Register substance and will not be considered in this FGE.

1.2. Isomers

1.2.1. JECFA Status

Two of the three JECFA evaluated substances possess a chiral centre [FL-no: 10.037 and 10.044].

1.2.2. EFSA Considerations

The Flavouring Industry has provided information about the configuration of the chiral centre for [FL-no: 10.037 and 10.044] (EFFA, 2011a), as each exist as racemate.

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all three substances.

1.3.2. EFSA Considerations

The specifications are not considered adequate for the three substances. Data on solubility in ethanol are lacking for [FL-no: 10.031 and 10.037] and data on solubility in water is lacking for [FL-no: 10.044] (See Section 1.2).

2. Intake Estimations

2.1. JECFA Status

European production volumes are available for all three JECFA evaluated substances.

2.2. EFSA Considerations

No comments.

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text taken[4] from the JECFA (JECFA, 1998a)

In vitro / *in vivo*

There are *in vitro* / *in vivo* genotoxicity studies available for seven of the 35 JECFA evaluated lactones. No description or conclusion has been given by JECFA on these genotoxicity studies.

A summary of the studies are given in Table 2.1.

3.2. Genotoxicity Studies - Text taken[5] from EFSA FGE.10Rev2 (EFSA, 2011p)

Only text relevant for the evaluation of the three alpha,beta-unsaturated lactones is included:

Genotoxicity data were provided for two candidate substances, pentano-1,5-lactone [FL-no: 10.055] and 5,6-dimethyl-tetrahydro-pyran-2-one [FL-no: 10.168], which both were reported to be negative in microbial mutagenicity assays (Kuroda et al., 1986; Uhde, 2004a).

Genotoxicity tests are available for ten supporting substances. Some positive results from *in vitro* studies are reported for 4-hydroxybutyric acid lactone [FL-no: 10.006], which, however, was found

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

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

negative in a *Drosophila* sex-linked recessive lethal mutation assay (Table 2.3). Results of *in vivo* bone marrow micronucleus assays in mice available for 4-hydroxybutyric acid lactone were also negative, however, since the PCE/NCE ratio was not reported it is not clear if the test substance reached the bone marrow (Table 2.3). Positive *in vitro* data that cannot be evaluated are reported for hexano-1,5-lactone [FL-no: 10.010], nonano-1,4-lactone [FL-no: 10.001], undecano-1,4-lactone [FL-no: 10.002] and undecano-1,5-lactone [FL-no: 10.011] (Table 2.2).

Conclusions on genotoxicity

For the candidate lactones, the genotoxic potential cannot be assessed adequately, however, from the limited data available there were no indications that genotoxicity for these substances should give rise to safety concern.

For a summary of *in vitro* / *in vivo* genotoxicity data considered by EFSA see Tables 2.2 and 2.3.

3.3. EFSA Considerations

The genotoxicity data available do not preclude the evaluation of the candidate substances through the Procedure.

4. Application of the Procedure

4.1. Application of the Procedure to three aliphatic lactones considered by JECFA (JECFA, 1998a)

The JECFA did not evaluate the three aliphatic lactones through the Procedure as the evaluation were deferred pending evaluation of other alpha,beta-unsaturated substances.

4.2. Application of the Procedure by EFSA in FGE.10Rev2 (EFSA, 2011p)

Only text relevant for the evaluation of the three candidate aliphatic alpha,beta-unsaturated lactones in the present FGE has been included.

For the safety evaluation of the 14 candidate lactones from chemical groups 9 the Procedure as outlined in Annex I (of FGE.10Rev2) was applied, based on the MSDI approach. The stepwise evaluations of the 14 substances are summarised in Table 3.2.

Step 1

The 14 candidate lactones are classified according to the decision tree approach by Cramer *et al.* (1978) into structural class I.

Step 2

The 14 candidate lactones are considered to be metabolised to innocuous products, accordingly the evaluation of these 14 substances proceeds via the A-side of the Procedure.

Step A3

Step A3 applies to 14 candidate lactones from structural class I [FL-no: 10.038, 10.039, 10.040, 10.045, 10.047, 10.048, 10.049, 10.052, 10.055, 10.058, 10.059, 10.063, 10.068 and 10.168].

The 14 candidate substances which have been assigned to structural class I have estimated European daily *per capita* intakes (MSDI) ranging from 0.0061 to 48 microgram. These intakes are below the thresholds of concern of 1800 microgram/person/day for structural class I.

Accordingly, these 14 candidate lactones do not pose a safety concern when used at estimated levels of intake as flavouring substances, based on the MSDI approach.

4.3. EFSA Considerations

The metabolism of alpha,beta-unsaturated delta-lactones has been previously discussed by the JECFA at the 49th meeting in 1997. Based upon a study by Köppel and Tenczer (1991), the JECFA concluded that hydrolysis of the alpha,beta-unsaturated delta-lactones to the corresponding ring-opened hydroxycarboxylic acids may occur, but that there is no information available to predict that this is the major route of metabolism. However, Köppel and Tenczer (1991) analysed the metabolism of D,L-kawain ((2R)-4-methoxy-2-[(E)-2-phenylethenyl]-2,3-dihydropyran-6-one). Due to the aromatic ring and the hydroxyl-group the Panel considered that this substance is not sufficiently structurally related to the candidate substances [FL-no: 10.031, 10.037 and 10.044]. Therefore, no conclusion on the hydrolysis of the candidate substances can be drawn from the study by Köppel and Tenczer (Köppel & Tenczer, 1991).

Alternatively, the JECFA considered that alpha,beta-unsaturated delta-lactones may be conjugated with glutathione and be excreted as the cysteine or mercapturic acid adducts. The study by Boyland and Chassaud (1970) revealed that a high dose of 5-hydroxyhexenoic acid lactone (0.134 mg/kg) significantly reduced rat liver glutathione levels upon intraperitoneal injection. However, the use of the intraperitoneal route of administration circumvents the gastroinstestinal tract where environmental conditions favour hydrolysis of lactones. In FGE.05 data have described that esters of alpha,beta-unsaturated carboxylic acids will deplete liver GSH levels after intraperitoneal administration. Pretreatment with an inhibitor of esterase activity resulted in a much larger GSH depletion which indicates that ester hydrolysis e.g. by favourable conditions in the G.I.-tract, will reduce the toxicity of these lactones. Therefore, the Panel considered the study by Boyland and Chassaud (Boyland & Chasseaud, 1970) of little relevance for the evaluation of the candidate substances [FL-no: 10.031, 10.037 and 10.044] when used as flavouring substances in food.

Overall, the Panel concluded that in line with the candidate lactones in FGE.10Rev2, the three JECFA evaluated lactones [FL-no: 10.031, 10.037 and 10.044] are anticipated to be metabolised to innocuous products and can accordingly be evaluated via the A-side of the Procedure. The three lactones were allocated to structural class III to which a threshold of concern of 90 microgram per person per day has been assigned. The estimated European daily *per capita* intakes for these three substances [FL-no: 10.031, 10.037 and 10.044] are 84, 830 and 0.12 microgram, respectively. The intakes are below the class threshold of 90 microgram per person per day for the two substances [FL-no: 10.031 and 10.044] but above for [FL-no: 10.037].

Accordingly, two of the three lactones do not pose a safety concern when used at estimated levels of intake as flavouring substances, based on the MSDI approach. As the substance [FL-no: 10.037] is not endogenous a NOAEL for the substance or a structural related substance has to be provided. In a 90 day study in rats by Cox et al. (Cox et al., 1974h) a NOAEL of 12.1 mg/kg bw/day could be established for the structural related substance [FL-no: 10.031]. This carefully performed one dose study is not in compliance with a specific testing guideline but is of sufficient quality to accept the data. Compared to the MSDI of 830 microgram/*capita*/day (equal to 13.8 microgram/kg bw/day), this NOAEL provides a margin of safety of *ca.* 900.

5. Conclusion

The present flavouring group evaluation concerns the EFSA consideration of three of four alpha,beta-unsaturated delta-lactones previously evaluated by the JECFA at its 49th meeting in 1997. At this meeting the Committee considered that “For the four lactones in class III that contain alpha,beta-unsaturation metabolism may occur either via hydrolysis followed by *beta*-oxidation or via conjugation with glutathione. There was insufficient information from consideration of these four

substances alone to predict the route of metabolism with confidence. The Committee considered that further information on the metabolism of these four substances was required and that they should be evaluated together with other substances containing alpha,beta-unsaturation and that, therefore, their evaluation should be deferred."

Three of the four JECFA evaluated substances are Register substances ([FL-no: 10.031], JECFA-no: 245; [FL-no: 10.037], JECFA-no: 246 and [FL-no: 10.044], JECFA-no: 438). The mixture is not a Register substance and will not be considered in this FGE.

The Panel has considered that these three JECFA evaluated aliphatic lactones can be hydrolysed and metabolised to innocuous products in line with the aliphatic lactones evaluated by EFSA in FGE.10Rev2. The Panel concluded that the three lactones are structurally related to the group of 14 aliphatic lactones evaluated by EFSA in FGE.10Rev2.

The genotoxicity data available for the candidate and supporting lactones do not preclude their evaluation using the Procedure.

European production volumes are available for all three substances from which a MSDI can be derived.

No use levels are available for the three lactones evaluated through the Procedure. Use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

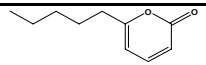
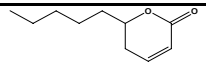
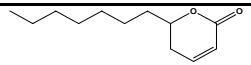
In order to determine whether the conclusion for the three JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including purity criteria and identity are available for all three JECFA evaluated substances. However, data on solubility in ethanol are lacking for [FL-no: 10.031 and 10.037] and data on solubility in water is lacking for [FL-no: 10.044].

For all three substances [FL-no: 10.031, 10.037 and 10.044] the Panel concluded that their is "no safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY

Table 1: Specifications Summary for the JECFA Evaluated Substances in the Present Group (JECFA, 1998b; JECFA, 2000d)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of three aliphatic lactones (JECFA, 1998b; JECFA, 2000d)

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
10.031 245	6-Pentyl-2H-pyran-2-one		3696 10967 27593-23-3	Liquid $C_{10}H_{14}O_2$ 166.22	Insoluble	85 (3 hPa) IR 98.7 %	1.501-1.509 1.000-1.009	
10.037 246	Dec-2-eno-1,5-lactone 6)		3744 54814-64-1	Liquid $C_{10}H_{16}O_2$ 168.24	Insoluble	112 (2 hPa) IR 95 %	1.462-1.482 0.947-0.987 (20°/20°	JECFA evaluated 5-hydroxy-2-decenoic acid delta-lactone (CASrn no. 51154-96-2, corresponding to R-enantiomer). Register CASrn no refers to the racemate. Racemate (EFFA, 2011a).
10.044 438	Dodec-2-eno-1,5-lactone 6)		3802 16400-72-9	Liquid $C_{12}H_{20}O_2$ 196.3	Soluble	115 (3 hPa) IR 95 %	1.467-1.473 1.470-1.480	Racemate (EFFA, 2011a).

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

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (in vitro / in vivo) for Aliphatic Lactones (JECFA, 1998a)

Table 2.1: Summary of Genotoxicity Data of Aliphatic Lactones Evaluated by the JECFA (JECFA, 1998a)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference
4-Hydroxybutyric acid lactone (gamma-Butyrolactone)	Gene mutation	*S. typhimurium* TA1535, TA98, TA100	0.1-50 µmoles/plate[1]	negative	(Loquet et al., 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA102	0.013-1.3 mmol[1]	negative	(Aeschbacher et al., 1989)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100-10 000 µg/plate[1]	negative	(NTP, 1992e)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	0-10 000 µg/plate[1]	negative	(Haworth et al., 1983)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1537	5000 µg/plate[1]	negative	(MacDonald, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	500 µg/plate[1]	negative	(Garner et al., 1981)
	Gene mutation	*S. typhimurium* TA100, TA1535, TA1537, TA1538	4-2500 µg/plate[1]	negative	(Trueman, 1981)
	Gene mutation	*S. typhimurium* TA92, TA98, TA100, TA1537, TA1538, TA1535	0.2-2000 µg/plate[1]	negative	(Brooks and Dean, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1000 µg/plate	negative	(Baker and Bonin, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	500 µg/plate	negative	(Rowland and Severn, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	500 µg/plate[1]	negative	(Simmon and Shephard, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1537	not reported[1]	negative	(Nagao and Takahashi, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10-10 000 µg/plate[1]	negative	(Richold and Jones, 1981)
	Gene mutation	*S. typhimurium* TA98, TA100	500 - 1000 µg/ml	negative	(Ichinotsubo et al., 1981a)
	Fluctuation Test	*S. typhimurium* TA98, TA100	500 µg/ml[1]	negative	(Hubbard et al., 1981)
	Forward mutation	*S. typhimurium* TM677	1000 µg/ml[2]	negative	(Skopeck et al., 1981)
	Microtiter fluctuation	*S. typhimurium* TA98, TA1535, TA1537	10-1000 µg/ml[1]	negative	(Gatehouse, 1981)
	Gene mutation	*E. coli*	500 µg/plate[1]	negative	(Venitt and Crofton-Sleigh, 1981)
	Gene mutation	*E. coli* SA500	250 µg/plate	lethal	(Dambly et al., 1981)
	Differential killing test	*E. coli* WP2, WP67 & M871	2500 µg/plate[1]	negative	(Green, 1981)
	Differential killing assay	*E. coli* P2,WP67 & CM871	1000 µg/ml[1]	negative	(Tweats, 1981)
	Microtiter fluctuation	*E. coli* WP2 uvrA	10-1000 µg/ml[1]	negative	(Gatehouse, 1981)
	Gene mutation	*E. coli* WP2 uvrA pKM102	not reported[1]	negative	(Matsushima et al., 1981)
	Sister chromatid exchange	Chinese hamster ovary cells	148-1480 µg/ml[3] 494-4940 µg/ml[2] 3010-5010 µg/ml[2]	negative positive (weak)[6] positive[6]	(NTP, 1992e)

Table 2.1: Summary of Genotoxicity Data of Aliphatic Lactones Evaluated by the JECFA (JECFA, 1998a)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference
	Chromosome aberration	Chinese hamster ovary cells	500-4990 µg/ml[3] 400-3990 µg/ml[2] 2210-2950 µg/ml[2]	negative positive[6] positive[6]	(NTP, 1992e)
	ADP-ribosyl transf. act.	Human FL cells	10^{-3} to 10^{-7} mol/l	negative	(Yingnian et al., 1990)
	Polyploidy	Human leucocyte	0.7 mmol/litre	negative	(Withers, 1966)
	Gene Mutation	Schizosaccha romyces pombe	20 µg/ml[1]	negative	(Loprieno, 1981)
	Mitotic crossing- over	*S. cervevisiae*	1000 µg/ml	negative	(Kassinova et al., 1981)
	Rec assay	*B. subtilis* H17, M45	20 µl/disc[4]	positive[6]	(Kada, 1981)
	Unscheduled DNA synthesis	Human HeLa S3 cells	0.1-100 µg/ml[1]	negative	(Martin and McDermid, 1981)
	Mitotic gene conversion	*S. cerevisiae*	750 µg/ml[1]	negative	(Sharp and Parry, 1981)
	Clastogenic activity	Rat liver cell line RL1	250 µg/ml	negative	(Dean, 1981)
	Mammalian cell transformation	BHK21C1B/HRC1 cells	2500 µg/ml[1]	?[5]	(Daniel and Dehnel, 1981)
	Mammalian cell transformation	BHK-21 hamster kidney cells	250 µg/ml[2]	positive	(Styles, 1981)
	Degranulation assay	Rat	25 mg/ml	positive	(Fey et al., 1981)
	Cell growth inhibition	*S. cerevisiae*	750 µg/ml[1]	negative	(Sharp and Parry, 1981)
	Haploid yeast reversion	*S. cerevisiae*	222 µg/ml[1]	?[5]	(Mehta and von Borstel, 1981)
	DNA pol I inhibition	*E. coli* W3110 & P3478	330 µg/plate	positive[3] negative[2]	(Rosenkranz et al., 1981)
	Sperm head abnormality	(CBA x Balb/c)F[1] mice	0.1-1.0 mg/kg/ day ip (5 days)	negative	(Topham, 1981)
	Sex-linked recessive test	*Drosophila melanogaster*	20 000 or 28 000 mg/ kg (diet) or 15 000 mg/kg (injection)	negative	(Foureman et al., 1994)
	Micronucleus test	B6C3F[1] mice	0.7 mg/kg/day ip (2 days)	negative	(Katz et al., 1981)
	Micronucleus test	B6C3F[1] mice	80 % LD_{50} ip (2 days)	negative	(Salamone et al., 1981)
	Micronucleus test	CD-1 mice	0.11-0.44 mg/kg/day ip (2 days)	negative	(Tsuchimoto and Matter, 1981)
gamma-Heptalactone	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	100 000 µg/plate[1]	negative	(Heck et al., 1989)
	UDS	Rat hepatocytes	3000 µg/ml	negative	(Heck et al., 1989)
gamma-Nonalactone	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	37 500 µg/plate[1]	negative	(Heck et al., 1989)
	Gene mutation	Human leucocytes	0.7 mM	positive	(Withers, 1966)
	Gene mutation	Mouse lymphoma L5178y $TK^{+/-}$	1000 µg/ml 400 µg/ml	negative[3] positive[2]	(Heck et al., 1989)
	UDS	Rat hepatocytes	500 µg/ml	negative	(Heck et al., 1989)
	Gene mutation	*E. coli* WP2 uvrA	0.2-1.6 mg/plate	negative	(Yoo, 1986)
	Rec-assay	*B. subtilis*	20 µl/disk	positive	(Yoo, 1986)
gamma-Undecalactone	Gene mutation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	5000 µg/plate[1]	negative	(Ishidate et al., 1984)

Table 2.1: Summary of Genotoxicity Data of Aliphatic Lactones Evaluated by the JECFA (JECFA, 1998a)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference
	Gene mutation	*S. typhimurium* TA97, TA102	100 µg/plate	negative	(Fujita and Sasaki, 1987)
	Chromosome aberration	Chinese hamster fibroblast	500 µg/ml	negative	(Ishidate et al., 1984)
	Rec-assay	*B. subtilis* H17 & M45	19 µg/disc	negative	(Oda et al., 1978)
	Rec-assay	*B. subtilis* H17 & M45	10 µl/disc	positive	(Yoo, 1986)
	Rec-assay	*B. subtilis* H17 & M45	10 µl/disc	positive[2] negative[1]	(Kuroda et al., 1984a)
	Mouse micronucleus	2-6 ddY male mice	250-2000 mg/kg/day ip (2 days)	negative	(Hayashi et al., 1988)
5-Hydroxyundecanoic acid delta-lactone	Rec-assay	*B. subtilis* H17 & M45	19 µg/disc	negative	(Oda et al., 1978)
omega-Pentadecalactone	Gene mutation	*S. typhimurium* TA98, TA100, TA102	50 µmol/plate[1]	negative	(Aeschbacher et al., 1989)
	Chromosome aberration	Human leukocytes	70 µmole/ml	negative	(Withers, 1966)
1,4-Dodec-6-enolactone	Gene mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	500 µg/plate[1]	negative	(Watanabe and Kinosaki, 1990)
	Rec-assay	*E. coli* WP2 uvrA	500 µg/plate[1]	negative	(Watanabe and Kinosaki, 1990)

[1] With and without rat liver S-9 metablic activation.

[2] With rat liver S-9 metabolic activation.

[3] Without rat liver S-9 metabolic activation.

[4] With yellowtail S-9 metabolic activation.

[5] Ambiguous result.

[6] These positive results with gamma-butyrolacone were only seen at relatively high dose levels and may be artifactual. There was no evidence of positive genotoxicity in *in vivo* studies. Overall, the genotoxicity of gamma-butyrolactone was considered to be negative.

Table 2.2: Genotoxicity Data (in vitro) EFSA / FGE.10Rev2 (EFSA, 2011p)

Only studies relevant for the evaluation of the three candidate aliphatic alpha,beta-unsaturated lactones in the present FGE has been included

Table 2.2: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference	Comments
(Butyro-1,4-lactone [10.006])	Ames test	*S. typhimurium* TA98, TA100, TA1535	0.1-50 µmoles/plate (8.6 - 4305 µg/plate)	Negative[1]	(Loquet et al., 1981)	No control values are given for inactive compounds. Conclusion not comprehensible.
	Ames test	*S. typhimurium* TA98, TA100, TA102	0.013 -1.3 mmol (11.2 - 1120 µg/ml)	Negative[1]	(Aeschbacher et al., 1989)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	100-10000 µg/plate	Negative[1]	(NTP, 1992e)	
	Ames test	*S. typhimurium* TA98, TA100, TA1537,	5,000 or 2000 µg/plate	Negative[1]	(MacDonald, 1981)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	0-10000 µg/plate	Negative[1]	(Haworth et al., 1983)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	NR	Negative[1]	(Garner et al., 1981)	
	Ames test	*S. typhimurium* TA98,TA100, TA1535, TA1537, TA1538	4-2500 µg/plate	Negative[1]	(Trueman, 1981)	
	Ames test	*S. typhimurium* TA92, TA98, TA100, TA1535, TA1537, TA1538	0.2-2000 µg/plate	Negative[1]	(Brooks and Dean, 1981)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10000 µg/ml	Negative[1]	(Baker and Bonin, 1981)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	500 µg/plate	Negative[1]	(Rowland and Severn, 1981)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	500 µg/plate	Negative[1]	(Simmon and Shephard, 1981)	
	Ames test	*S. typhimurium* TA98, TA100, TA1537	NR	Negative[1]	(Nagao and Takahashi, 1981)	
	Ames test	*S. typhimurium* TA98, TA100,	1000 mg	Negative[1]	(Ichinotsubo et al., 1981a)	
	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	10 - 10000 µg/plate	Negative[3]	(Richold and Jones, 1981)	
	Reverse bacterial mutation assay	*E. coli* WP2 (p)	up to 500 µg/plate (high dose studies) up to 100 µg/plate (low dose studies)	Negative[3]	(Venitt and Crofton-Sleigh, 1981)	
	Reverse bacterial mutation assay	*E. coli* SA500	NR	Lethal[4]	(Dambly et al., 1981)	Authors state "toxic, preventing adequate testing".
	Reverse mutation assay	*E. coli* WP2 *uvrA* pKM102	NR	Negative[1]	(Matsushima et al., 1981)	
	Forward mutation assay	*S. typhimurium* TM677	1000 µg/ml	Negative[3]	(Skopeck et al., 1981)	
	Microtiter fluctuation test	*S. typhimurium* TA98, TA1535, TA1537	10 - 1000 µg/ml	Negative[3]	(Gatehouse, 1981)	
	Microtiter fluctuation test	*S. typhimurium* TA98, TA100	NR	Negative[3]	(Hubbard et al., 1981)	
	Microtiter fluctuation test	*E. coli* WP2 *uvrA*	10 - 1000 µg/ml	Negative[3]	(Gatehouse, 1981)	
	Rec-assay	*Bacillus subtilis* H17, M45	20 µl (20000 µg)	Positive[1]	(Kada, 1981)	Reliable study, conclusion comprehensible.
	Differential killing test	*E. coli* WP2 *pol A*, WP2 *uvrA*, WP67 *uvrA*, WP67 *pol A*, CM871 *uvrA recA*,	NR	Negative[1]	(Green, 1981)	

Table 2.2: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference	Comments
		LexA				
	Differential killing test	*E. coli* WP2 *pol A*, WP2 *uvrA*, WP67 *uvrA*, WP67 *pol A*, CM871 *uvrA recA*, *LexA*	1000 µg/ml	Negative[2]	(Tweats, 1981)	
	Mitotic crossing-over	*S. cerevisiae*	1000 µg/ml	Negative[1]	(Kassinova et al., 1981)	
	Mitotic gene conversion	*S. cerevisiae* (JDI)	750 µg/ml	Negative[2]	(Sharp and Parry, 1981)	
	Cell growth inhibition	*S. cerevisiae* (JDI)	750 µg/ml	Negative[2]	(Sharp and Parry, 1981)	
	DNA polymerase I inhibition test	*E. coli* W3110 & P3478	10 µl (10000 µg)	Positive[2] Negative[3]	(Rosenkranz et al., 1981)	Reliable study, conclusion comprehensible.
	Forward mutation assay	*S. Pombe*	20 µg/ml[1]	Negative[3]	(Loprieno, 1981)	
	Unscheduled DNA synthesis	Human HeLa S3 cells	0.1-100 µg/ml	Negative[1]	(Martin and McDermid, 1981)	
	ADP-ribosyl transferase activity	Human FL cells	10^{-3} to 10^{-7} mol/L (0.0086 – 86 µg/ml)[3]	Negative	(Yingnian et al., 1990)	
	Clastogenic activity	Rat liver cell line RL1	250 µg/ml	Negative	(Dean, 1981)	
	Mammalian cell transformation	BHK-21 hamster kidney cells	250 µg/ml	Positive[1]	(Styles, 1981)	No specific genotoxicity endpoint.
	Degranulation assay	Rat	25 mg/ml (25000 µg/ml)	Positive	(Fey et al., 1981)	No genetic endpoint (displacement of polysomes from ER).
	Sister chromatid exchange	Chinese hamster ovary cells	494-4940 µg/ml 494-1480 µg/ml 3010-4940 µg/ml	Negative[2] Negative[3] Positive[3]	(NTP, 1992e)	Study in complinace with NTP laboratory health and safety requirements, conclusion comprehensible.
	Chromosomal aberration	Chinese hamster ovary cells	400-2580 µg/ml 400-1500 µg/ml >2580 µg/ml	Negative[2] Negative[3] Positive[3]	(NTP, 1992e)	Study in complinace with NTP laboratory health and safety requirements, conclusion comprehensible. Cells were selected for scoring on the basis of good morphology and completeness of karyotype.
Pentano-1,5-lactone [10.055]	Microbial assay	*E. coli* B/rWP2(*trp*$^-$), WP2(*trp*$^-$), WP2(*uvrA*$^-$)	1 – 3 mg/plate (1000-3000 µg/plate)	Negative[5]	(Kuroda et al., 1986)	Review, data cannot be validated.
(Hexano-1,5-lactone [10.010])	Ames test	*S. typhimurium* TA98, TA100	NR	Negative[2]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.
	Rec-assay	*B. subtilis*	NR	Negative[2]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.
	Sister chromatid exchange	Hamster lung fibroblast cells	NR	Negative[3]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.
	Chromosomal aberration	Hamster lung fibroblast cells	NR	Positive[2]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.

Table 2.2: GENOTOXICITY (*in vitro*)

Chemical Name [FL-no:]	Endpoint	Test Object	Concentration / Dose	Result	Reference	Comments
	Chromosomal aberration	Human embryo fibroblast cells	NR	Negative[3]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.
(Heptano-1,4-lactone [10.020])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	100,000 µg/plate	Negative[1]	(Heck et al., 1989)	Abstract only, study cannot be validated.
	Unscheduled DNA synthesis	Rat hepatocytes	3000 µg	Negative[1]	(Heck et al., 1989)	Abstract only, study cannot be validated.
(Nonano-1,4-lactone [10.001])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	37500 µg/plate	Negative[1]	(Heck et al., 1989)	Abstract only, study cannot be validated.
	Mammalian	Mouse lymphoma L5178y $TK^{+/-}$	1000 µg/ml 600 µg/ml	Negative[2] Positive[3]	(Heck et al., 1989)	Abstract only, study cannot be validated.
	Unscheduled DNA synthesis	Rat hepatocytes	500 µg	Negative[1]	(Heck et al., 1989)	Abstract only, study cannot be validated.
	Mutation assay	*E. coli* WP2 *uvrA*	0.2-1.6 mg/plate (200-1600 µg/plate)	Negative[4]	(Yoo, 1986)	Methods in Japanese, tables only in English. Study cannot be validated.
	Rec-assay	*B. subtilis* M45 & H17	20 µl/disk (20000 µg/disk)	Positive[4]	(Yoo, 1986)	Methods in Japanese, tables only in English. Study cannot be validated.
(Undecano-1,4-lactone [10.002])	Ames test	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537, TA2637	5 mg/plate (5000 µg/plate)	Negative[1]	(Ishidate et al., 1984)	
	Ames test	*S. typhimurium* TA97, TA98, TA100, TA102	0.1 mg/disk (100 µg/disk)	Negative[1]	(Fujita and Sasaki, 1987)	
	Rec-assay	*B. subtilis* H17 & M45	19 µg	Negative[1]	(Oda et al., 1979)	
	Rec-assay	*B. subtilis* H17 & M45	10 µl/plate (10000 µg/plate)	Positive[6]	(Yoo, 1986)	Methods in Japanese, tables only in English. Study cannot be validated.
	Rec-assay	*B. subtilis* H17 & M45	10 µl/plate (10000 µg/plate)	Positive[3] Negative[2]	(Kuroda et al., 1984a)	Abstract only translated, study cannot be validated.
	Chromosomal aberration	Chinese hamster fibroblast	0.5 mg/ml (500 µg/ml)	Negative[1]	(Ishidate et al., 1984)	
(Undecano-1,5-lactone [10.011])	Rec-assay	*B. subtilis* H17 & M45	19 µg	Negative[1]	(Oda et al., 1979)	
	Rec-assay	*B. subtilis*	10 µl/plate (10000 µg/plate)	Positive[1]	(Kuroda et al., 1984a)	Abstract only translated, study cannot be validated.
(Pentadecano-1,15-lactone [10.004])	Ames test	*S. typhimurium* TA98, TA100, TA102	50 µmol (12 µg/ml)	Negative[1]	(Aeschbacher et al., 1989)	
(5-Methylfuran-2(3H)-one [10.012])	Ames test	*S. typhimurium* TA98, TA100	5 - 50 µg/plate	Negative[1]	(Turek et al., 1997)	
(Dodec-6-eno-1,4-lactone [10.009])	Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537	500 µg/plate	Negative[1]	(Watanabe and Morimoto, 1990)	
	Rec-assay	*E. coli* WP2 *uvrA*	500 µg/plate	Negative[1]	(Watanabe and Morimoto, 1990)	
(3-Hydroxy-4,5-dimethylfuran-2(5H)-one [10.030])	Formation of 32P-labelled DNA fragment (test on isolated DNA).	*p53* tumour suppression gene	1mM (128 µg/ml)	Negative[7]	(Yamashita et al., 1998)	
5,6-Dimethyl-tetrahydro-pyran-2-one [10.168]	Ames test	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537	5000 microgram/plate	Negative[1]	(Uhde, 2004a)	Test performed both in the incorporation and preincubation assays.

NR: Not reported

[1] With and without S-9 metabolic activation.

[2] Without S-9 metabolic activation.

[3] With S-9 metabolic activation.

[4] Presence or absence of metabolic activation not specified.

[5] Anti-mutagenic effects study.

[6] Presence or absence of metabolic activation not specified.

[7] 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one did not form DNA adducts, but 2,5-DMHF does. Study addresses mechanism of chemical reaction of 2,5-dimethyl-4-hydroxy-3(2H)-furanone with DNA.

[8] The concentrations used were 10-fold higher than that of spontaneous revertants.

Table 2.3: Genotoxicity Data (in vivo) EFSA / FGE.10Rev2 (EFSA, 2011p)

Only studies relevant for the evaluation of the three candidate aliphatic alpha,beta-unsaturated lactones in the present FGE has been included

Table 2.3: GENOTOXICITY (*In vivo*)

Chemical Name [FL-no:]	Test system	Test Object	Route	Dose	Result	Reference	Comments
(Butyro-1,4-lactone [10.006])	*In vivo* Bone- marrow micronucleus assay	B6C3F1 mice	Single dose *via* intraperitoneal injection	80 % of LD_{50}	Negative	(Salamone et al., 1981)	Limited relevance because PCE/NCE ratio was not reported, thus it is not clear if the test substance reached the bone marrow.
	In vivo Bone- marrow micronucleus assay	CD-1 mice		0.11 - 0.44 ml/kg (110 - 440 mg/kg)	Negative	(Tsuchimoto and Matter, 1981)	Limited relevance because PCE/NCE ratio was not reported, thus it is not clear if the test substance reached the bone marrow.
	In vivo micronucleus assay	Mice (B6C3F1/BR hybrid)		80 % of LD_{50}	Negative	(Katz et al., 1981)	Limited relevance because PCE/NCE ratio was not reported, thus it is not clear if the test substance reached the bone marrow.
	In vivo sperm abnormality	Mice (CBA X Balb/c)F1	Daily exposure for five days *via* intraperitoneal injection	0.1 - 1.0 mg/kg bw/day	Negative	(Topham, 1981)	Sperm head abnormality test does not make use of a genetic endpoint.
	In vivo sex- linked recessive test	*D. melanogaster*	*A: via* diet B: injection	A: 20000 or 28000 ppm B. 15.000 ppm	Negative	(Foureman et al., 1994)	Study in compliance with OECD 477.
(Hexano-1,5-lactone [10.010])	Chromosomal aberration *in vivo*	Rat bone-marrow cell		NR	Negative[1]	(Kawachi et al., 1980b)	Summary of results on 186 compounds. No details on methods, concentrations and data given, results cannot be validated.
(Undecano-1,4-lactone [10.002])	*In vivo* mouse micronucleus test	2-6 ddY male mice	*Via* intraperitoneal injection	250-2000 mg/kg	Negative	(Hayashi et al., 1988)	Single application, only one sampling time. Not in compliance with current OECD 474.

NR: Not reported.

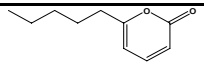
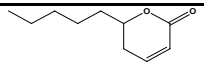
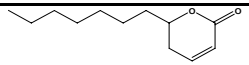
1) Presence or absence of metabolic activation not specified.

TABLE 3: SUMMARY OF SAFETY EVALUATION

Table 3: Summary of Safety Evaluation

Table 3.1: Summary of Safety Evaluation of Three Aliphatic Lactones evaluated by JECFA at their 49th meeting (JECFA, 1998a)

Table 3.1: Summary of Safety Evaluation of three aliphatic lactones *(JECFA, 1998a)*

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
10.031 245	6-Pentyl-2H-pyran-2-one		84 0.1	Class III Not evaluation through the Procedure (JECFA)		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.
10.037 246	Dec-2-eno-1,5-lactone		830 0.1	Class III Not evaluation through the Procedure (JECFA)		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. Racemate (EFFA, 2011c).
10.044 438	Dodec-2-eno-1,5-lactone		0.12 8.6	Class III Not evaluation through the Procedure (JECFA)		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. Racemate (EFFA, 2011c).

1) EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
2) Thresholds of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
4) No safety concern based on intake calculated by the MSDI approach of the named compound.
5) Data must be available on the substance or closely related substances to perform a safety evaluation.

Table 3.2: Summary of Safety Evaluation Applying the Procedure (EFSA / FGE.10Rev2) (EFSA, 2011p)

Only evaluation summaries relevant for the evaluation of the three candidate aliphatic alpha,beta-unsaturated lactones in the present FGE has been included

Table 3.2: Summary of Safety Evaluation Applying the Procedure (based on intakes calculated by the MSDI approach)

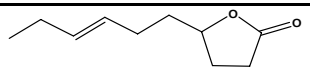
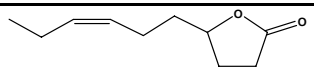
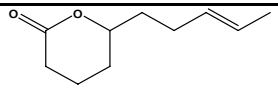
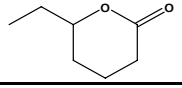
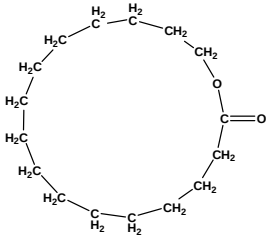
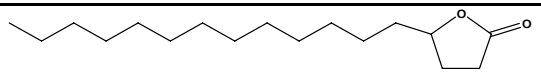
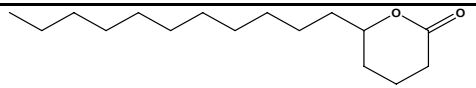
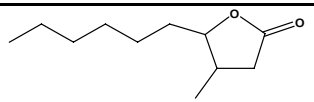
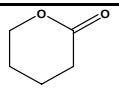
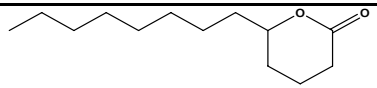
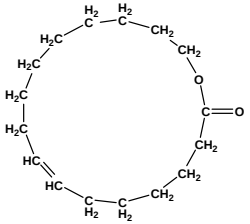
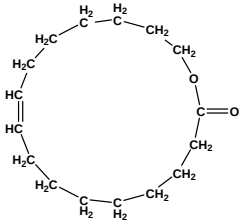
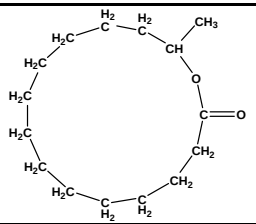
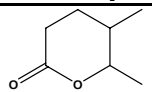
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
10.038	Dec-7-eno-1,4-lactone		0.37	Class I A3: Intake below threshold	4)	7)	
10.039	cis-Dec-7-eno-1,4-lactone		1.2	Class I A3: Intake below threshold	4)	6)	
10.040	Dec-8-eno-1,5-lactone		0.011	Class I A3: Intake below threshold	4)	7)	
10.045	Heptano-1,5-lactone		0.012	Class I A3: Intake below threshold	4)	6)	
10.047	Hexadecano-1,16-lactone		0.024	Class I A3: Intake below threshold	4)	6)	
10.048	Hexadecano-1,4-lactone		0.0061	Class I A3: Intake below threshold	4)	6)	
10.049	Hexadecano-1,5-lactone		0.024	Class I A3: Intake below threshold	4)	6)	
10.052	3-Methylnonano-1,4-lactone		0.61	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)

FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
10.055	Pentano-1,5-lactone		0.012	Class I A3: Intake below threshold	4)	6)	
10.058	Tridecano-1,5-lactone		0.61	Class I A3: Intake below threshold	4)	6)	
10.059	Hexadec-7-en-1,16-lactone	 **Z-isomer shown**	1.9	Class I A3: Intake below threshold	4)	7)	
10.063	Hexadec-9-en-1,16 lactone	 **Z-isomer shown**	48	Class I A3: Intake below threshold	4)	7)	
10.068	Pentadecano-1,14-lactone		0.9	Class I A3: Intake below threshold	4)	6)	
10.168	5,6-Dimethyl-tetrahydro-pyran-2-one		1.2	Class I A3: Intake below threshold	4)	6)	

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.
6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

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ABBREVIATIONS

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
ER	Endoplasmatic reticulum
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)
G.I.	Gastrointestinal
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