EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 3, Revision 2 (FGE.03Rev2): Acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, an ester of a hemiacetal and an orthoester of formic acid, from chemical groups 1, 2 and 4

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Link to article, DOI:
10.2903/j.efsa.2011.2312

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 3, Revision 2 (FGE.03Rev2):

Acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, an ester of a hemiacetal and an orthoester of formic acid, from chemical groups 1, 2 and 4 [1]

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

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to evaluate one flavouring substance, acetaldehyde ethyl isopropyl acetal [FL-no: 06.137], structurally related to the 58 flavouring substances in the Flavouring Group Evaluation 03, in a Revision 2, using the Procedure in Commission Regulation (EC) No 1565/2000. None of the substances were considered to have genotoxic potential. The new substance was along with the remaining 58 substances evaluated through a stepwise approach (the Procedure) 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 as for the other already evaluated substances that the substance [FL-no: 06.137] do not give rise to safety concern at its level of dietary intake, estimated on the basis of the MSDI approach. Besides the safety assessment of this flavouring substance, the specifications for the materials of commerce have also been considered, and since the publication of FGE.03Rev1 additional information on chirality on 30 substances is made available and has been incorporated into the present Revision 2 of FGE.03.

1 On request from the Commission, Question No EFSA-Q-2011-00300 adopted on 6 July 2011.

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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Flavourings for the preparation of this Opinion: Ulla Beckman Sundh, Vibe Beltoft, Wilfried Bursch, Angelo Carere, Karl-Heinz Engel, Henrik Frandsen, Rainer Gürtler, Frances Hill, Trine Husøy, John Christian Larsen, Pia Lund, Wim Mennes, Gerard Mulder, Karin Nørby, Iona Pratt, Gerrit Speijers, Harriet Wallin and EFSA's staff member Kim Rygaard Nielsen for the preparatory work on this scientific Opinion.

Suggested citation: EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF); Scientific Opinion on Flavouring Group Evaluation 3, Revision 2 (FGE.03Rev2):
Acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, an ester of a hemiacetal and an orthoester of formic acid, from chemical groups 1, 2 and 4 . EFSA Journal 2011; 9(10):2312. [65 pp.]. doi:10.2903/j.efsa.2011.2312. Available online: www.efsa.europa.eu/efsajournal.htm

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to evaluate 59 flavouring substances in the Flavouring Group Evaluation 03, Revision 2 (FGE.03Rev2), using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These 59 flavouring substances belong to chemical groups 1, 2 and 4, Annex I of the Commission Regulation (EC) No 1565/2000.

The present Flavouring Group Evaluation deals with 57 acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, one orthoester of formic acid and one ester of a hemiacetal.

Thirty-three of the 59 flavouring substances possess one or more chiral centres. For all of these substances the stereoisomeric composition has been specified.

One of the 59 substances can exist as a geometrical isomer [FL-no: 06.063] and no indication has been given that one of the possible isomers has preponderance in the commercial flavouring material.

Fifty-eigth of the flavouring substances are classified into structural class I and the orthoester [FL-no: 06.096] into structural class III.

Forty-three of the substances in the present group of 59 substances have been reported to occur naturally in a wide range of food items.

In its evaluation, the Panel as a default used the "Maximised Survey-derived Daily Intakes" (MSDIs) approach to estimate the *per capita* intakes of the flavouring substances in Europe. However, when the Panel examined the information provided by the European Flavouring 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.

In the absence of more precise 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. In those cases where the mTAMDI approach indicated that the intake of a flavouring substance might exceed its corresponding threshold of concern, the Panel decided not to carry out a formal safety assessment using the Procedure. In these cases the Panel requires more precise data on use and use levels.

According to the default MSDI approach, the 59 flavouring substances have intakes in Europe from 0.001 to 14 microgram/*capita*/day, which are below the threshold of concern value for structural class I of 1800 microgram/person/day. Likewise the estimated level of intake for the orthoester [FL-no: 06.096] of 0.013 microgram/*capita*/day is below the threshold of concern for structural class III of 90 microgram/person/day.

Adequately reported genotoxicity studies are only available for one of the flavouring substances. These studies do not give rise to safety concern with respect to genotoxicity of the flavouring substance in this Flavouring Group Evaluation. Consideration was given to methanol, formaldehyde, ethanol and acetaldehyde that are potential hydrolysis products of several of the acetals in the present Flavouring Group Evaluation. Because of the natural occurrence in food and the endogenous formation in humans of considerably larger amounts of these compounds, their formation from

hydrolysis of the acetals were not considered to be of safety concern with respect to genotoxicity at their estimated levels of intakes, based on the MSDI approach.

The 59 candidate substances are expected to be metabolised to innocuous products.

There are no toxicological studies available on the 59 flavouring substances or on structurally related acetals other than data on acute toxicity.

On the basis of the default MSDI approach the Panel concluded that the 57 acetals, the orthoester and the ester of a hemiacetal would not give rise to safety concerns at levels of intake arising from their use as flavouring substances.

When the estimated intakes were based on the mTAMDI approach they ranged from 3 to 9500 microgram/person/day for the 58 substances from structural class I. For 16 of the substances the intakes were above the threshold of concern for structural class I of 1800 microgram/person/day. For the one substance from structural class III [FL-no: 06.096] the mTAMDI is 1600 microgram/person/day, which is above the threshold of concern for structural class III of 90 microgram/person/day.

Thus, for 17 of the 59 flavouring substances considered in this Opinion, the intakes, estimated on the basis of the mTAMDI, exceed the relevant threshold for their structural class to which the flavouring substance has been assigned. Therefore, for these 17 substances more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be reconsidered using the Procedure. Subsequently, additional data might become necessary.

In order to determine whether this evaluation could be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity tests for the materials of commerce have been provided for 42 of the 59 flavouring candidate substances. The specifications are not adequate for 17 substances [FL-no: 03.023, 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.128 and 06.129] as identity tests are lacking and for one of substances [FL-no: 06.063] has the stereoisomeric composition to be specified. Thus, the final evaluation of the materials of commerce cannot be performed for 17 substances ([FL-no: 03.023, 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.128, 06.129]), pending further information.

For the remaining 42 substances [FL-no: 06.044, 06.048, 06.049, 06.050, 06.051, 06.052, 06.053, 06.054, 06.055, 06.057, 06.058, 06.059, 06.061, 06.062, 06.064, 06.065, 06.066, 06.067, 06.069, 06.070, 06.071, 06.073, 06.074, 06.075, 06.076, 06.079, 06.082, 06.083, 06.084, 06.085, 06.086, 06.091, 06.092, 06.096, 06.100, 06.111, 06.114, 06.125, 06.127, 06.130, 06.131 and 06.137] the Panel concluded that they would present no safety concern at the levels of intake estimated on the basis of the MSDI approach.

KEY WORDS

Straight-chain; branched-chain; acetals; saturated; acyclic; primary alcohols; aldehydes; orthoester; formic acid; flavourings; safety; FGE.03.

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BACKGROUND

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

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000 (EC, 2000a), which is broadly based on the Opinion of the Scientific Committee on Food (SCF, 1999a). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

The FGE is revised to include substances for which data were submitted after the deadline as laid down in Commission Regulation (EC) No 622/2002 and to take into account additional information that has been made available since the previous Opinion on this FGE.

The Revision also includes newly notified substances belonging to the same chemical groups evaluated in this FGE.

After the completion of the evaluation programme the Union 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, 1996a).

HISTORY OF THE EVALUATION

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.03	7 October 2004	http://www.efsa.eu.int/science/afc/afc_opinions/671_en.html	42
FGE.03Rev1	18 April 2007	http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178689852831.htm	58
FGE.03Rev2	6 July 2011		59

The present revision of FGE.03, FGE.03Rev2, includes the assessment of one additional candidate substance, acetaldehyde ethyl isopropyl acetal, [FL-no: 06.137]. No new toxicity or metabolism data were available for this substance However, the Panel is aware of the BfR discussion[4] on acetaldehyde (which is the hydrolysis product of [FL-no: 06.137]. A search in open literature did not reveal any relevant information for [FL-no: 06.137].

Since the publication of FGE.03Rev1 additional information on geometrical isomerism / chirality on 30 substances is made available and has been incorporated into the present FGE (EFFA, 2010a).

Furthermore, the Industry has submitted data to support the change of structural class from Cramer Class III to II for triethoxymethane [FL-no: 06.096] (EFFA, 2011a).

[4] http://www.bfr.bund.de/cm/343/5_sitzung_der_bfr_kommission_fuer_lebensmittelzusatzstoffe_aromastoffe_und_verarbeitungshilfsstoffe.pdf

TERMS OF REFERENCE

The European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances in the Register prior to their authorisation and inclusion in a Union List according to Commission Regulation (EC) No 1565/2000 (EC, 2000a). In addition, the Commission requested EFSA to evaluate newly notified flavouring substances, where possible, before finalising the evaluation programme. The evaluation programme was finalised by 31 December 2009.

In addition, in letter of 18 March 2011 the Commission requested EFSA to carry out a risk assessment on acetaldehyde ethyl isopropyl acetal [FL-no: 06.137] in accordance with Commission Regulation (EC) No 1565/2000 (EC, 2000a) by 31 December 2011.

ASSESSMENT

1. Presentation of the Substances in Flavouring Group Evaluation 3, Revision 2

1.1. Description

The present Flavouring Group Evaluation 3, Revision 2 (FGE.03Rev2) using the procedure as referred to in the Commission Regulation (EC) No 1565/2000 (EC, 2000a) (the Procedure - shown in schematic form in Annex I), deals with 59 acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, one orthoester of formic acid and one ester of a hemiacetal. These 59 flavouring substances (candidate substances) belong to chemical groups 1, 2 and 4, Annex I of the Commission Regulation EC No 1565/2000 (EC, 2000a).

The 59 candidate substances under consideration, with their chemical Register names, FLAVIS- (FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufactures Association- (FEMA-) numbers, structure and specifications, are listed in Table 1.

The 59 candidate substances are closely related structurally to ten acetals (supporting substances) evaluated at the 57th JECFA meeting (JECFA, 2002a) as well as to two acetals (supporting substances) evaluated by the Council of Europe (CoE, 1992).

The flavouring substances under consideration in the present evaluation are listed in Tables 1 and 2a, the hydrolysis products of the candidate substances are listed in Table 2b, and the supporting substances are listed in Table 3.

1.2. Stereoisomers

It is recognised that geometrical and optical isomers of substances may have different properties. Their flavour may be different, they may have different chemical properties resulting in possible variability in their absorption, distribution, metabolism, elimination and toxicity. Thus, information must be provided on the configuration of the flavouring substance, i.e. whether it is one of the geometrical/optical isomers, or a defined mixture of stereoisomers. The available specifications of purity will be considered in order to determine whether the safety evaluation carried out for candidate substances for which stereoisomers may exist can be applied to the material of commerce. Flavouring substances with different configurations should have individual chemical names and codes (CAS number, FLAVIS number etc.).

Thirty-three of the 59 substances possess a chiral centre. In most of these cases, the chirality results solely because the acetal is asymmetric, i.e. it is formed from an aldehyde and two different alcohols, none of which contains a chiral centre [FL-no: 03.023, 06.041, 06.042, 06.043, 06.044, 06.045, 06.046, 06.047, 06.048, 06.050, 06.082, 06.083, 06.084, 06.085, 06.086, 06.091, 06.092, 06.111,

06.114, 06.115, 06.123, 06.127, 06.128, 06.129, 06.130, 06.131 and 06.137]. In these cases, the Industry has informed that all these acetal derivatives occur as their mixtures of optical isomers (of the acetal moiety), i.e. as the racemates (EFFA, 2010a; Flavour Industry, 2011c). This new information has implications for two of the substances in the present FGE, [FL-no: 06.043 and 06.127], as the Industry has informed that both are racemic mixtures of isomers and they then turned out to be identical substances. For three substances either the aldehyde [FL-no: 06.057 and 06.109] or the alcohol moiety [FL-no: 06.051] contain one chiral centre. According to the information provided [FL-no: 06.051, 06.057 and 06.109] are used as a racemic mixture (EFFA, 2001a; EFFA, 2001b; EFFA, 2001c; EFFA, 2010a). Three of the substances [FL-no: 06.049, 06.079 and 06.107] have one chiral centre in the aldehyde moiety and one in the alcohol moiety. According to the information provided by Industry since the publication of FGE.03Rev1, both the alcohol and the aldehyde moiety occur as their racemic mixtures (mixtures of R- and S-enantiomers) (EFFA, 2010a).

Due to the presence and the position of a double bond, one of the 59 substances can exist as geometrical isomers [FL-no: 06.063]. No indication has been given that one of the possible isomers has preponderance in the commercial flavouring material (see Table 1).

1.3. Natural Occurrence in Food

Forty-three of the of the 59 substances in the present FGE have been reported to occur in the following food items: alcoholic beverages, cocoa, chinese quince peel, fruits and fruit juices (primarily apple and grape juice), tomatoes, potatoes, fish, meat, bread and butter. Quantitative data on the natural occurrence in food have been reported for 34 of these substances (TNO, 2000; TNO, 2011).

Most of the substances occur in alcoholic beverages, e.g. rum:

Table 1.3.1 Quantitative data for natural occurrence in food

FL-no	Name	Found in
06.041	1-Isobutoxy-1-ethoxy-2-methylpropane	0.1 mg/kg in rum
06.042	1-Isobutoxy-1-ethoxy-3-methylbutane	5 mg/kg in rum
06.044	1-Isobutoxy-1-ethoxypropane	0.25 mg/kg in rum
06.045	1-Isobutoxy-1-isopentyloxy-2-methylpropane	0.8 mg/kg in rum
06.046	1-Isobutoxy-1-isopentyloxy-3-methylbutane	0.25 mg/kg in rum
06.047	1-Isopentyloxy-1-propoxyethane	2.5 mg/kg in rum
06.050	1-Butoxy-1-ethoxyethane	0.5 mg/kg in rum
06.052	1,1-Di-isobutoxy-2-methylpropane	0.5 mg/kg in rum
06.053	1,1-Di-isobutoxyethane	1.5 mg/kg in rum, 1 mg/kg in cider
06.054	1,1-Di-isobutoxypentane	0.05 mg/kg in rum
06.055	1,1-Di-isopentyloxyethane	7.5 mg/kg in rum, 2 mg/kg in cider, 0.04 in cognac
06.057	1,1-Diethoxy-2-methylbutane	2.5 mg/kg in rum
06.058	1,1-Diethoxy-2-methylpropane	6 mg/kg in rum, 1.7 mg/kg in cognac
06.059	1,1-Diethoxy-3-methylbutane	13 mg/kg in rum, 0.2 mg/kg in cognac
06.061	1,1-Diethoxybutane	0.1 mg/kg in rum
06.064	Diethoxymethane	0.8 mg/kg in rum
06.065	1,1-Diethoxynonane	10 mg/kg in rum, 0.05 mg/kg in cider, 0.01 mg/kg in cognac
06.067	1,1-Diethoxypentane	0.03 mg/kg in weinbrand, 0.004 mg/kg in cranberry
06.069	1,1-Diethoxypropane	1.2 mg/kg in rum
06.071	1,1-Dihexyloxyethane	0.01 mg/kg in cider
06.079	1-Ethoxy-1-(2-methylbutoxy)ethane	2.5 mg/kg in rum
06.083	1-Ethoxy-1-isopentyloxyethane	10 mg/kg in rum, 0.05 mg/kg in cider, 0.008-0.01 mg/kg in grape brandy, up to 0.17 mg/kg in wine
06.084	1-Ethoxy-1-methoxyethane	0.3 mg/kg in rum
06.085	1-Ethoxy-1-pentyloxyethane	0.5 mg/kg in rum
06.086	1-Ethoxy-1-propoxyethane	1.2 mg/kg in rum

Table 1.3.1 Quantitative data for natural occurrence in food

FL-no	Name	Found in
06.091	1-Isobutoxy-1-ethoxyethane	1.5 mg/kg in rum
06.092	1-Isobutoxy-1-isopentyloxyethane	5 mg/kg in rum, 0.05 mg/kg in cider
06.105	3-Methyl-1,1-di-isopentyloxybutane	0.1 mg/kg in rum
06.106	2-Methyl-1,1-di-isopentyloxypropane	0.1 mg/kg in rum
06.107	1-(2-Methylbutoxy)-1-isopentyloxyethane	2.3 mg/kg in rum
06.123	1-Butoxy-1-isopentyloxyethane	0.5 mg/kg in rum
06.124	1,1-Di-isobutoxy-3-methylbutane	0.8 mg/kg in rum
06.129	1-Ethoxy-2-methyl-1-isopentyloxypropane	5 mg/kg in rum
06.131	1-Ethoxy-1-(3-methylbutoxy)-3-methylbutane	4 mg/kg in rum

Sixteen of the candidate substances have not been reported to occur naturally in any food items according to TNO (TNO, 2000) (see Table 1.3.2). Triethoxymethane [FL-no: 06.096] has been reported in amounts below the quantitation limits in butteroil examined after 6 – 8½ months of storage at – 18° C (Siek and Lindsay, 1968). The Panel concluded that these findings do not fulfil the Cramer class criteria of natural occurrence in food (Cramer et al., 1978).

Table 1.3.2 Candidate substances not reported to occur naturally

FL-no	Name
06.043	1-Isoamyloxy-1-ethoxypropane
06.048	1-Isopentyloxy-1-propoxypropane
06.051	1,1-Di-(2-methylbutoxy)ethane
06.062	1,1-Diethoxydodecane
06.063	1,1-Diethoxyhex-3-ene
06.075	1,1-Dimethoxypentane
06.076	1,1-Dimethoxypropane
06.100	1,1-Dipentyloxyethane
06.109	1,1-Diethoxy-3,7-dimethyloct-6-ene
06.111	1-Ethoxy-1-methoxypropane
06.114	1-Hexyloxy-1-isopentyloxyethane
06.115	1-Isopentyloxy-1-pentyloxyethane
06.125	1,1-Di-isobutoxypropane
06.127	1-Ethoxy-1-isopentyloxypropane
06.128	1-Ethoxy-1-pentyloxybutane
06.130	1-Ethoxy-2-methyl-1-propoxypropane

2. Specifications

Purity criteria for the 59 substances have been provided by the Flavour Industry (EFFA, 2001b; EFFA, 2002a; EFFA, 2003s; Flavour Industry, 2007a; Flavour Industry, 2011c) (Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000a), the specifications for 17 of the candidate substances, ([FL-no: 03.023, 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.128 and 06.129]), are insufficient, as identity tests are lacking and for one of the substances [FL-no: 06.063] has the stereoisomeric composition to be specified. The specifications are adequate for the other 42 candidate substances (see Section 1.2 and Table1).

3. Intake Data

Annual production volumes of the flavouring substances as surveyed by the Industry can be used to calculate the "Maximised Survey-derived Daily Intake" (MSDI) by assuming that the production figure only represents 60 % of the use in food due to underreporting and that 10 % of the total EU population are consumers (SCF, 1999a).

However, the Panel noted that due to year-to-year variability in production volumes, to uncertainties in the underreporting correction factor and to uncertainties in the percentage of consumers, the reliability of intake estimates on the basis of the MSDI approach is difficult to assess.

The Panel also noted that in contrast to the generally low *per capita* intake figures estimated on the basis of this MSDI approach, in some cases the regular consumption of products flavoured at use levels reported by the Flavour Industry in the submissions would result in much higher intakes. In such cases, the human exposure thresholds below which exposures are not considered to present a safety concern might be exceeded.

Considering that the MSDI model may underestimate the intake of flavouring substances by certain groups of consumers, the SCF recommended also taking into account the results of other intake assessments (SCF, 1999a).

One of the alternatives is the "Theoretical Added Maximum Daily Intake" (TAMDI) approach, which is calculated on the basis of standard portions and upper use levels (SCF, 1995) for flavourable beverages and foods in general, with exceptional levels for particular foods. This method is regarded as a conservative estimate of the actual intake by most consumers because it is based on the assumption that the consumer regularly eats and drinks several food products containing the same flavouring substance at the upper use level.

One option to modify the TAMDI approach is to base the calculation on normal rather than upper use levels of the flavouring substances. This modified approach is less conservative (e.g., it may underestimate the intake of consumers being loyal to products flavoured at the maximum use levels reported) (EC, 2000a). However, it is considered as a suitable tool to screen and prioritise the flavouring substances according to the need for refined intake data (EFSA, 2004a).

3.1. Estimated Daily *per Capita* Intake (MSDI Approach)

The intake estimation is based on the Maximised Survey-derived Daily Intake (MSDI) approach, which involves the acquisition of data on the amounts used in food as flavourings (SCF, 1999a). These data are derived from surveys on annual production volumes in Europe. These surveys were conducted in 1995 by the International Organization of the Flavour Industry, in which flavour manufacturers reported the total amount of each flavouring substance incorporated into food sold in the EU during the previous year (IOFI, 1995). The intake approach does not consider the possible natural occurrence in food.

Average *per capita* intake (MSDI) is estimated on the assumption that the amount added to food is consumed by 10 % of the population[5] (Eurostat, 1998). This is derived for candidate substances from estimates of annual volume of production provided by Industry and incorporates a correction factor of 0.6 to allow for incomplete reporting (60 %) in the Industry surveys (SCF, 1999a).

The total annual volume of production of the 59 candidate substances in the present Flavouring Group Evaluation (FGE.03Rev2) from use as flavouring substances in Europe has been reported to be

[5] EU figure 375 millions. This figure relates to EU population at the time for which production data are available, and is consistent (comparable) with evaluations conducted prior to the enlargement of the EU. No production data are available for the enlarged EU.

approximately 310 kg (EFFA, 2001d; EFFA, 2002a; EFFA, 2003s; Flavour Industry, 2007a; Flavour Industry, 2011c). Only two of the 59 substances have reported annual volumes over 10 kg (1,1-di-isopentyloxyethane [FL-no: 06.055]: 111 kg/year and acetaldehyde ethyl isopropyl acetal [FL-no: 06.137]: 100 kg/year). Four of the substances have annual production volumes over 6 kg and the estimated daily *per capita* intakes on the basis of the reported annual volume are 0.85 microgram for 1,1-dipentyloxyethane [FL-no: 06.100], 1.2 microgram for 1-ethoxy-1-isopentyloxyethane [FL-no: 06.083], 14 microgram for 1,1-di-isopentyloxyethane [FL-no: 06.055] and 0.77 microgram for 1,1-diethoxypropane [FL-no: 06.069] (Table 2a).

The orthoester [FL-no: 06.096] triethoxymethane has a reported annual production volume of 0.11 kg and the daily *per capita* intake based on this figure is 0.013 microgram (Table 2a).

3.2. Intake Estimated on the Basis of the Modified TAMDI (mTAMDI)

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995).

The assumption is that a person may consume a certain amount of flavourable foods and beverages per day.

For the 59 candidate substances information on food categories and normal and maximum use levels[6,7,8] were submitted by the Flavour Industry (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c). The 59 candidate substances are used in flavoured food products divided into the food categories, outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000a), as shown in Table 3.1. For the present calculation of mTAMDI, the reported normal use levels were used. In the case where different use levels were reported for different food categories the highest reported normal use level was used.

Table 3.1 Use of Candidate Substances. Use levels have been provided for all 59 candidate substances

Food category	Description	Flavourings used
01.0	Dairy products, excluding products of category 2	All except [FL-no: 06.076, 06.137]
02.0	Fats and oils, and fat emulsions (type water-in-oil)	All except [FL-no: 03.023, 06.137]
03.0	Edible ices, including sherbet and sorbet	All
04.1	Processed fruits	All except [FL-no: 03.023, 06.137]
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	None
05.0	Confectionery	All except [FL-no: 06.137]
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	All except [FL-no: 03.023, 06.049, 06.066, 06.137]
07.0	Bakery wares	All except [FL-no: 03.023, 06.137]
08.0	Meat and meat products, including poultry and game	All except [FL-no: 03.023, 06.137]

[6] "Normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i).
[7] The normal and maximum use levels in different food categories (EC, 2000) have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).
[8] The use levels from food category 5 "Confectionery" have been inserted as default values for food category 14.2 "Alcoholic beverages" for substances for which no data have been given for food category 14.2 (EFFA, 2007a).

09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	All except [FL-no: 03.023, 06.127, 06.137]
10.0	Eggs and egg products	None
11.0	Sweeteners, including honey	Only [FL-no: 06.096]
12.0	Salts, spices, soups, sauces, salads, protein products etc.	All except [FL-no: 06.096, 06.137]
13.0	Foodstuffs intended for particular nutritional uses	All except [FL-no: 03.023, 06.137]
14.1	Non-alcoholic ("soft") beverages, excl. dairy products	All except [FL-no: 03.023]
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts	All
15.0	Ready-to-eat savouries	All except [FL-no: 06.106, 06.137]
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15	All except [FL-no: 06.137]

According to the Flavour Industry the normal use levels for the candidate substances are in the range of 0.003 - 20 mg/kg food, and the maximum use levels are in the range of 0.005 to 150 mg/kg (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c) (see Table II.1.2, Annex II).

The mTAMDI values for the 58 candidate substances from structural class I (see Section 5) range from 3 to 9500 microgram/person/day. For the one candidate substance from structural class III [FL-no: 06.096] the mTAMDI is 1600 microgram/person/day.

For detailed information on use levels and intake estimations based on the mTAMDI approach, see Section 6 and Annex II.

4. Absorption, Distribution, Metabolism and Elimination

It is anticipated that the acetals, the ester of the hemiacetal and the orthoester in the present Flavouring Group Evaluation (FGE.03Rev2) will undergo hydrolysis under acidic condition. The hydrolysis products are all relatively simple alcohols and aldehydes, and carboxylic acid which may be assumed to be rapidly absorbed and metabolised to innocuous products as discussed in more detail in Annex III, including references.

However, there are few data available concerning hydrolysis of acetals in biological systems. From the available data on *in vitro* studies it can be concluded that simple acetals from linear or branched-chain alcohols and aldehydes may be hydrolysed in an acid environment such as artificial gastric juice (pH 1.2), presumed to reflect the environment in the stomach, but hardly in a basic environment such as artificial intestinal fluid (pH 7.5), reflecting the situation in the gut. There is little information as to rates of hydrolysis.

Enzymatic cleavage of acetals and further metabolism has been observed *in vitro* as well as *in vivo*. A few studies demonstrate that acetals may be hydrolysed enzymatically in liver microsomal preparations. Studies on conversion rate of the cyclic acetal paraldehyde to acetaldehyde also show that liver may contribute to enzymatical hydrolysis after oral intake or i.p. injection, and that hydrolysis may also take place in other tissues.

There is very little information available on hydrolysis of the candidate acetals in the present flavouring group (FGE.03Rev2). From available data on supporting substances as well as on acetals with differing chemical structures it is clear that the rates of both acid hydrolysis and enzymatic hydrolysis will vary with different chemical structure of the acetals, and that hydrolysis sometimes may be slow and incomplete. Data submitted show that the rate of hydrolysis may vary considerably, even within groups of closely related substances with simple structures. The rate of hydrolysis may also depend on the solubility of the substance in aqueous media. There is currently not enough information to draw general conclusions on hydrolysis rates of acetals.

Nevertheless, hydrolysis data on compounds with structural similarity to the candidate substances show that the candidate acetals may be predicted to be hydrolysed, but it cannot be excluded that some amounts of the parent acetals may reach the systemic circulation. However, experimental studies indicate that acetals may also be hydrolysed enzymatically in the liver and probably also in other tissues.

It is expected that the orthoester will be hydrolysed to innocuous compounds prior to absorption and that possible small amounts of the parent compound absorbed would be hydrolysed in the tissues.

For more detailed information, see Annex III.

5. Application of the Procedure for the Safety Evaluation of Flavouring Substances

The application of the Procedure is based on intakes estimated on the basis of the MSDI approach. Where the mTAMDI approach indicates that the intake of a flavouring substance might exceed its corresponding threshold of concern, a formal safety assessment is not carried out using the Procedure. In these cases the Panel requires more precise data on use and use levels. For comparison of the intake estimations based on the MSDI approach and the mTAMDI approach, see Section 6.

For the safety evaluation of the 59 candidate substances from chemical groups 1, 2 and 4, the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluations of the substances are summarised in Table 2a.

Step 1

All but one of the 59 substances are classified according to the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978) into structural class I suggesting a low order of oral toxicity.

One substance is triethoxymethane [FL-no: 06.096], an orthoester of formic acid, and is classified into structural class III, which means that it has a chemical structure that permits no strong initial presumption of safety.

Step 2

All candidate substances are expected to be metabolised into innocuous products at their estimated levels of intake based on the MSDI approach, and accordingly pass through the A-side of the Procedure for Safety Evaluation.

Step A3

The 58 candidate acetals from chemical groups 1, 2 and 4, which have all been assigned to class I, have estimated European daily *per capita* intakes from 0.001 to 14 microgram, which are below the threshold of concern of 1800 microgram/person/day for structural class I.

The European daily *per capita* intake of the orthoester [FL-no: 06.096], assigned to structural class III, is 0.013 microgram, which is below the threshold of concern for structural class III compounds of 90 microgram/person/day.

The response for the 59 candidate substances to step A3 (of the Procedure, Appendix I) is “No” and the substances are accordingly not expected to be of safety concern at the levels of intakes based on the MSDI approach.

6. Comparison of the Intake Estimations Based on the MSDI Approach and the mTAMDI Approach

The estimated intakes for the 58 candidate substances in structural class I based on the mTAMDI range from 3 to 9500 microgram/person/day. For 16 of the substances [FL-no: 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.129 and 06.137] the mTAMDI is above the threshold of concern of 1800 microgram/person/day

The estimated intake of the orthoester [FL-no: 06.096], assigned to structural class III, based on the mTAMDI, is 1600 microgram/person/day, which is above the threshold of concern for structural class III substances of 90 microgram/person/day.

Thus, for 17 of the substances further information is required. This would include more reliable intake data and then where required additional toxicity data.

For comparison of the MSDI and mTAMDI values, see Table 6.1

Table 6.1 Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
03.023	1-Ethoxyethyl acetate	7.1	2.6	Class I	1800
06.041	1-Isobutoxy-1-ethoxy-2-methylpropane	0.012	3900	Class I	1800
06.042	1-Isobutoxy-1-ethoxy-3-methylbutane	0.012	3900	Class I	1800
06.043	1-Isoamyloxy-1-ethoxypropane	0.012	3900	Class I	1800
06.044	1-Isobutoxy-1-ethoxypropane	0.012	1600	Class I	1800
06.045	1-Isobutoxy-1-isopentyloxy-2-methylpropane	0.012	3900	Class I	1800
06.046	1-Isobutoxy-1-isopentyloxy-3-methylbutane	0.012	3900	Class I	1800
06.047	1-Isopentyloxy-1-propoxyethane	0.037	3900	Class I	1800
06.048	1-Isopentyloxy-1-propoxypropane	0.012	1600	Class I	1800
06.049	1-Butoxy-1-(2-methylbutoxy)ethane	0.0061	1600	Class I	1800
06.050	1-Butoxy-1-ethoxyethane	0.012	1300	Class I	1800
06.051	1,1-Di-(2-methylbutoxy)ethane	0.012	1600	Class I	1800
06.052	1,1-Di-isobutoxy-2-methylpropane	0.39	1600	Class I	1800
06.053	1,1-Di-isobutoxyethane	0.13	1600	Class I	1800
06.054	1,1-Di-isobutoxypentane	0.12	1600	Class I	1800
06.055	1,1-Di-isopentyloxyethane	14	1600	Class I	1800
06.057	1,1-Diethoxy-2-methylbutane	0.73	1600	Class I	1800
06.058	1,1-Diethoxy-2-methylpropane	0.67	1600	Class I	1800
06.059	1,1-Diethoxy-3-methylbutane	0.51	1600	Class I	1800
06.061	1,1-Diethoxybutane	0.69	1600	Class I	1800
06.062	1,1-Diethoxydodecane	0.37	1700	Class I	1800
06.063	1,1-Diethoxyhex-3-ene	0.097	3900	Class I	1800
06.064	Diethoxymethane	0.097	1600	Class I	1800
06.065	1,1-Diethoxynonane	0.52	1600	Class I	1800
06.066	1,1-Diethoxyoctane	0.0012	1600	Class I	1800
06.067	1,1-Diethoxypentane	0.12	1600	Class I	1800
06.069	1,1-Diethoxypropane	0.77	1600	Class I	1800
06.070	1,1-Diethoxyundecane	0.0012	1600	Class I	1800
06.071	1,1-Dihexyloxyethane	0.67	1600	Class I	1800
06.073	1,1-Dimethoxyhexane	0.56	1600	Class I	1800
06.074	Dimethoxymethane	0.012	1600	Class I	1800
06.075	1,1-Dimethoxypentane	0.73	1600	Class I	1800
06.076	1,1-Dimethoxypropane	0.12	1600	Class I	1800
06.079	1-Ethoxy-1-(2-methylbutoxy)ethane	0.073	1600	Class I	1800
06.082	1-Ethoxy-1-hexyloxyethane	0.37	1600	Class I	1800
06.083	1-Ethoxy-1-isopentyloxyethane	1.2	1600	Class I	1800
06.084	1-Ethoxy-1-methoxyethane	0.12	1600	Class I	1800
06.085	1-Ethoxy-1-pentyloxyethane	0.012	1600	Class I	1800
06.086	1-Ethoxy-1-propoxyethane	0.012	1600	Class I	1800
06.091	1-Isobutoxy-1-ethoxyethane	0.097	1600	Class I	1800
06.092	1-Isobutoxy-1-isopentyloxyethane	0.37	1600	Class I	1800
06.100	1,1-Dipentyloxyethane	0.85	1600	Class I	1800
06.105	3-Methyl-1,1-di-isopentyloxybutane	0.012	3900	Class I	1800
06.106	2-Methyl-1,1-di-isopentyloxypropane	0.26	4900	Class I	1800
06.107	1-(2-Methylbutoxy)-1-isopentyloxyethane	0.024	3900	Class I	1800
06.109	1,1-Diethoxy-3,7-dimethyloct-6-ene	0.24	3900	Class I	1800

Table 6.1 Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
06.111	1-Ethoxy-1-methoxypropane	0.012	1600	Class I	1800
06.114	1-Hexyloxy-1-isopentyloxyethane	0.061	1600	Class I	1800
06.115	1-Isopentyloxy-1-pentyloxyethane	0.24	3900	Class I	1800
06.123	1-Butoxy-1-isopentyloxyethane	0.0061	3900	Class I	1800
06.124	1,1-Di-isobutoxy-3-methylbutane	0.037	3900	Class I	1800
06.125	1,1-Di-isobutoxypropane	0.37	1600	Class I	1800
06.127	1-Ethoxy-1-isopentyloxypropane	0.012	1600	Class I	1800
06.128	1-Ethoxy-1-pentyloxybutane	0.012	1600	Class I	1800
06.129	1-Ethoxy-2-methyl-1-isopentyloxypropane	0.012	3900	Class I	1800
06.130	1-Ethoxy-2-methyl-1-propoxypropane	0.012	1600	Class I	1800
06.131	1-Ethoxy-1-(3-methylbutoxy)-3-methylbutane	0.012	1600	Class I	1800
06.137	Acetaldehyde ethyl isopropyl acetal	12	9500	Class I	1800
06.096	Triethoxymethane	0.013	1600	Class III	90

7. Considerations of Combined Intakes from Use as Flavouring Substances

Because of structural similarities of candidate and supporting substances, it can be anticipated that many of the flavourings are metabolised through the same metabolic pathways and that the metabolites may affect the same target organs. Further, in case of combined exposure to structurally related flavourings, the pathways could be overloaded. Therefore, combined intake should be considered. As flavourings not included in this FGE may also be metabolised through the same pathways, the combined intake estimates presented here are only preliminary. Currently, the combined intake estimates are only based on MSDI exposure estimates, although it is recognised that this may lead to underestimation of exposure. After completion of all FGEs, this issue should be readdressed.

The total estimated combined daily *per capita* intake of structurally related flavourings is estimated by summing the MSDI for individual substances.

On the basis of the reported annual production volumes in Europe (EFFA, 2001d; EFFA, 2002a; EFFA, 2003s; Flavour Industry, 2007a; Flavour Industry, 2011c), the estimated combined daily *per capita* intake of the 58 flavouring substances assigned to structural class I is 45 microgram, which does not exceed the threshold of concern for the structural class of 1800 microgram/person/day.

The 58 candidate substances are structurally related to 12 supporting substances of which ten have been evaluated by the JECFA at its 57th session (JECFA, 2002b) and classified into structural class I, and two have been evaluated by CoE, 1992. It was noted that the estimated combined intake (in Europe) is approximately 270 microgram/*capita*/day for 11 of the 12 substances belonging to structural class I. The estimated level of intake in Europe was not reported for one of the supporting substances [FL-no: 06.081]. The total estimated combined intake of the 58 candidate and 11 supporting substances (in Europe) based on the intake calculation by the MSDI approach is 315 microgram/*capita*/day, which is below the threshold of concern for structural class I of 1800 microgram/person/day.

8. Toxicity

8.1. Acute Toxicity

Data are available for four candidate substances and for two supporting substances. The acute toxicity data are summarised in Annex IV, Table IV.1.

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

No studies were available on the candidate substances or on the supporting substances.

8.3. Developmental / Reproductive Toxicity Studies

No studies were available on the candidate substances or on the supporting substances.

8.4. Genotoxicity Studies

Genotoxicity has been tested *in vitro* for three out of the 59 candidate substances. These are two acetals (dimethoxymethane [FL-no: 06.074] and diethoxymethane [FL-no: 06.064]) and one orthoester of formic acid (triethoxymethane [FL-no: 06.096]). One of the acetals [FL-no: 06.074] has been tested *in vivo*. Genotoxicity data are also available for some alcohols and aldehydes resulting from hydrolysis of acetals. The genotoxicity data are summarised in Annex IV, Table IV.4 and Table IV.5.

Conclusion on genotoxicity:

Dimethoxymethane [FL-no: 06.074] induced gene mutations in a bacterial reversion assay (Ames test) without metabolic activation but not in mammalian (CHO) cells at the HPRT locus in the presence and absence of metabolic activation. It was negative in a mouse bone marrow micronucleus assay. The studies on diethoxymethane [FL-no: 06.064] and triethoxymethane [FL-no: 06.096] were not adequately reported and the results obtained cannot be assessed. Additionally, there are some positive findings with potential hydrolysis products of acetals *in vitro* and *in vivo*, such as formaldehyde, methanol, ethanol and acetaldehyde. The genotoxicity of these compounds is well known. However, ethanol (and acetaldehyde) are endogenously synthesised and the daily *in vivo* formation of ethanol has been estimated to be 40 - 80 mg/kg body weight/day (JECFA, 1997a). Also, methanol and formaldehyde occur in mg amount in a number of foods (TNO, 2000; EFSA, 2006i) and are also endogenous metabolites. It has for instance been estimated that one cup of coffee containing 50 - 150 mg caffeine may give rise to the formation of about 3 - 7.5 mg formaldehyde in the liver (Rubach, 1987).

It is concluded that the available data on genotoxicity do not give rise to safety concern with respect to genotoxicity for the candidate flavouring substances of FGE.03Rev2 at the estimated level of intake based on MSDI.

Genotoxicity data are summarised in Annex IV, Table IV.4 and Table IV.5.

9. Conclusions

Of the 59 flavouring substances 57 are acetals of branched- and straight-chain aliphatic saturated primary alcohols and branched- and straight-chain saturated or unsaturated aldehydes, one is an orthoester of formic acid and one is an ester of a hemiacetal. The substances belong to chemical groups 1, 2 and 4.

Thirty-three of the 59 substances possess a chiral centre. In most of these cases, the chirality results solely because the acetal is asymmetric, i.e. it is formed from an aldehyde and two different alcohols, none of which contains a chiral centre [FL-no: 03.023, 06.041, 06.042, 06.043, 06.044, 06.045, 06.046, 06.047, 06.048, 06.050, 06.082, 06.083, 06.084, 06.085, 06.086, 06.091, 06.092, 06.111, 06.114, 06.115, 06.123, 06.127, 06.128, 06.129, 06.130, 06.131 and 06.137]. According to the information provided by Industry since the publication of FGE.03Rev1,all these acetal derivatives occur as their mixtures of optical isomers (of the acetal moiety), i.e. as the racemates. This new information has implications for two of the substances in the present FGE, [FL-no: 06.043 and 06.127], as the Industry has informed that both are racemic mixtures of isomers and they then turned out to be identical substances. For three substances either the aldehyde [FL-no: 06.057 and 06.109] or the alcohol moiety [FL-no: 06.051] contain one chiral centre. According to the information provided [FL-no: 06.051, 06.057 and 06.109] are used as a racemic mixture. Three of the substances [FL-no: 06.049, 06.079 and 06.107] have one chiral centre in the aldehyde moiety and one in the alcohol

moiety. According to the information provided by Industry both the alcohol and the aldehyde moiety occur as their racemic mixtures (mixtures of R- and S-enantiomers).

Due to the presence and the position of a double bond, one of the 59 substances can exist as geometrical isomers [FL-no: 06.063]. No indication has been given that one of the possible isomers has preponderance in the commercial flavouring material.

Fifty-eight of the flavouring substances belong to structural class I and the orthoester [FL-no: 06.096] belongs to structural class III.

Forty-three of the substances in the present group of 59 substances have been reported to occur naturally in a wide range of food items.

According to the default MSDI approach, the 58 candidate substances assigned to structural class I have intakes in Europe from 0.001 to 14 microgram/*capita*/day, which are below the threshold of concern for structural class I of 1800 microgram/person/day. Likewise the estimated level of intake for the orthoester of 0.013 microgram/*capita*/day is below the threshold of concern for structural class III of 90 microgram/person/day.

On the basis of the reported annual production volumes in Europe (MSDI approach) the combined intake of the 58 candidate substances is 45 microgram/person/day. The total combined intake of the 58 candidate and 11 supporting substances for which intake data are available is 315 microgram/person/day, which is below the threshold of concern for structural class I.

Adequately reported genotoxicity studies are only available for one candidate substance [FL-no: 06.074] and not for any of the supporting substances. These studies do not give rise to safety concern with respect to genotoxicity of this candidate flavouring substance. Consideration was given to methanol, formaldehyde, ethanol and acetaldehyde that are potential hydrolysis products of several of the acetals in the present Flavouring Group Evaluation. In the light of the endogenous formation in humans of considerably larger amounts of the compounds without harmful effects, humans are considered to sufficiently metabolise the compounds formed from hydrolysis of the acetals at the estimated per capita intakes, based on maximised annual production volumes. Their use as flavouring substances at such level of intake is therefore not considered to be of safety concern.

The 59 candidate substances are expected to be metabolised to innocuous products.

There are no toxicological studies available on the 59 candidate substances or the supporting substances other than some data on acute toxicity.

It is considered that on the basis of the default MSDI approach, the 57 candidate acetals, the one candidate orthoester [FL-no: 06.096] and the ester of a hemiacetal [FL-no: 03.023] would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

When the estimated intakes were based on the mTAMDI approach they ranged from 3 to 9500 microgram/person/day for the 58 candidate substances from structural class I. The intakes were above the threshold of concern for structural class I of 1800 microgram/person/day for 16 of the flavouring substances [FL-no: 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.129 and 06.137]. For the one candidate substance from structural class III [FL-no: 06.096], the mTAMDI is 1600 microgram/person/day, which is above the threshold of concern for structural class III of 90 microgram/person/day. The 42 substances which have mTAMDI intake estimates below the threshold of concern for structural class I, are also expected to be metabolised to innocuous products.

Thus, for 17 of the 59 flavouring substances considered in this Opinion, the intakes, estimated on the basis of the mTAMDI, exceed the relevant threshold for their structural class to which the flavouring substance has been assigned. Therefore, for these 17 substances more reliable exposure data are

required. On the basis of such additional data, these flavouring substances should be reconsidered using the Procedure. Subsequently, additional data might become necessary.

In order to determine whether the conclusion for the 59 candidate substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Adequate specifications including complete purity criteria and identity tests for the materials of commerce have been provided for 42 of the 59 flavouring candidate substances. The specifications are not adequate for 17 substances [FL-no: 03.023, 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.128 and 06.129] as identity tests are lacking and for one of substances [FL-no: 06.063] has the stereoisomeric composition to be specified. Thus, the final evaluation of the materials of commerce cannot be performed for 17 substances ([FL-no: 03.023, 06.041, 06.042, 06.043, 06.045, 06.046, 06.047, 06.063, 06.105, 06.106, 06.107, 06.109, 06.115, 06.123, 06.124, 06.128, 06.129]), pending further information.

For the remaining 42 substances [FL-no: 06.044, 06.048, 06.049, 06.050, 06.051, 06.052, 06.053, 06.054, 06.055, 06.057, 06.058, 06.059, 06.061, 06.062, 06.064, 06.065, 06.066, 06.067, 06.069, 06.070, 06.071, 06.073, 06.074, 06.075, 06.076, 06.079, 06.082, 06.083, 06.084, 06.085, 06.086, 06.091, 06.092, 06.096, 06.100, 06.111, 06.114, 06.125, 06.127, 06.130, 06.131 and 06.137] the Panel concluded that they would present no safety concern at the estimated levels of intake based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 3, REVISION 2

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

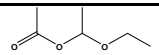
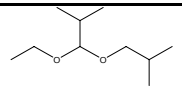
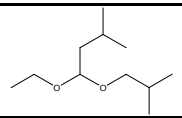
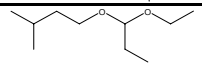
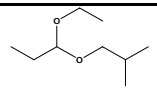
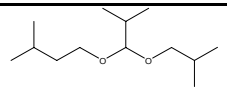
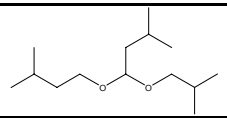
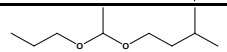
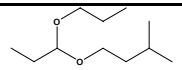
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
03.023	1-Ethoxyethyl acetate		4069 1608-72-6	Liquid $C_6H_{12}O_3$ 132.16	Very soluble Mostly soluble	137.14 n.a. 95 %	1.390-1.391 0.946-0.956	ID 7). Racemate (EFFA, 2010a).
06.041	1-Isobutoxy-1-ethoxy-2-methylpropane		10055	Liquid $C_{10}H_{22}O_2$ 174.28	Slightly soluble Freely soluble	170 95 %	1.398-1.404 0.824-0.830	ID 7). Racemate (EFFA, 2010a). CASrn is missing.
06.042	1-Isobutoxy-1-ethoxy-3-methylbutane		10057 85136-40-9	Liquid $C_{11}H_{24}O_2$ 188.31	Slightly soluble Freely soluble	191 95 %	1.397-1.403 0.838-0.844	ID 7). Racemate (EFFA, 2010a).
06.043	1-Isoamyloxy-1-ethoxypropane		10038 238757-30-7	Liquid $C_{10}H_{22}O_2$ 174.28	Practically insoluble or insoluble Freely soluble	183 95 %	1.398-1.404 0.837-0.843	ID 7). Racemate (2010a). This substance is identical to [FL-no: 06.127].
06.044	1-Isobutoxy-1-ethoxypropane		10058 67234-04-2	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Freely soluble	162 MS 95 %	1.395-1.401 0.840-0.845	Racemate (EFFA, 2010a).
06.045	1-Isobutoxy-1-isopentyloxy-2-methylpropane		10061	Liquid $C_{13}H_{28}O_2$ 216.36	Slightly soluble Freely soluble	219 95 %	1.407-1.412 0.828-0.834	ID 7). Racemate (EFFA, 2010a). CASrn is missing.
06.046	1-Isobutoxy-1-isopentyloxy-3-methylbutane		10060	Liquid $C_{14}H_{30}O_2$ 230.39	Slightly soluble Freely soluble	237 95 %	1.404-1.410 0.836-0.842	ID 7). Racemate (EFFA, 2010a). CASrn is missing.
06.047	1-Isopentyloxy-1-propoxyethane		10065 238757-63-6	Liquid $C_{10}H_{22}O_2$ 174.28	Slightly soluble Freely soluble	183 95 %	1.395-1.401 0.836-0.842	ID 7). Racemate EFFA, 2010a). Missing CASrn.
06.048	1-Isopentyloxy-1-propoxypropane		10066 238757-56-8	Liquid $C_{11}H_{24}O_2$ 188.31	Insoluble Freely soluble	203 NMR 95 %	1.403-1.409 0.840-0.845	Racemate (EFFA, 2010a). CASrn in Register not valid. The

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

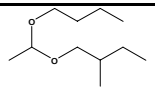
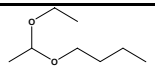
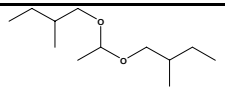
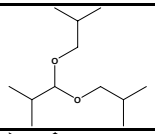
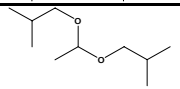
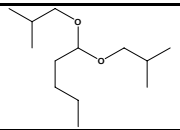
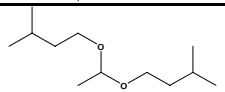
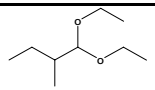
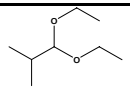
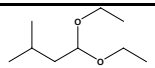
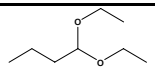
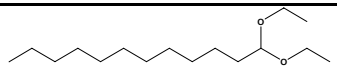
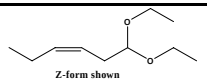
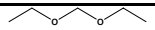
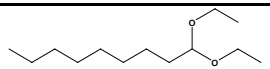
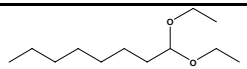
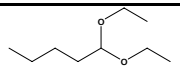
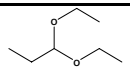
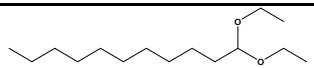
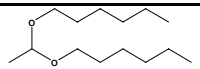
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
								CASrn to be changed to 238757-65-8.
06.049	1-Butoxy-1-(2-methylbutoxy)ethane		77249-20-8	Liquid $C_{11}H_{24}O_2$ 188.31	Insoluble Freely soluble	203 NMR 95 %	1.401-1.407 0.839-0.844	Racemate: Alcohol moiety: racemic. Aldehyde moity: racemic (EFFA, 2010a)
06.050	1-Butoxy-1-ethoxyethane		10003 57006-87-8	Liquid $C_8H_{18}O_2$ 146.23	Slightly soluble Freely soluble	148 MS 95 %	1.396-1.402 0.826-0.832	Racemate (EFFA, 2010a).
06.051	1,1-Di-(2-methylbutoxy)ethane		13535-43-8	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	205 MS 95 %	1.413-1.419 0.823-0.829	Racemate.
06.052	1,1-Di-isobutoxy-2-methylpropane		10025 13262-24-3	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	194 MS 95 %	1.406-1.412 0.823-0.829	
06.053	1,1-Di-isobutoxyethane		10023 5669-09-0	Liquid $C_{10}H_{22}O_2$ 174.28	Insoluble Freely soluble	171 MS 95 %	1.399-1.405 0.817-0.823	
06.054	1,1-Di-isobutoxypentane		10026 13262-27-6	Liquid $C_{13}H_{28}O_2$ 216.36	Insoluble Freely soluble	230 NMR 95 %	1.415-1.421 0.838-0.843	
06.055 1729	1,1-Di-isopentyloxyethane		10028 13002-09-0	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	210 MS 95 %	1.411-1.417 0.826-0.832	
06.057	1,1-Diethoxy-2-methylbutane		10013 3658-94-4	Liquid $C_9H_{20}O_2$ 160.26	Slightly soluble Freely soluble	162 MS 95 %	1.393-1.399 0.837-0.842	Racemate.
06.058	1,1-Diethoxy-2-methylpropane		10015 1741-41-9	Liquid $C_8H_{18}O_2$ 146.23	Slightly soluble Freely soluble	135 MS 95 %	1.390-1.396 0.826-0.832	

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

FL-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)	Specification comments
06.059 1730	1,1-Diethoxy-3-methylbutane		4371 10014 3842-03-3	Liquid $C_9H_{20}O_2$ 160.26	Slightly soluble Freely soluble	156 MS 95 %	1.398-1.404 0.832-0.838	
06.061	1,1-Diethoxybutane		10009 3658-95-5	Liquid $C_8H_{18}O_2$ 146.23	Slightly soluble Freely soluble	143 MS 97 %	1.393-1.399 0.820-0.829	
06.062	1,1-Diethoxydodecane		53405-98-4	Liquid $C_{16}H_{34}O_2$ 258.44	Insoluble Freely soluble	300 MS 95 %	1.429-1.435 0.842-0.847	
06.063	1,1-Diethoxyhex-3-ene 6)		73545-18-3	Liquid $C_{10}H_{20}O_2$ 172.27	Practically insoluble or insoluble Freely soluble	65 (0.3 hPa) 95 %	1.408-1.414 0.856-0.862	ID 7). CASrn in Register refers to the (Z)-isomer.
06.064	Diethoxymethane		10012 462-95-3	Liquid $C_5H_{12}O_2$ 104.15	Soluble Freely soluble	88 MS 95 %	1.370-1.379 0.827-0.833	
06.065	1,1-Diethoxynonane		10016 54815-13-3	Liquid $C_{13}H_{28}O_2$ 216.36	Insoluble Freely soluble	106 (13 hPa) MS 95 %	1.419-1.425 0.842-0.847	
06.066	1,1-Diethoxyoctane		54889-48-4	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	222 MS 95 %	1.414-1.420 0.829-0.835	
06.067	1,1-Diethoxypentane		10017 3658-79-5	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Freely soluble	163 MS 95 %	1.399-1.405 0.826-0.832	
06.069	1,1-Diethoxypropane		10018 4744-08-5	Liquid $C_7H_{16}O_2$ 132.20	Slightly soluble Freely soluble	123 MS 95 %	1.386-1.392 0.824-0.830	
06.070	1,1-Diethoxyundecane		53405-97-3	Liquid $C_{15}H_{32}O_2$ 244.42	Insoluble Freely soluble	285 MS 95 %	1.426-1.432 0.842-0.847	
06.071	1,1-Dihexyloxyethane		10022 5405-58-3	Liquid $C_{14}H_{30}O_2$ 230.39	Insoluble Freely soluble	153 (32 hPa) MS 95 %	1.420-1.426 0.833-0.839	

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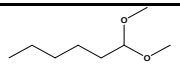
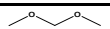
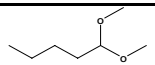
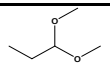
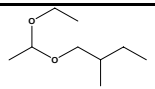
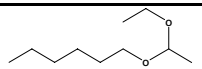
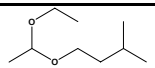
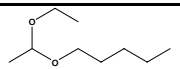
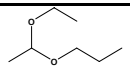
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
06.073	1,1-Dimethoxyhexane		 1599-47-9	Liquid $C_8H_{18}O_2$ 146.23	Slightly soluble Freely soluble	158 MS 95 %	1.403-1.409 0.843-0.849	
06.074	Dimethoxymethane		 10031 109-87-5	Liquid $C_3H_8O_2$ 76.10	Soluble Freely soluble	42 0 MS 95 %	1.350-1.356 0.855-0.862	
06.075	1,1-Dimethoxypentane		 26450-58-8	Liquid $C_7H_{16}O_2$ 132.20	Slightly soluble Freely soluble	131 MS 95 %	1.394-1.400 0.839-0.844	
06.076	1,1-Dimethoxypropane		 4744-10-9	Liquid $C_5H_{12}O_2$ 104.15	Slightly soluble Freely soluble	88 MS 95 %	1.376-1.382 0.842-0.848	
06.079	1-Ethoxy-1-(2-methylbutoxy)ethane		 10040 13602-09-0	Liquid $C_9H_{20}O_2$ 160.26	Slightly soluble Freely soluble	162 NMR 95 %	1.392-1.398 0.838-0.843	Racemate: Alcohol moiety: racemic. Aldehyde moiety: racemic (EFFA, 2010a).
06.082	1-Ethoxy-1-hexyloxyethane		 11948 54484-73-0	Liquid $C_{10}H_{22}O_2$ 174.28	Slightly soluble Freely soluble	66 (17 hPa) MS 95 %	1.408-1.414 0.829-0.835	Racemate (EFFA, 2010a).
06.083	1-Ethoxy-1-isopentyloxyethane		 10037 13442-90-5	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Freely soluble	166 MS 95 %	1.401-1.407 0.838-0.843	Racemate (EFFA, 2010a).
06.084	1-Ethoxy-1-methoxyethane		 10039 10471-14-4	Liquid $C_5H_{12}O_2$ 104.15	Slightly soluble Freely soluble	85 MS 95 %	1.372-1.378 0.825-0.831	Racemate (EFFA, 2010a).
06.085	1-Ethoxy-1-pentyloxyethane		 10046 59184-43-9	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Freely soluble	175 MS 95 %	1.404-1.410 0.840-0.845	Racemate (EFFA, 2010a). CASrn in Register to be changed to 13442-89-2.
06.086	1-Ethoxy-1-propoxyethane		 10050 20680-10-8	Liquid $C_7H_{16}O_2$ 132.20	Slightly soluble Freely soluble	126 MS 95 %	1.389-1.395 0.827-0.837	Racemate (EFFA, 2010a).

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

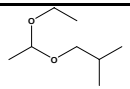
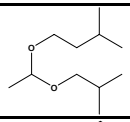
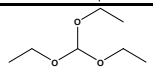
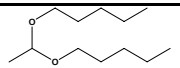
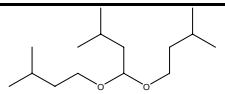
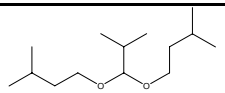
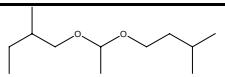
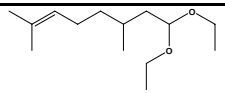
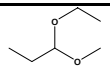
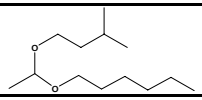
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
06.091	1-Isobutoxy-1-ethoxyethane		10054 6986-51-2	Liquid $C_8H_{18}O_2$ 146.23	Slightly soluble Freely soluble	155 MS 95 %	1.381-1.387 0.818-0.824	Racemate (EFFA, 2010a).
06.092	1-Isobutoxy-1-isopentyloxyethane		10059 75048-15-6	Liquid $C_{11}H_{24}O_2$ 188.31	Insoluble Freely soluble	191 NMR 95 %	1.406-1.412 0.838-0.843	Racemate (EFFA, 2010a).
06.096	Triethoxymethane		10903 122-51-0	Liquid $C_7H_{16}O_3$ 148.20	Slightly soluble Freely soluble	144 MS 98 %	1.389-1.395 0.886-0.895	
06.100	1,1-Dipentyloxyethane		10032 13002-08-9	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	224 NMR MS 95 %	1.414-1.420 0.833-0.839	
06.105	3-Methyl-1,1-di-isopentyloxybutane		10070 13285-51-3	Liquid $C_{15}H_{32}O_2$ 244.42	Slightly soluble Freely soluble	252 95 %	1.411-1.417 0.846-0.852	ID 7).
06.106	2-Methyl-1,1-di-isopentyloxypropane		10071 13112-63-5	Liquid $C_{14}H_{30}O_2$ 230.39	Slightly soluble Freely soluble	100 (11 hPa) 95 %	1.416-1.422 0.835-0.841	ID 7).
06.107	1-(2-Methylbutoxy)-1-isopentyloxyethane		10068 13548-84-0	Liquid $C_{12}H_{26}O_2$ 202.33	Slightly soluble Freely soluble	223 95 %	1.413-1.419 0.824-0.830	ID 7). Racemate: Alcohol moiety: racemic. Aldehyde moiety: racemic (EFFA, 2010a).
06.109	1,1-Diethoxy-3,7-dimethyloct-6-ene		71662-17-4	Liquid $C_{14}H_{28}O_2$ 228.37	Practically insoluble or insoluble Freely soluble	232 95 %	1.411-1.417 0.857-0.863	ID 7). Racemate (EFFA, 2010a).
06.111	1-Ethoxy-1-methoxypropane		- - 127248-84-4	Liquid $C_6H_{14}O_2$ 118.18	Slightly soluble Freely soluble	108 MS 95 %	1.378-1.384 0.838-0.843	Racemate (EFFA, 2010a).
06.114	1-Hexyloxy-1-isopentyloxyethane		233665-90-2	Liquid $C_{13}H_{28}O_2$ 216.36	Insoluble Freely soluble	241 NMR 95 %	1.415-1.421 0.837-0.842	Racemate (EFFA, 2010a)

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

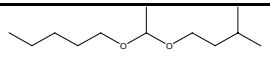
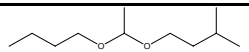
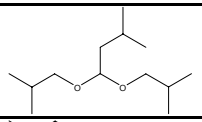
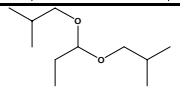
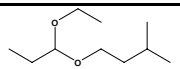
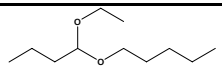
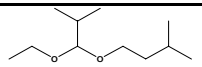
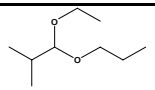
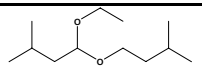
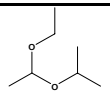
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	Specification comments
06.115	1-Isopentyloxy-1-pentyloxyethane		13442-92-7	Liquid $C_{12}H_{26}O_2$ 202.33	Slightly soluble Freely soluble	222 95 %	1.410-1.416 0.827-0.833	ID 7). Racemate (EFFA, 2010a).
06.123	1-Butoxy-1-isopentyloxyethane		10004 238757-27-2	Liquid $C_{11}H_{24}O_2$ 188.31	Slightly soluble Freely soluble	202 95 %	1.412-1.418 0.837-0.843	ID 7). Racemate (EFFA, 2010a).
06.124	1,1-Di-isobutoxy-3-methylbutane		10024 13439-98-0	Liquid $C_{13}H_{28}O_2$ 216.36	Slightly soluble Freely soluble	219 95 %	1.416-1.422 0.840-0.846	ID 7).
06.125	1,1-Di-isobutoxypropane		10027 13002-11-4	Liquid $C_{11}H_{24}O_2$ 188.31	Insoluble Freely soluble	82 (26 hPa) MS 95 %	1.404-1.410 0.838-0.843	
06.127	1-Ethoxy-1-isopentyloxypropane		10036 238757-30-7	Liquid $C_{10}H_{22}O_2$ 174.28	Insoluble Freely soluble	183 MS 95 %	1.403-1.409 0.839-0.844	Racemate (EFFA, 2010a). This substance is identical to [FL-no: 06.043].
06.128	1-Ethoxy-1-pentyloxybutane		10045 3658-92-2	Liquid $C_{11}H_{24}O_2$ 188.31	Insoluble Freely soluble	99 (33 hPa) 95 %	1.409-1.415 0.836-0.842	ID 7). Racemate (EFFA, 2010a)
06.129	1-Ethoxy-2-methyl-1-isopentyloxypropane		10043 253679-74-2	Liquid $C_{11}H_{24}O_2$ 188.31	Slightly soluble Freely soluble	191 95 %	1.396-1.402 0.825-0.831	ID 7). Racemate (EFFA, 2010a).
06.130	1-Ethoxy-2-methyl-1-propoxypropane		10044 238757-42-1	Liquid $C_9H_{20}O_2$ 160.26	Insoluble Freely soluble	162 NMR 95 %	1.394-1.400 0.838-0.843	Racemate (EFFA, 2010a)
06.131	1-Ethoxy-1-(3-methylbutoxy)-3-methylbutane		10042	Liquid $C_{12}H_{26}O_2$ 202.34	Insoluble Freely soluble	211 NMR 95 %	1.405-1.411 0.839-0.844	Racemate (EFFA, 2010a). CASrn is missing.
06.137	Acetaldehyde ethyl isopropyl acetal		4432 25334-93-4	Liquid $C_7H_{16}O_2$ 132.20	Slightly soluble Soluble	126 IR NMR MS 90 %	1.396 0.840	Racemate. 90 % Acet-aldehyde ethyl isopropyl acetal, 8

Table 1: Specification Summary of the Substances in the Flavouring Group Evaluation 3, Revision 2

FL-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)	Specification comments
								% Acetaldehyde diethylacetal and less than 0.5 % of each: isopropyl vinyl ether, ethyl acetate, isopropyl acetate and acetaldehyde (Flavour Industry, 2011 c).

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.*
7) *ID: Missing identification test.*

TABLE 2A: SUMMARY OF SAFETY EVALUATION APPLYING THE PROCEDURE (BASED ON INTAKES CALCULATED BY THE MSDI APPROACH)

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

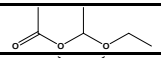
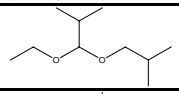
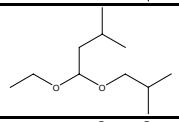
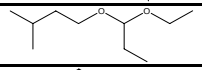
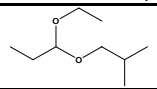
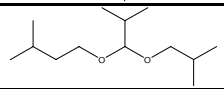
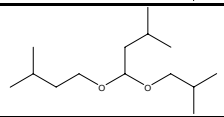
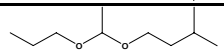
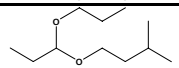
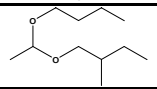
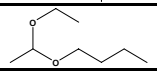
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
03.023	1-Ethoxyethyl acetate		7.1	Class I A3: Intake below threshold	4)	7)	
06.041	1-Isobutoxy-1-ethoxy-2-methylpropane		0.012	Class I A3: Intake below threshold	4)	7)	
06.042	1-Isobutoxy-1-ethoxy-3-methylbutane		0.012	Class I A3: Intake below threshold	4)	7)	
06.043	1-Isoamyloxy-1-ethoxypropane		0.012	Class I A3: Intake below threshold	4)	7)	
06.044	1-Isobutoxy-1-ethoxypropane		0.012	Class I A3: Intake below threshold	4)	6)	
06.045	1-Isobutoxy-1-isopentyloxy-2-methylpropane		0.012	Class I A3: Intake below threshold	4)	7)	
06.046	1-Isobutoxy-1-isopentyloxy-3-methylbutane		0.012	Class I A3: Intake below threshold	4)	7)	
06.047	1-Isopentyloxy-1-propoxyethane		0.037	Class I A3: Intake below threshold	4)	7)	
06.048	1-Isopentyloxy-1-propoxypropane		0.012	Class I A3: Intake below threshold	4)	6)	
06.049	1-Butoxy-1-(2-methylbutoxy)ethane		0.0061	Class I A3: Intake below threshold	4)	6)	
06.050	1-Butoxy-1-ethoxyethane		0.012	Class I A3: Intake below threshold	4)	6)	

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

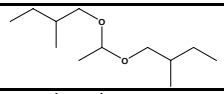
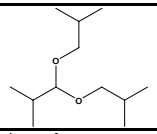
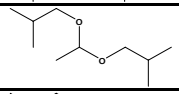
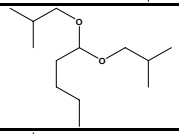
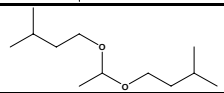
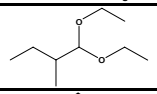
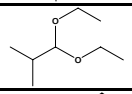
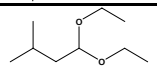
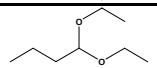
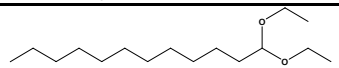
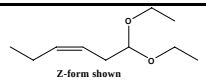
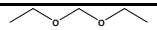
FL-no	EU Register name	Structural formula	MSDI 1) (μg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
06.051	1,1-Di-(2-methylbutoxy)ethane		0.012	Class I A3: Intake below threshold	4)	6)	
06.052	1,1-Di-isobutoxy-2-methylpropane		0.39	Class I A3: Intake below threshold	4)	6)	
06.053	1,1-Di-isobutoxyethane		0.13	Class I A3: Intake below threshold	4)	6)	
06.054	1,1-Di-isobutoxypentane		0.12	Class I A3: Intake below threshold	4)	6)	
06.055 1729	1,1-Di-isopentyloxyethane		14	Class I A3: Intake below threshold	4)	6)	
06.057	1,1-Diethoxy-2-methylbutane		0.73	Class I A3: Intake below threshold	4)	6)	
06.058	1,1-Diethoxy-2-methylpropane		0.67	Class I A3: Intake below threshold	4)	6)	
06.059 1730	1,1-Diethoxy-3-methylbutane		0.51	Class I A3: Intake below threshold	4)	6)	
06.061	1,1-Diethoxybutane		0.69	Class I A3: Intake below threshold	4)	6)	
06.062	1,1-Diethoxydodecane		0.37	Class I A3: Intake below threshold	4)	6)	
06.063	1,1-Diethoxyhex-3-ene	 Z-form shown	0.097	Class I A3: Intake below threshold	4)	7)	
06.064	Diethoxymethane		0.097	Class I A3: Intake below threshold	4)	6)	

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

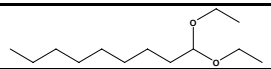
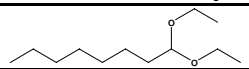
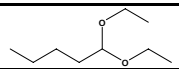
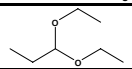
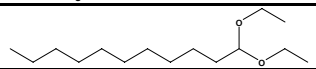
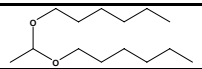
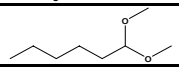
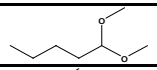
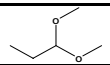
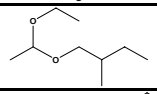
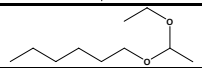
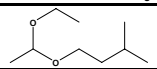
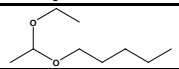
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
06.065	1,1-Diethoxynonane		0.52	Class I A3: Intake below threshold	4)	6)	
06.066	1,1-Diethoxyoctane		0.0012	Class I A3: Intake below threshold	4)	6)	
06.067	1,1-Diethoxypentane		0.12	Class I A3: Intake below threshold	4)	6)	
06.069	1,1-Diethoxypropane		0.77	Class I A3: Intake below threshold	4)	6)	
06.070	1,1-Diethoxyundecane		0.0012	Class I A3: Intake below threshold	4)	6)	
06.071	1,1-Dihexyloxyethane		0.67	Class I A3: Intake below threshold	4)	6)	
06.073	1,1-Dimethoxyhexane		0.56	Class I A3: Intake below threshold	4)	6)	
06.074	Dimethoxymethane		0.012	Class I A3: Intake below threshold	4)	6)	
06.075	1,1-Dimethoxypentane		0.73	Class I A3: Intake below threshold	4)	6)	
06.076	1,1-Dimethoxypropane		0.12	Class I A3: Intake below threshold	4)	6)	
06.079	1-Ethoxy-1-(2-methylbutoxy)ethane		0.073	Class I A3: Intake below threshold	4)	6)	
06.082	1-Ethoxy-1-hexyloxyethane		0.37	Class I A3: Intake below threshold	4)	6)	
06.083	1-Ethoxy-1-isopentyloxyethane		1.2	Class I A3: Intake below threshold	4)	6)	
06.084	1-Ethoxy-1-methoxyethane		0.12	Class I A3: Intake below threshold	4)	6)	
06.085	1-Ethoxy-1-pentyloxyethane		0.012	Class I A3: Intake below threshold	4)	6)	

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

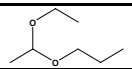
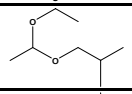
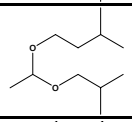
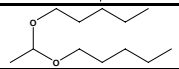
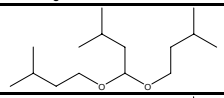
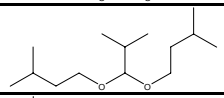
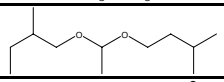
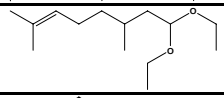
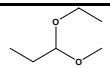
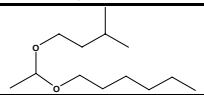
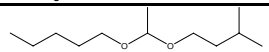
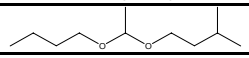
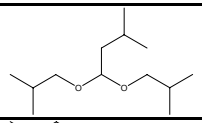
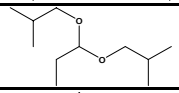
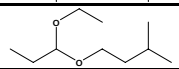
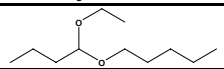
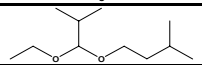
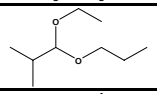
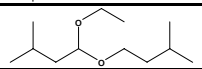
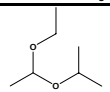
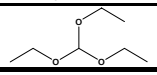
FL-no	EU Register name	Structural formula	MSDI 1) (µg/capita/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5]	Outcome on the material of commerce [6), 7), or 8)]	Evaluation remarks
06.086	1-Ethoxy-1-propoxyethane		0.012	Class I A3: Intake below threshold	4)	6)	
06.091	1-Isobutoxy-1-ethoxyethane		0.097	Class I A3: Intake below threshold	4)	6)	
06.092	1-Isobutoxy-1-isopentyloxyethane		0.37	Class I A3: Intake below threshold	4)	6)	
06.100	1,1-Dipentyloxyethane		0.85	Class I A3: Intake below threshold	4)	6)	
06.105	3-Methyl-1,1-di-isopentyloxybutane		0.012	Class I A3: Intake below threshold	4)	7)	
06.106	2-Methyl-1,1-di-isopentyloxypropane		0.26	Class I A3: Intake below threshold	4)	7)	
06.107	1-(2-Methylbutoxy)-1-isopentyloxyethane		0.024	Class I A3: Intake below threshold	4)	7)	
06.109	1,1-Diethoxy-3,7-dimethyloct-6-ene		0.24	Class I A3: Intake below threshold	4)	7)	
06.111	1-Ethoxy-1-methoxypropane		0.012	Class I A3: Intake below threshold	4)	6)	
06.114	1-Hexyloxy-1-isopentyloxyethane		0.0	Class I A3: Intake below threshold	4)	6)	
06.115	1-Isopentyloxy-1-pentyloxyethane		0.24	Class I A3: Intake below threshold	4)	7)	
06.123	1-Butoxy-1-isopentyloxyethane		0.0061	Class I A3: Intake below threshold	4)	7)	

Table 2a: 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
06.124	1,1-Di-isobutoxy-3-methylbutane		0.037	Class I A3: Intake below threshold	4)	7)	
06.125	1,1-Di-isobutoxypropane		0.37	Class I A3: Intake below threshold	4)	6)	
06.127	1-Ethoxy-1-isopentyloxypropane		0.012	Class I A3: Intake below threshold	4)	6)	
06.128	1-Ethoxy-1-pentyloxybutane		0.012	Class I A3: Intake below threshold	4)	7)	
06.129	1-Ethoxy-2-methyl-1-isopentyloxypropane		0.012	Class I A3: Intake below threshold	4)	7)	
06.130	1-Ethoxy-2-methyl-1-propoxypropane		0.012	Class I A3: Intake below threshold	4)	6)	
06.131	1-Ethoxy-1-(3-methylbutoxy)-3-methylbutane		0.012	Class I A3: Intake below threshold	4)	6)	
06.137	Acetaldehyde ethyl isopropyl acetal		12	Class I A3: Intake below threshold	4)	6)	
06.096	Triethoxymethane		0.013	Class III 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 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.

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

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

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

6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).

7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.

8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.

TABLE 2B: EVALUATION STATUS OF HYDROLYSIS PRODUCTS OF CANDIDATE ESTERS

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

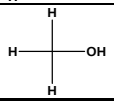
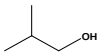
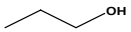
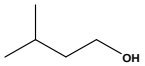
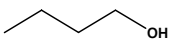
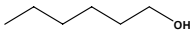
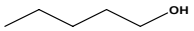
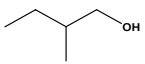
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
	Formaldehyde CH_2O 30.03		Not evaluated as flavouring substance		Not in EU-Register.
	Methanol CH_3O 31.03		Not evaluated as flavouring substance		Not in EU-Register.
02.001	2-Methylpropan-1-ol 251		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.002	Propan-1-ol 82		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.003	Isopentanol 52		Category 1 a) No safety concern d) Category A c)	Class I A3: Intake below threshold	
02.004	Butan-1-ol 85		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.005	Hexan-1-ol 91		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
02.040	Pentan-1-ol 88		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
02.076	2-Methylbutan-1-ol 1199		Category 1 a) No safety concern e) Category B c)	Class I A3: Intake below threshold	
02.078	Ethanol 41		Category 1 a) No safety concern d)	No evaluation	At the forty-sixth JECFA meeting (JECFA, 1997a), the Committee concluded that ethanol posed no safety concern at its current level of intake when ethyl esters are used as flavouring agents.

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

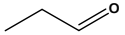
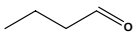
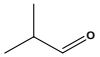
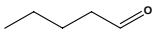
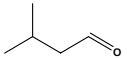
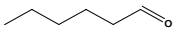
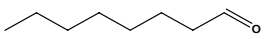
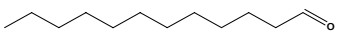
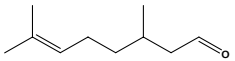
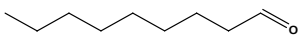
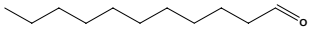
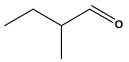
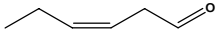
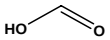
FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
02.079	Isopropanol 277		Category 1 a) No safety concern f)	Class I A3: Intake above threshold, A4: Endogenous	
05.001	Acetaldehyde 80		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
05.002	Propanal 83		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.003	Butanal 86		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.004	2-Methylpropanal 252		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.005	Pentanal 89		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	
05.006	3-Methylbutanal 258		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.008	Hexanal 92		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.009	Octanal 98		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.011	Dodecanal 110		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.021	Citronellal 1220		No safety concern e) Category A c)	Class I A3: Intake below threshold	

Table 2b: Evaluation Status of Hydrolysis Products of Candidate Esters

FL-no	EU Register name JECFA no	Structural formula	SCF status 1) JECFA status 2) CoE status 3) EFSA status	Structural class 4) Procedure path (JECFA) 5)	Comments
05.025	Nonanal 101		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.034	Undecanal 107		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.049	2-Methylbutyraldehyde 254		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake below threshold	
05.075	Hex-3(cis)-enal 316		No safety concern f) Category B c)	Class I A3: Intake below threshold	
08.001	Formic acid 79		Category 1 a) No safety concern b) Deleted c)	Class I A3: Intake below threshold	
08.002	Acetic acid 81		Category 1 a) No safety concern b) Category A c)	Class I A3: Intake above threshold, A4: Endogenous	

1) Category 1: Considered safe in use Category 2: Temporarily considered safe in use Category 3: Insufficient data to provide assurance of safety in use Category 4): Not acceptable due to evidence of toxicity.

2) No safety concern at estimated levels of intake.

3) Category A: Flavouring substance, which may be used in foodstuffs Category B: Flavouring substance which can be used provisionally in foodstuffs

4) Threshold of concern: Class I = 1800 µg/person/day, Class II = 540 µg/person/day, Class III = 90 µg/person/day.

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

a) (SCF, 1995).

b) (JECFA, 1999b).

c) (CoE, 1992).

d) (JECFA, 1997a).

e) (JECFA, 2004a).

f) (JECFA, 2000a).

ND: Not detected.

TABLE 3: SUPPORTING SUBSTANCES SUMMARY

Table 3: Supporting Substances Summary

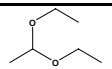
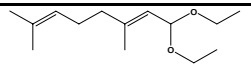
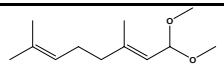
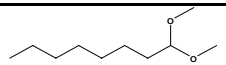
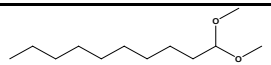
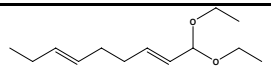
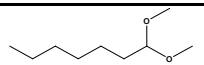
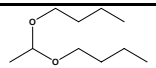
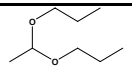
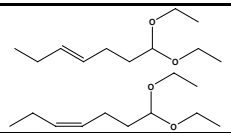
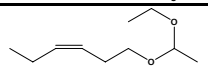
FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (μg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
06.001	1,1-Diethoxyethane		2002 35 105-57-7	941 JECFA specification (JECFA, 2001c)	200	No safety concern a) Category A b)	
06.004	Citral diethyl acetal	 (E)-isomer shown	2304 38 7492-66-2	948 JECFA specification (JECFA, 2001c)	3.4	No safety concern a) Category A b)	GrADI: 0-0.5 (JECFA, 1980a).
06.005	Citral dimethyl acetal	 (E)-isomer shown	2305 39 7549-37-3	944 JECFA specification (JECFA, 2001c)	2.6	No safety concern a) Category A b)	
06.008	1,1-Dimethoxyoctane		2798 42 10022-28-3	942 JECFA specification (JECFA, 2001c)	0.97	No safety concern a) Category A b)	
06.009	10,10-Dimethoxydecane		2363 43 7779-41-1	945 JECFA specification (JECFA, 2001c)	0.024	No safety concern a) Category B b)	
06.015	1,1-Dimethoxyethane		3426 510 534-15-6	940 JECFA specification (JECFA, 2001c)	61	No safety concern a) Category A b)	
06.025	1,1-Diethoxynona-2,6-diene		3378 660 67674-36-6	946 JECFA specification (JECFA, 2001c)	0.037	No safety concern a) Category B b)	CASrn refers to (2Z,6Z)-isomer.
06.028	1,1-Dimethoxyheptane		2541 2015 10032-05-0	947 JECFA specification (JECFA, 2001c)	0.037	No safety concern a) Category A b)	
06.033	1,1-Dibutoxyethane		2341 871-22-7		0.073	Category A b)	
06.034	1,1-Dipropoxyethane		4688 2342 105-82-8		0.71	Category A b)	
06.037	1,1-Diethoxyhept-4-ene (cis and trans)		3349 10011 18492-65-4	949 JECFA specification (JECFA, 2001c)	0.037	No safety concern a)	CASrn refers to (Z)-isomer.
06.081	1-Ethoxy-1-(3-hexenyloxy)ethane		3775 10034	943 JECFA specification (JECFA,	4.6	No safety concern a)	Register name to be changed to 1-Ethoxy-1-

Table 3: Supporting Substances Summary

FL-no	EU Register name	Structural formula	FEMA no CoE no CAS no	JECFA no Specification available	MSDI (EU) 1) (µg/capita/day)	SCF status 2) JECFA status 3) CoE status 4)	Comments
			28069-74-1	2002d)			(3Z-hexenyloxy)ethane. Racemate of 1-Ethoxy-1-(3Z-hexenyloxy)ethane (EFFA, 2010a).

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

2) Category 1: Considered safe in use, Category 2: Temporarily considered safe in use, Category 3: Insufficient data to provide assurance of safety in use, Category 4: Not acceptable due to evidence of toxicity.

3) No safety concern at estimated levels of intake.

4) Category A: Flavouring substance, which may be used in foodstuffs, Category B: Flavouring substance which can be used provisionally in foodstuffs.

a) (JECFA, 2002b).

b) (CoE, 1992).

ND) No intake data reported.

ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), named the "Procedure", is shown in schematic form in Figure I.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999a), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b).

The Procedure is a stepwise approach that integrates information on intake from current uses, structure-activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II, III) for which thresholds of concern (human exposure thresholds) have been specified. Exposures below these thresholds are not considered to present a safety concern.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1800, 540 or 90 microgram/person/day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996a).

In Step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- can the flavourings be predicted to be metabolised to innocuous products[9] (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous[10] (Step A4)?
- does a NOAEL exist on the flavourings or on structurally related substances (Step A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure.

The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

[9] *"Innocuous metabolic products": Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent" (JECFA, 1997a).*

[10] *"Endogenous substances": Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997a).*

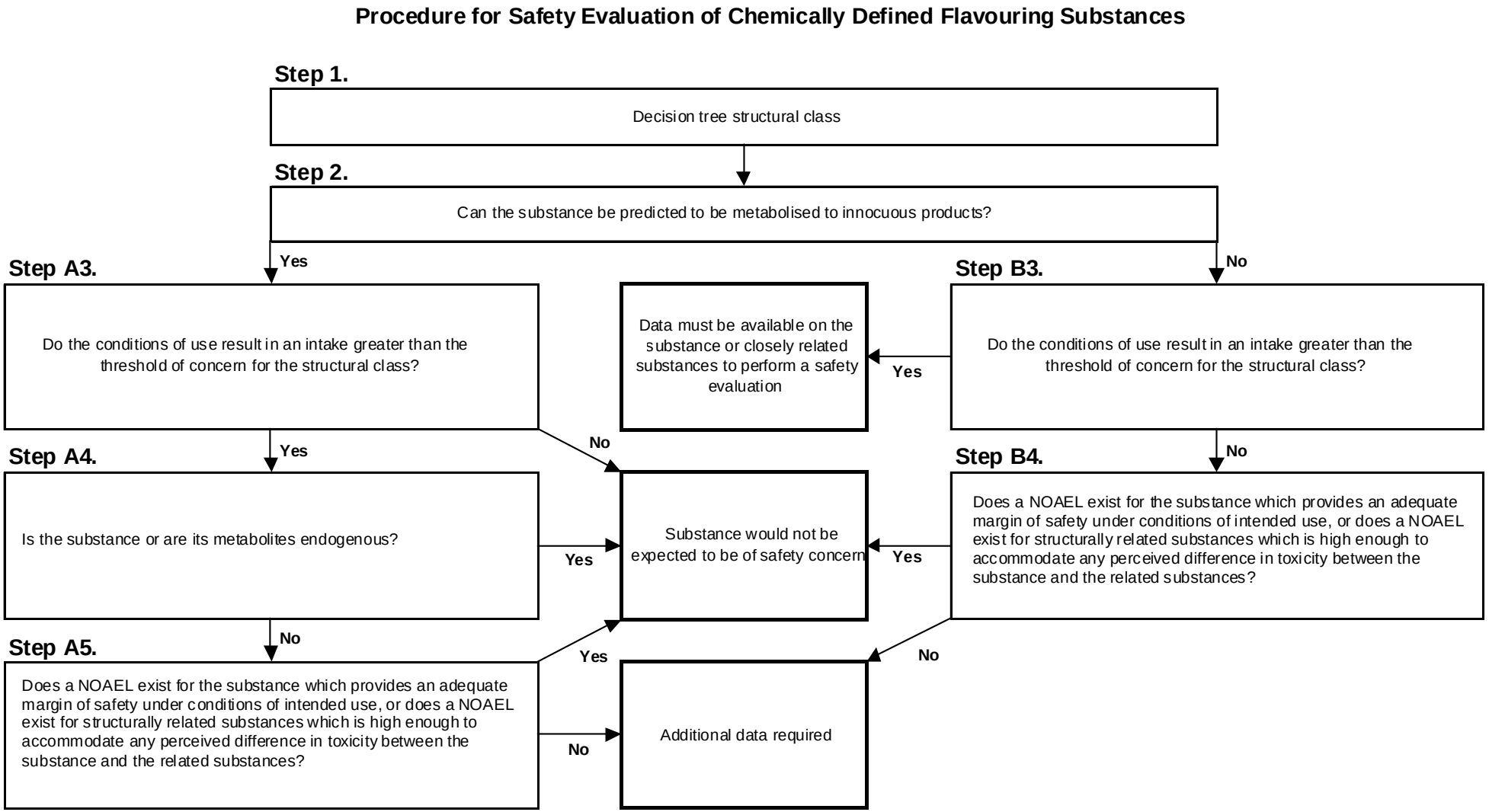


Figure I.1 *Procedure for Safety Evaluation of Chemically Defined Flavouring Substances*

ANNEX II: USE LEVELS / MTAMDI

II.1 Normal and Maximum Use Levels

For each of the 18 Food categories (Table II.1.1) in which the candidate substances are used, Flavour Industry reports a "normal use level" and a "maximum use level" (EC, 2000a). According to the Industry the "normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

Table II.1.1 Food categories according to Commission Regulation (EC) No 1565/2000 (EC, 2000a)

Food category	Description
01.0	Dairy products, excluding products of category 02.0
02.0	Fats and oils, and fat emulsions (type water-in-oil)
03.0	Edible ices, including sherbet and sorbet
04.1	Processed fruit
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds
05.0	Confectionery
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery
07.0	Bakery wares
08.0	Meat and meat products, including poultry and game
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms
10.0	Eggs and egg products
11.0	Sweeteners, including honey
12.0	Salts, spices, soups, sauces, salads, protein products, etc.
13.0	Foodstuffs intended for particular nutritional uses
14.1	Non-alcoholic ("soft") beverages, excl. dairy products
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts
15.0	Ready-to-eat savouries
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0

The "normal and maximum use levels" are provided by Industry (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c) for the 59 candidate substances in the present flavouring group (Table II.1.2).

Table II.1.2.Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.03Rev2 (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c).

FL-no	Food Categories																	
	Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
03.023	0,00 5 0,00 5	- -	0,01 0,1	- -	- -	0,00 5 0,1	- -	- -	- -	- -	- -	- -	0,01 0,1	- -	0,00 2 0,05	0,00 3 0,1	0,01 0,1	0,00 5 0,1
06.041	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
06.042	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
06.043	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 60	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	10 50
06.044	3 15	2 10	3 15	2 10	- -	4 20	2 10	5 25	1 5	1 5	- -	- -	2 10	3 15	2 10	4 20	5 25	2 10
06.045	7 35	5 25	10 50	7 35	- -	10 50	5 25	10 50	2 10	2 10	- -	- -	5 25	10 50	5 25	10 50	20 100	5 25
06.046	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5

Table II.1.2.Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.03Rev2 (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c).

FL-no	Food Categories																	
	Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.047	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.048	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.049	3	2	3	2	-	4	-	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	-	25	5	5	-	-	10	15	10	20	25	10
06.050	3	2	3	2	-	4	2	2	1	1	-	-	2	3	2	4	2	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.051	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.052	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.053	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.054	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.055	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	2	5
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.057	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.058	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.059	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	150	30	100	5	5	-	-	10	15	15	150	25	10
06.061	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.062	3	2	3	2	-	4	2	5	1	1	-	-	3	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	15	15	10	20	25	10
06.063	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.064	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.065	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.066	3	2	3	2	-	4	-	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	-	25	5	5	-	-	10	15	10	20	25	10
06.067	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.069	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.070	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.071	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.073	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.074	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.075	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.076	-	2	3	3	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	-	10	15	15	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.079	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.082	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.083	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	2	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.084	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.085	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.086	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	2	2

Table II.1.2.Normal and Maximum use levels (mg/kg) for the candidate substances in FGE.03Rev2 (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; EFFA, 2007a; Flavour Industry, 2007a; Flavour Industry, 2011c).

FL-no	Food Categories Normal use levels (mg/kg) Maximum use levels (mg/kg)																	
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.091	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.092	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.096	3	2	3	2	-	4	2	5	1	1	-	2	-	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	10	-	15	10	20	25	10
06.100	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.105	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.106	7	5	10	7	-	10	5	10	2	2	-	-	5	20	5	10	-	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	100	25	50	-	25
06.107	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.109	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.111	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.114	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.115	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.123	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.124	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.125	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.127	3	2	3	2	-	4	2	5	1	-	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	-	-	-	10	15	10	20	25	10
06.128	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.129	7	5	10	7	-	10	5	10	2	2	-	-	5	10	5	10	20	5
	35	25	50	35	-	50	25	50	10	10	-	-	25	50	25	50	100	25
06.130	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.131	3	2	3	2	-	4	2	5	1	1	-	-	2	3	2	4	5	2
	15	10	15	10	-	20	10	25	5	5	-	-	10	15	10	20	25	10
06.137	-	-	20	-	-	-	-	-	-	-	-	-	-	-	20	20	-	-
	-	-	30	-	-	-	-	-	-	-	-	-	-	-	30	30	-	-

II.2 mTAMDI Calculations

The method for calculation of modified Theoretical Added Maximum Daily Intake (mTAMDI) values is based on the approach used by SCF up to 1995 (SCF, 1995). The assumption is that a person may consume the amount of flavourable foods and beverages listed in Table II.2.1. These consumption estimates are then multiplied by the reported use levels in the different food categories and summed up.

Table II.2.1 Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995)

Class of product category	Intake estimate (g/day)
Beverages (non-alcoholic)	324.0
Foods	133.4
Exception a: Candy, confectionery	27.0

Table II.2.1 Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995)

Class of product category	Intake estimate (g/day)
Exception b: Condiments, seasonings	20.0
Exception c: Alcoholic beverages	20.0
Exception d: Soups, savouries	20.0
Exception e: Others, e.g. chewing gum	e.g. 2.0 (chewing gum)

The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 (EC, 2000a) and reported by the Flavour Industry in the following way (see Table II.2.2):

- Beverages (SCF, 1995) correspond to food category 14.1 (EC, 2000a)
- Foods (SCF, 1995) correspond to the food categories 1, 2, 3, 4.1, 4.2, 6, 7, 8, 9, 10, 13, and/or 16 (EC, 2000a)
- Exception a (SCF, 1995) corresponds to food category 5 and 11 (EC, 2000a)
- Exception b (SCF, 1995) corresponds to food category 15 (EC, 2000a)
- Exception c (SCF, 1995) corresponds to food category 14.2 (EC, 2000a)
- Exception d (SCF, 1995) corresponds to food category 12 (EC, 2000a)
- Exception e (SCF, 1995) corresponds to others, e.g. chewing gum.

Table II.2.2 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995)

	Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories		
Key	Food category	Food	Beverages	Exceptions
01.0	Dairy products, excluding products of category 02.0	Food		
02.0	Fats and oils, and fat emulsions (type water-in-oil)	Food		
03.0	Edible ices, including sherbet and sorbet	Food		
04.1	Processed fruit	Food		
04.2	Processed vegetables (incl. mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds	Food		
05.0	Confectionery			Exception a
06.0	Cereals and cereal products, incl. flours & starches from roots & tubers, pulses & legumes, excluding bakery	Food		
07.0	Bakery wares	Food		
08.0	Meat and meat products, including poultry and game	Food		
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms	Food		
10.0	Eggs and egg products	Food		
11.0	Sweeteners, including honey			Exception a
12.0	Salts, spices, soups, sauces, salads, protein products, etc.			Exception d
13.0	Foodstuffs intended for particular nutritional uses	Food		
14.1	Non-alcoholic ("soft") beverages, excl. dairy products		Beverages	
14.2	Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts			Exception c
15.0	Ready-to-eat savouries			Exception b

Table II.2.2 Distribution of the 18 food categories listed in Commission Regulation (EC) No 1565/2000 (EC, 2000a) into the seven SCF food categories used for TAMDI calculation (SCF, 1995)

	Food categories according to Commission Regulation (EC) No1565/2000	Distribution of the seven SCF food categories
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0	Food

The mTAMDI values (see Table II.2.3) are presented for each of the 59 flavouring substances in the present flavouring group, for which Industry has provided use and use levels (EFFA, 2001c; EFFA, 2001d; EFFA, 2002a; EFFA, 2002i; EFFA, 2003s; Flavour Industry, 2007a; Flavour Industry, 2011c). The mTAMDI values are only given for the highest reported normal use levels.

TableII.2.3 Estimated intakes based on the mTAMDI approach

FL-no	EU Register name	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
03.023	1-Ethoxyethyl acetate	2.6	Class I	1800
06.041	1-Isobutoxy-1-ethoxy-2-methylpropane	3900	Class I	1800
06.042	1-Isobutoxy-1-ethoxy-3-methylbutane	3900	Class I	1800
06.043	1-Isoamyloxy-1-ethoxypropane	3900	Class I	1800
06.044	1-Isobutoxy-1-ethoxypropane	1600	Class I	1800
06.045	1-Isobutoxy-1-isopentyloxy-2-methylpropane	3900	Class I	1800
06.046	1-Isobutoxy-1-isopentyloxy-3-methylbutane	3900	Class I	1800
06.047	1-Isopentyloxy-1-propoxyethane	3900	Class I	1800
06.048	1-Isopentyloxy-1-propoxypropane	1600	Class I	1800
06.049	1-Butoxy-1-(2-methylbutoxy)ethane	1600	Class I	1800
06.050	1-Butoxy-1-ethoxyethane	1300	Class I	1800
06.051	1,1-Di-(2-methylbutoxy)ethane	1600	Class I	1800
06.052	1,1-Di-isobutoxy-2-methylpropane	1600	Class I	1800
06.053	1,1-Di-isobutoxyethane	1600	Class I	1800
06.054	1,1-Di-isobutoxypentane	1600	Class I	1800
06.055	1,1-Di-isopentyloxyethane	1600	Class I	1800
06.057	1,1-Diethoxy-2-methylbutane	1600	Class I	1800
06.058	1,1-Diethoxy-2-methylpropane	1600	Class I	1800
06.059	1,1-Diethoxy-3-methylbutane	1600	Class I	1800
06.061	1,1-Diethoxybutane	1600	Class I	1800
06.062	1,1-Diethoxydodecane	1700	Class I	1800
06.063	1,1-Diethoxyhex-3-ene	3900	Class I	1800
06.064	Diethoxymethane	1600	Class I	1800
06.065	1,1-Diethoxynonane	1600	Class I	1800
06.066	1,1-Diethoxyoctane	1600	Class I	1800
06.067	1,1-Diethoxypentane	1600	Class I	1800
06.069	1,1-Diethoxypropane	1600	Class I	1800
06.070	1,1-Diethoxyundecane	1600	Class I	1800
06.071	1,1-Dihexyloxyethane	1600	Class I	1800
06.073	1,1-Dimethoxyhexane	1600	Class I	1800
06.074	Dimethoxymethane	1600	Class I	1800
06.075	1,1-Dimethoxypentane	1600	Class I	1800
06.076	1,1-Dimethoxypropane	1600	Class I	1800
06.079	1-Ethoxy-1-(2-methylbutoxy)ethane	1600	Class I	1800
06.082	1-Ethoxy-1-hexyloxyethane	1600	Class I	1800
06.083	1-Ethoxy-1-isopentyloxyethane	1600	Class I	1800
06.084	1-Ethoxy-1-methoxyethane	1600	Class I	1800
06.085	1-Ethoxy-1-pentyloxyethane	1600	Class I	1800
06.086	1-Ethoxy-1-propoxyethane	1600	Class I	1800
06.091	1-Isobutoxy-1-ethoxyethane	1600	Class I	1800
06.092	1-Isobutoxy-1-isopentyloxyethane	1600	Class I	1800
06.100	1,1-Dipentyloxyethane	1600	Class I	1800
06.105	3-Methyl-1,1-di-isopentyloxybutane	3900	Class I	1800
06.106	2-Methyl-1,1-di-isopentyloxypropane	4900	Class I	1800
06.107	1-(2-Methylbutoxy)-1-isopentyloxyethane	3900	Class I	1800
06.109	1,1-Diethoxy-3,7-dimethyloct-6-ene	3900	Class I	1800
06.111	1-Ethoxy-1-methoxypropane	1600	Class I	1800

TableII.2.3 Estimated intakes based on the mTAMDI approach

FL-no	EU Register name	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
06.114	1-Hexyloxy-1-isopentyloxyethane	1600	Class I	1800
06.115	1-Isopentyloxy-1-pentyloxyethane	3900	Class I	1800
06.123	1-Butoxy-1-isopentyloxyethane	3900	Class I	1800
06.124	1,1-Di-isobutoxy-3-methylbutane	3900	Class I	1800
06.125	1,1-Di-isobutoxypropane	1600	Class I	1800
06.127	1-Ethoxy-1-isopentyloxypropane	1600	Class I	1800
06.128	1-Ethoxy-1-pentyloxybutane	1600	Class I	1800
06.129	1-Ethoxy-2-methyl-1-isopentyloxypropane	3900	Class I	1800
06.130	1-Ethoxy-2-methyl-1-propoxypropane	1600	Class I	1800
06.131	1-Ethoxy-1-(3-methylbutoxy)-3-methylbutane	1600	Class I	1800
06.137	Acetaldehyde ethyl isopropyl acetal	9500	Class I	1800
06.096	Triethoxymethane	1600	Class III	90

ANNEX III: METABOLISM

III.1. Absorption, Distribution and Elimination

The 59 acetals derived from aliphatic, saturated, acyclic alcohols and saturated or monounsaturated aldehydes, the orthoester of formic acid and the ester of a hemiacetal in the present Flavouring Group Evaluation are predicted to by hydrolysed in the gastrointestinal tract. The hydrolysis products are all relatively simple alcohols and aldehydes, which may be assumed to be rapidly absorbed and metabolised. There are only few data on absorption, distribution and excretion available for the candidate and supporting substances:

Dogs were treated with 1, 1.5 or 2 ml paraldehyde/kg body weight (bw) and subsequently kept in metabolism cages. Urine and expired air were analysed for paraldehyde. Pulmonary excretion of paraldehyde amounted to 11 to 28 % of the dose, while urinary excretion amounted to 0.1 to 2.5 % of the dose, indicating that about 70 to 88 % of the dose had been metabolised (faeces and tissues not studied). In dogs in which liver damage was induced by pre-treatment with chloroform, the pulmonary elimination of paraldehyde was considerably increased. In these animals, renal elimination of paraldehyde was hardly affected. In animals without liver damage, the concentration of paraldehyde in the expired air decreased with a half-life of roughly four to five hours (Levine et al., 1940). The analytical methods in this study do not discriminate between paraldehyde and acetaldehyde. However, if it is assumed that acetaldehyde is rapidly incorporated in the normal metabolism, it can be concluded that up to 90 % of an oral dose of paraldehyde is metabolised.

Paraldehyde was administered at different dose levels, either orally or via i.p. injection, to normal and carbon tetrachloride-pretreated mice. Pulmonary elimination of paraldehyde (0.25 to 1 g/kg bw; i.p or p.o.) amounted to ca 4 - 10 % of the dose in normal mice, whereas CCl_4-pretreated animals excreted 27 to 30 % of the dose (0.25 or 0.5 g/kg bw; i.p. or p.o.). At lower dose levels (0.05 to 0.1 g/kg bw; i.p. or p.o.) the total amount excreted via the lungs amounted 1.5 to 5 % in normal animals, while CCl_4-pretreated mice exhaled 3 - 5 % after an oral dose (0.05 or 0.1 g/kg bw) or 6 - 26 % after i.p. administration. In addition, at higher dose levels and after pre-treatment with CCl_4, exhalation of paraldehyde took more time than at lower dose levels (several hours vs. one hour), which finding was also reflected in retarded blood and total body clearance of paraldehyde. No acetaldehyde could be determined in the exhaled air of mice that were treated with paraldehyde. Exhalation of acetaldehyde by animals treated with acetaldehyde (p.o. or i.p.) showed a very rapid decrease in time, which was independent of pre-treatment with CCl_4. The data indicate that the hydrolysis of paraldehyde is the rate-limiting step in the elimination of this substance, and that the liver contributes to a major extent to this hydrolysis. In addition, the elimination rate is saturable at high dose levels of paraldehyde (> 0.25 g/kg bw) (Hitchcock and Nelson, 1943).

Serum levels of paraldehyde were assessed in five children who had received paraldehyde by i.m. injection as treatment of epileptic convulsions. This study reports blood-concentration-time curves for paraldehyde. After a rapid increase in blood levels, shortly after injection, paraldehyde was eliminated from the blood with an average half-life of 7.5 hours. Paraldehyde in the blood was determined after treatment of blood samples with 0.1 N HCl at 100ºC for 15 minutes to convert it completely to acetaldehyde, which was quantified by measuring NADH oxidation linked to enzyme-catalysed acetaldehyde reduction. No information on acetaldehyde levels in non-acid treated blood samples was gathered, but if it is assumed that acetaldehyde is rapidly incorporated in the normal physiology of the body, the study shows that paraldehyde is only slowly hydrolysed in biological tissues. In the children, the i.m. treatment with paraldehyde (0.25 or 0.33 ml/kg bw of a solution containing 0.2 mg/ml) caused narcosis (Thurston et al., 1968).

III.2. Biotransformation

Acetals are stable in neutral or basic environment, but when treated with aqueous acid they are hydrolysed and reconverted to alcohol and aldehyde (Streitwieser et al, 1992; Carey, 1992; Carey and Sundberg, 1990; Vollhardt, 1988; Sykes, 1982; Beyer and Walter, 1984).

The hydrolysis of acetals may occur either as a specific acid catalysed hydrolysis or as a general acid catalysed hydrolysis. The hydrolysis rate is clearly influenced by the nature of substituents on the carbonyl moiety. Electron-donor substituents on the carbon atom of the acetal group accelerate hydrolysis, while electron-acceptor substituents slow hydrolysis. Generally, there is an increase in hydrolysis rate with a higher degree of substitution at the central carbon atom at each functional group, and when a hydrocarbon atom is replaced by an alkyl or an alkoxy group (Deslongchamps et al., 2000; Kreevoy and Taft, 1955a; Pchelintsev et al., 1988).

Ethoxy compounds are hydrolysed four to nine times faster than the corresponding methoxy derivatives because the ethoxy group is more basic (more readily protonated) than the methoxy group and therefore a better leaving group. Some increase in rate was observed as a result of lengthening or branching of the alcohol molecule chain, some increase in rate is also found by changing from a primary alcohol to a secondary alcohol. These experiments were executed with acetals in dioxolane-water (49.6 – 50.4 %) solution (Pchelintsev et al., 1988). The hydrolysis of acetals in aqueous solution containing in their molecule two to eight oxyethylene units and three alkyl groups of varying lengths was examined by Sokolowski & Burczyk, (1979). Considerable differences were found in reaction rates between acetals obtained from acetaldehyde and from formaldehyde, with the former having the greater reaction rate. The increase in size of alkyl groups derived from aldehyde moiety in one acetal series resulted in a small reduction of acetal stability in water. The size of alkyl groups in the alcohol moiety and the number of oxyethylene groups have a small effect on rate constants (Sokolowski and Burczyk, 1979).

In vitro experiments using simulated gastric fluid revealed the rates of hydrolysis of acetals to be dependent on the structures of the aldehyde and alcohol moieties. Acetals derived from short straight chain saturated aldehydes, up to C8 were hydrolysed instantly. For decanal-derived homologues (diethyl and dimethyl acetals) half-lives in the order of 30 minutes were observed (Engel, 2003). On the basis of structural similarity these data indicate that the candidate acetals can be predicted to be hydrolysed.

A few studies demonstrate that acetals may be hydrolysed enzymatically in microsome preparations and studies on conversion rate of the cyclic acetal paraldehyde to acetaldehyde show that liver may contribute to hydrolysis to a major extent after oral intake or i.p. injection, but that hydrolysis also takes place in other biological tissues. The process may however be slow and incomplete (Edsbacker et al., 1987; Levine et al., 1940; Hitchcock and Nelson, 1943; Thurston et al., 1968).

III.2.1. Hydrolysis of Acetals

Hydrolysis data from studies referred to below are summarised in Table III.1.

In vitro – acid hydrolysis of acetals

Hydrolysis of four acetals in simulated gastric juice (pH 1.2) and simulated intestinal fluid (pH 7.5) was monitored by the formation rate of aldehyde liberated during treatment. 1,1-Diethoxyethane (DEE), hydroxy-citronellal-dimethyl-acetal (8,8-dimethoxy-2,6-dimethyl-2-octanol, DDO) and hydrotropic aldehyde dimethyl acetal (1,1-dimethoxy-2-phenylpropane, DMPP) were completely hydrolysed after one hour in simulated gastric juice at 37°C. However, benzaldehyde propylene glycol acetal (4-methyl-2-phenyl-1,3-dioxolane, MPD) was only hydrolysed to an extent of around 50 % after one hour in simulated gastric juice and no further hydrolysis was observed after five hours. Reflux of MPD for five hours in 0.1N HCl also resulted in hydrolysis to an extent of 50 % of the theoretical maximum. Due to the same poor hydrolysis of

MPD (to around 50 % again) even after five hours reflux in 0.1 N HCl the author questioned the chemical identity of the sample (Morgareidge, 1962a). Accordingly, these data on hydrolysis of MPD are rather inconclusive.

In simulated intestinal fluid 5 - 10 % hydrolysis was observed with DEE, DDO or DMPP after five hours. With MPD about 17 % of the substance was hydrolysed after the same period of time (Morgareidge, 1962a).

Sokolowski and Burczyk studied the hydrolysis of acetals formed from aliphatic aldehydes and monoalkyl ethers of ethylene glycols. Hydrolysis was carried out in 1 M HCl at either 50ºC or 20ºC. The $T_{½}$ of the acetals varied from about six to 27 minutes. The data indicated that the rate of hydrolysis increases with increasing length of the carbon chain at the aldehyde part of the molecule as well as at the ether part of the molecule. Results are summarised in Table III.2 (Sokolowski and Burczyk, 1979).

Potassium 2-(1'-ethoxy)ethoxypropanoate (PEEP), the salt of an acetal of lactic acid, was designed to hydrolyse to acetaldehyde when used in beverage and dessert powders, and to hydrolyse at a greater rate than 1,2-di[(1'-ethoxy)ethoxy]propane (DEEP) (FEMA No. 3534). The hydrolysis of PEEP in simulated stomach fluid showed 100 % hydrolysis in ten minutes (pH 2.4, 37°C). PEEP was shown to release acetaldehyde quicker than DEEP at pH 3 and 25°C (Moreno et al., 1984).

A comparative study of the regeneration of citral from the corresponding dimethyl and propylene glycol acetals (CDMA and CPGA respectively) under mild acidic conditions showed that, although the former decomposed to an extent of 85 % in 15 minutes, the latter formed a near 1:1 equilibrium mixture with the generated aldehyde. The conditions employed for the decomposition of CDMA and CPGA were catalytic amounts of 1:1 aqueous HCl in acetone medium at 65°C. CPGA failed to undergo complete cleavage even under drastic conditions of refluxing with 10 % phosphoric acid, which indicated the remarkable stability of the five-membered 1,3-dioxolane ring with substituents at positions 2 and 4. The conclusion of the authors was that propyleneglycol acetals were not suitable as aldehydic flavourings because the aldehydes could be only partly recovered under normal hydrolytic conditions (Sharma et al., 1998).

In a similar *in vitro* study hydrolysis of three acetals 1,2,3-tris((1'-ethoxy)-ethoxy)propane (TEEP), 1,2-di[(1'-ethoxy)-ethoxy]propane (DEEP) and 4-(1'-ethoxy)ethoxymethyl-2-methyl-1,3-dioxolane (EEMMD) was monitored by the formation rate of acetaldehyde liberated during treatment in simulated gastric juice and simulated gastric juice without pepsin, pH 1.2 and temperature 37°C. The rate of hydrolysis was determined by comparison of the liberated amount of acetaldehyde with the theoretical maximal amount that could be produced. TEEP and DEEP were completely hydrolysed within 30 minutes. EEMMD was hydrolysed for about 60 % after 15 minutes and for about 80 % after one hour. The remainder of the acetaldehyde was liberated during the next two hours. It was speculated for EEMMD that the first rapid part of the hydrolysis represented mainly the hydrolysis of the linear acetal part of the molecule, while the slower second part of the degradation reflected the hydrolysis of the cyclic dioxolane moiety (DeSimone, 1976).

In vitro – enzymatic hydrolysis of acetals

One study has been conducted on hydrolysis of 2-propylpentanal acetals by liver microsomes *in vitro*. A study was conducted on the feasibility of using acetals of 2-propylpentanal as pro-drugs in valproic acid (2-propylpentanoic acid) treatment. Incubation of dimethoxy, or dipropoxy derivatives of 2-propylpentanal with either rat liver 10000 g supernatant or rat liver microsomes yielded 2-propylpentanoic acid or 2-propyl pentanol. The formation rate of 2-propyl pentanol and 2-propylpentanoic acid from diethoxy-2-propylpentane was greatly reduced when deficient or defective microsomal systems were used. However, the study did not demonstrate that the hydrolysis of the acetals was solely mediated by cytochrome P-450 enzymes, because even in the deficient/defective systems some formation of free acid or alcohol did occur. In addition, the observation that in 100000 g supernatant systems, 2-propylpentanol was formed from diethoxy-2-propylpentane also show that the hydrolysis of this acetal is not completely dependent on cytochrome P-450 activity. Incubation of 1,1-diethoxy-3-phenyl propane yielded 3-phenyl propanoic acid, 3-

phenyl propanal and 3-phenyl propanol. The acid and alcohol derivatives of 2-propylpentanal were identified in the supernatant and microsomal fractions of rat liver incubated with 1 micro-mol of dimethyl, diethyl or di-isopropyl acetals of 2-propylpentanal (Vicchio and Callery, 1989).

In a similar study the topical glucocorticoid budesonide (16,17-butylidenedioxy-11,21-dihyroxypregna-1,4-diene-3,20-dione) was incubated with S-9 fractions from human liver, liver from male Sprague-Dawley rats, or liver from NMRI mice. Budesonide is chemically stable against non-enzymatical hydrolysis. A 16alfa,17alfa-acetal splitting was shown to occur in all three liver preparations. The conclusion drawn is that the systemic inactivation of budesonide is rapid due to extensive liver biotransformation, and that the acetal splitting of budesonide increases the overall rate of inactivation and may therefore reduce the risk of systemic side effects when using the drug topically (Edsbacker et al., 1987).

In vivo biotransformation of acetals

A few studies have been conducted *in vivo* on biotransformation (and excretion) of paraldehyde, the cyclic acetal formed from three molecules of acetaldehyde, which has been used as a hypnotic.

Rats and rabbits were dosed with acetals by i.p. injection or by gavage, respectively. The following acetals were studied: dimethoxymethane (DMM), diethoxymethane (DEM), di-(1-propoxy)methane (D1PM), di-(2-propoxy)methane (D2PM), di-(1-butoxy)methane (DBM), dimethoxyethane (DME), diethoxyethane (DEE), 1,1-diethoxypropane (11DEP), 2,2-diethoxypropane (22DEP), 2,2-diethoxyethanol (DEOH), 1,1,2-triethoxyethane (TrEE), 1,1,2,2-tetraethoxyethane (TeEE), triethoxymethane (TEM) and 2,4,6-trimethyl-1,3,5-trioxane (TMT). The studied effects in the animals were sleeping time (rats), posture changes (rabbits) and death (both species). The effects in rabbits occurred at higher dose levels than those in rats, possibly indicating an effect of dosing route, and possibly species sensitivity. Velocity constants for acid hydrolysis of the acetals were provided. Within the group of five methanal-derived acetals (DMM, DEM, D1PM, D2PM and DBM), the rate constants varied with 1-2 orders of magnitude, depending on alcohol chain length and position of hydroxyl group. For these methanal derivatives, the rate constants were 4-5 orders of magnitude less than for one ethanal-derived acetal (DEE). The hydrolysis rate constants for the one orthoester (TEM) and the ketal (22DEP) were about 2-3 orders higher than that of DEE. These findings indicate that rates of acetal acid hydrolysis may vary considerably, depending on molecular structure, even within this group of closely related substances (Knoefel, 1934).

It is also indicated in the above studies (Hitchcock and Nelson, 1943; Levine et al., 1940; Thurston et al., 1968), that *in vivo* hydrolysis of acetals may take place.

III.2.2. Hydrolysis of orthoesters

Orthoesters may be hydrolysed either by specific or by general hydrolysis (Kankaanperä and Lahti, 1970; Lahti and Kankaanperä, 1970). Like acetals, orthoesters that possess a good leaving group and are able to form stable oxo-carbonium ion intermediates show pronounced general acid catalysis (Anderson and Fife, 1972). Simple orthoesters such as triethyl orthoformate (triethoxymethane, [FL-no: 06.096]) undergo specific acid hydrolysis in water (Bunton and De Wolfe, 1965; Cordes and Bull, 1974).

In the study by Knoefel (Knoefel, 1934) (see above) the orthoester triethoxymethane [FL-no: 06.096] as well as several acetals were administered to rats i.p. and to rabbits by gavage in amounts great enough to give anaesthesia, which for most of the tested compounds were close to the lethal dose. For the orthoester, as well as for some of the acetals, there was a difference in duration of narcotic activity between rats and rabbits, with less activity in rabbits. The authors reasoned that the relative inactivity of the orthoester, as well as of some acetals, was due to decomposition by acid hydrolysis in the stomach of the rabbits. Comparisons of velocity constants of acid hydrolysis of the acetals and the orthoester were made, indicating that the large differences in velocity constants could explain differences in activity. It was also concluded that compounds with reduced solubility in water had an uncertain and weak narcotic action.

III.3. Fate of Hydrolysis Products

At low levels of exposure, the hydrolysis products from the 57 acetals, the orthoester and the ester of a hemiacetal are rapidly absorbed, distributed, and metabolised to carbon dioxide and water. At higher dose levels, minor amounts of low molecular weight alcohols and aldehydes may be excreted via exhaled air or in the urine.

In general, linear aliphatic acyclic alcohols (DeBruin, 1976; Lington and Bevan, 1994) and aldehydes (Brabec, 1993) and branched-chain aliphatic acyclic alcohols and aldehydes (Gaillard and Derache, 1965; Dawson et al., 1964a) are absorbed from the gastrointestinal tract, and rapidly eliminated from the blood primarily by metabolism in the liver. Plasma half-lives are normally difficult to measure since some low molecular weight alcohols (e.g., ethanol) and aldehydes (e.g., ethanal) are endogenous in humans (Lington and Bevan, 1994).

Based on experimental data, it may be concluded that simple aliphatic linear and branched-chain alcohols are rapidly absorbed, completely metabolised, and excreted within 24 hours. At very high dose levels, small amounts of the alcohol or its metabolite may be detected in the urine.

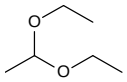
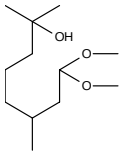
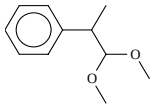
The component alcohols (or acetic acid) and the saturated and monounsaturated aldehydes (or formic acid) formed from this group of acetals (and one orthoester and one ester of a hemiacetal) are all metabolised by well-recognised pathways. The alcohols are oxidised by alcohol dehydrogenase to yield the corresponding aldehyde that may be further oxidised by aldehyde dehydrogenase or various oxidases to yield the corresponding carboxylic acids. The linear carboxylic acids then enter the fatty acid pathway in which they undergo beta-oxidation and cleavage to yield either propionyl coenzyme A (CoA) or acetyl coenzyme A. These CoA substrates are completely oxidised to carbon dioxide and water in the tricarboxylic acid cycle. The branched chain carboxylic acids also undergo beta-oxidation preferably in the longer chain to yield linear acid fragments that also become substrates for oxidation in the fatty acid pathway or tricarboxylic acid cycle. The three branched chain carboxylic acids, isobutyric, 2-methylbutyric, and 3-methylbutyric acids, formed from alcohols and aldehydes in this group are endogenous in humans as products of the oxidative de-amination of the amino acids valine, isoleucine and leucine, respectively (Michal, 1999a).

III.4. Conclusion

Data indicate that hydrolysis of acetals, the orthoester [FL-no: 06.096] and the ester of a hemiacetal [FL-no: 03.023] of the present Flavouring Group Evaluation (FGE.03Rev2) may occur *in vitro*, as well as *in vivo* under acidic circumstances. In addition, enzymatic cleavage of acetals and further metabolism has been observed *in vitro* as well as *in vivo*. At least part of this enzymatic cleavage and metabolism capacity is located in the liver. The data from studies on hydrolysis *in vitro* as well as the *in vivo* studies show that the time for hydrolysis may vary greatly even within groups of very closely related substances. Hydrolysis data on compounds with structural similarity to the candidate substances show that the candidate acetals may be predicted to be hydrolysed. However, it cannot be excluded that some amounts of the parent acetals may reach the systemic circulation. From experimental studies it is indicated that acetals may be hydrolysed enzymatically by liver microsomes and that hydrolysis also may take place in other tissues.

Results on hydrolysis studies abstracted in section III.2.

TABLE III.1

Name FL-, JECFA-no Structure	Test System	Results $T_{½}$	 % Hydrolysis (after hours)	Hydrolysis Chemical	 Enzymatic *in vivo//in vitro*	V_{max}	K_m	Reference	Evaluation status
1,1-Diethoxyethane (DEE) [06.001], 941 	Art. gastric juice; pH = 1.2.		Ca. 90 % after 1 h; no further increase after 5 h.					(Morgareidge, 1962a)	JECFA (JECFA, 2002b) CoE Cat. A (CoE, 1992)
	Art. pancreat. juice; pH = 7.5.		Ca. 6 % after 1 h; ca 10 % after 5 h.					(Morgareidge, 1962a)	
	In vivo in rabbits dosed by gavage.					'Considerable amounts' excreted by pulmonary excretion (no quantitative data).		(Knoefel et al., 1932) [11]	
	In vivo Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 15.0.	(Knoefel, 1934) [12]	
8,8-Dimethoxy-2,6-dimethyl-2-octanol (DDO) 1,1-dimethoxy-3,7-dimethyloctan-7-ol [06.011], 612 	Art. gastric juice; pH = 1.2		Ca. 100 % after 1 h.					(Morgareidge, 1962a)	JECFA (JECFA, 2000b) CoE Cat. A (CoE, 1992)
	Art. pancreat. juice; pH = 7.5.		Ca. 3 % after 1 h; ca 5 % after 5 h.					(Morgareidge, 1962a)	
1,1-Dimethoxy-2-phenylpropane (DMPP) [06.030] 	Art. gastric juice; pH = 1.2.		Ca. 97 % after 1 h.					(Morgareidge, 1962a)	CoE Cat. B (CoE, 1992)
	Art. pancreat. juice; pH = 7.5.		Ca. 5 % after 1 h; no further increase after 5 h.					(Morgareidge, 1962a)	

[11] *It is stated that the rates and duration of action are equal for the compounds when given in doses of equal effectiveness (hypnotic effect). This is what is stated as far as rates. All substances were excreted by the lungs in considerable amounts.*

[12] *In the study it is stated that route of administration is of importance, especially for the ethanals - ip do ethanals have half hypnotic activity as compared to methanals, po much less effect. For the methanals, the activity increases with chain length at first, but then with less solubility activity becomes uncertain and very low with butoxy-methanals. The propanals have low solubility and therefore uncertain (and low) activity.*

TABLE III.1

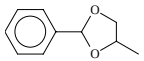
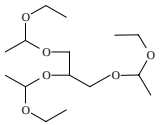
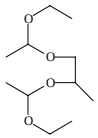
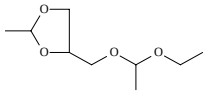
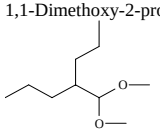
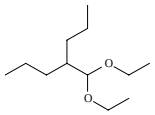
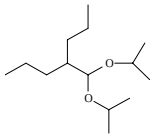
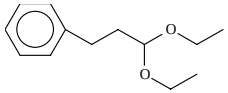
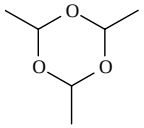
Name FL-, JECFA-no Structure	Test System	Results		Hydrolysis		V_{max}	K_m	Reference	Evaluation status
		$T_{½}$	% Hydrolysis (after hours)	Chemical	Enzymatic *in vivo//in vitro*				
4-Methyl-2-phenyl-1,3-dioxolane (MPD) [06.032], 839 	art. gastric juice; pH = 1.2.		Ca. 52 % after 1 h; no further increase after 5 h.					(Morgareidge, 1962a)	JECFA (JECFA, 2002b) CoE Cat. A (CoE, 1992)
	Art. pancreat. juice; pH = 7.5.		Ca. 17 % after 1 h; no further increase after 5 h.					(Morgareidge, 1962a)	
1,2,3-Tris((1'-ethoxy)-ethoxy)propane (TEEP) [06.040], 913 	art. gastric juice; pH = 1.2.		Complete within 30 min.					(DeSimone, 1976)	JECFA (JECFA, 2002b)
1,2-Di((1'-ethoxy)-ethoxy)propane (DEEP) [06.039], 927 	Art. gastric juice; pH = 1.2.		Complete within 30 min.					(DeSimone, 1976)	
4-(1'-Ethoxy)ethoxymethyl-2-methyl-1,3-dioxolane (EEMMD) 	Art. gastric juice; pH = 1.2.		61 % within 15 min (all of the linear part); complete within 120 min.					(DeSimone, 1976)	
1,1-Dimethoxy-2-propylpentane 	Rat liver 10000g supernatant with NADPH for 15 min.				Hydrolysis observed, but quantitative data not presented.			(Vicchio and Callery, 1989)	

TABLE III.1

Name FL-, JECFA-no Structure	Test System	Results		Hydrolysis		V_{max}	K_m	Reference	Evaluation status
		$T_{½}$	% Hydrolysis (after hours)	Chemical	Enzymatic *in vivo//in vitro*				
1,1-Diethoxy-2-propylpentane 	Rat liver 10000g supernatant with NADPH for 15 min.				47 % per gram liver per 15 min.			(Vicchio and Callery, 1989) [13]	
	Rat liver microsomes with NADPH for 15 min				41 % per gram liver per 15 min.			(Vicchio and Callery, 1989)	
1,1-Di-isopropoxy–2-propylpentane 	Rat liver 10000g supernatant with NADPH for 15 min.				Hydrolysis observed, but quantitative data not presented.			(Vicchio and Callery, 1989)	
1,1-Diethoxy-3-phenylpropane 	Rat liver microsomes with NADPH with or without 100000 g supernatant.				Hydrolysis observed, but quantitative data not presented.			(Vicchio and Callery, 1989)	

[13] *Tabulated data are calculated from the results presented in the study. % of hydrolysis refers to the amount of acetal that was present in the incubations. For supenatants, formation rate of free propyl-pentanoic acid was determined, for microsomes, hydrolysis rate was determined by formation of prolyl pentanol. In the paper, proten concentrations in the incubates were expressed as* "per gram liver".

TABLE III.1

Name FL-, JECFA-no Structure	Test System	Results $T_{½}$	 % Hydrolysis (after hours)	Hydrolysis Chemical	 Enzymatic *in vivo//in vitro*	V_{max}	K_m	Reference	Evaluation status
2,4,6-Trimethyl-1,3,5-trioxane (TMT) (paraldehyde) [05.053] 	*In vivo* in dogs, dosed by stomach tube.	For pulmonary excretion : 4-5 h.			70 - 88 % of the dose metabolised.			(Levine et al., 1940) [14]	SCF Cat. 1 (SCF, 1995) CoE Cat. A (CoE, 1992)
	In vivo in dogs, dosed by stomach tube; pretreated with chloroform.	For pulmonary excretion: 12-14 h.			60 - 80 % of the dose metabolised.			(Levine et al., 1940) [14]	
	In vivo in mice, dosed p.o or i.p.				Total amount metabolised 99 - 90 % (decreasing with increasing dose level).	Pulmonary excretion of parent compound: 1.5 to 10 % of the dose; pulmonary excretion increases with increasing dose.		(Hitchcock and Nelson, 1943) [15]	
	In vivo in mice, dosed p.o or i.p. after carbon tetrachloride pre-treatment.				Total amount metabolised 97 - 72 % (decreasing with increasing dose level of paraldehyde).	Pulmonary excretion of parent compound: 3 to 30 % of the dose; pulmonary excretion increases with increasing dose.		(Hitchcock and Nelson, 1943)	
	Children *in vivo*, i.m. administration.	Plasma half-life of paraldehyde: 7.5 h.						(Thurston et al., 1968)	
	In vivo in rabbits dosed by gavage.					Considerable amounts excreted by pulmonary excretion (no quantitative data).		(Knoefel et al., 1932)	
	In vivo. Rats dosed i.p. Rabbits dosed by gavage.							(Knoefel, 1934)	
Diethoxymethane (DEM) [06.064]	*In vivo* in rabbits dosed by gavage.					Considerable amounts excreted by pulmonary excretion (no		(Knoefel et al., 1932)	FGE.03

[14] *Extent of metabolism was determined from recovery of reducing equivalents in expired air and urine. No distinction was made between paraldehyde and acetaldehyde or other possible metabolites. If it is assumed that all primary metabolites / hydrolysis products are rapidly converted to endogenous intermediates and carbon dioxide, pulmonary and urinary excretion may reflect excretion of unchanged parent compound. The pulmonary excretion was studied up to the detection limit. Urinary excretion was studied for up to 24 hours after cessation of pulmonary excretion. In normal dogs pulmonary excretion lasted for 12 - 26 hours and comprised about 98 % of the total amount recovered.*

[15] *Estimates for the total extent of metabolism are based on the assumption that paraldehyde is eliminated either by exhalation or by metabolic conversion. No acetaldehyde could be detected in the expired air.*

TABLE III.1

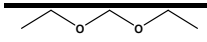
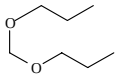
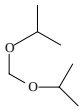
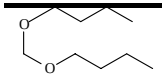
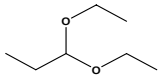
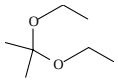
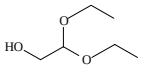
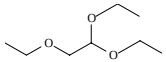
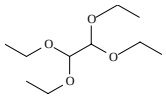
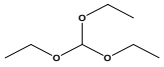
Name FL-, JECFA-no Structure	Test System	Results $T_{½}$	 % Hydrolysis (after hours)	Hydrolysis Chemical	 Enzymatic *in vivo//in vitro*	V_{max}	K_m	Reference	Evaluation status
						quantitative data).			
	In vivo. Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 0.00234.	(Knoefel, 1934)	
1,1-Dimethoxyethane (DME) [06.015], 940 	*In vivo* in rabbits dosed by gavage.					Considerable amounts excreted by pulmonary excretion (no quantitative data).		(Knoefel et al., 1932)	JECFA (JECFA, 2002b) CoE Cat. A (CoE, 1992)
	In vivo Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known).	(Knoefel, 1934)	
Dimethoxymethane (DMM) [06.074] 	*In vivo* in rabbits dosed by gavage.					Considerable amounts excreted by pulmonary excretion (no quantitative data).		(Knoefel et al., 1932)	FGE.03
	In vivo. Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 0.00038.	(Knoefel, 1934)	
Di-(1-propoxy)methane (D1PM) (1,1-dipropoxymethane) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 0.00360.	(Knoefel, 1934)	
Di-(2-propoxy)methane (D2PM) (2,2-dipropoxymethane) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 0.01810.	(Knoefel, 1934)	
Di-(1-butoxy)methane (DBM) (1,1-dibutoxymethane)	*In vivo.* Rats dosed i.p. Rabbits dosed by						Rate constant for acid hydrolysis *in vitro* (system not	(Knoefel, 1934)	

TABLE III.1

Name FL-, JECFA-no Structure	Test System	Results		Hydrolysis		V_{max}	K_m	Reference	Evaluation status
		$T_{½}$	% Hydrolysis (after hours)	Chemical	Enzymatic *in vivo//in vitro*				
	gavage.						known) 0.00358.		
1,1-Diethoxypropane (11DEP) [06.069], 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.							(Knoefel, 1934)	FGE.03
2,2-Diethoxypropane (22DEP) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 33,800.0.	(Knoefel, 1934)	
2,2-Diethoxyethanol (DEOH) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.							(Knoefel, 1934)	
1,1,2-Triethoxyethane (TrEE) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.							(Knoefel, 1934)	
1,1,2,2-Tetraethoxyethane (TeEE) 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.							(Knoefel, 1934)	
Triethoxymethane (TEM) [06.096], 	*In vivo.* Rats dosed i.p. Rabbits dosed by gavage.						Rate constant for acid hydrolysis *in vitro* (system not known) 7,800.0.	(Knoefel, 1934)	FGE.03

Hydrolysis study on acetals formed from aliphatic aldehydes and monoalkyl ethers of ethylene glycols (Sokolowski and Burczyk, 1979).

The group of substances studied can be described by the general formula: $RCH[O(CH_2CH_2O)_WR_1]_2$, where R = H, CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}; W = 1, 2, 3, 4; and R_1 = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9;

The hydrolysis study was performed in aqueous solutions of 1 M HCL at 20°C and 50°C, respectively.

TABLE III.2

Chemical Structure	Test System	Results $T_{½}$	Reference
$HCH(OCH_2CH_2OCH_3)_2$	1M HCl, 50°C	~ 20 min	(Sokolowski and Burczyk, 1979)
$HCH(OCH_2CH_2OC_2H_5)_2$	1M HCl, 50°C	~ 20 min	
$HCH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 50°C	~ 10 min	
$HCH[O(CH_2CH_2O)_2C_2H_5]_2$	1M HCl, 50°C	~ 14 min	
$HCH[O(CH_2CH_2O)_2\ C_3H_7]_2$	1M HCl, 50°C	~ 12 min	
$HCH[O(CH_2CH_2O)_3CH_3]_2$	1M HCl, 50°C	~ 6 min	
$HCH[O(CH_2CH_2O)_3C_2H_5]_2$	1M HCl, 50°C	~ 12 min	
$HCH[O(CH_2CH_2O)_3C_4H_9]_2$	1M HCl, 50°C	~ 6 min	
$HCH[O(CH_2CH_2O)_4CH_3]_2$	1M HCl, 50°C	~ 6 min	
$CH_3CH(OCH_2CH_2OCH_3)_2$	1M HCl, 20°C	~ 27 min	
n- $C_4H_9CH(OCH_2CH_2OCH_3)_2$	1M HCl, 20°C	~ 17 min	
$CH_3CH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 20°C	~ 19 min	
$C_2H_5CH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 20°C	~ 16 min	
n- $C_3H_7CH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 20°C	~ 16 min	
n- $C_4H_9CH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 20°C	~ 14 min	
n- $C_5H_{11}CH[O(CH_2CH_2O)_2CH_3]_2$	1M HCl, 20°C	~ 15 min	
$CH_3CH[O(CH_2CH_2O)_2\ C_2H_5]_2$	1M HCl, 20°C	~ 26 min	
$C_2H_5CH[O(CH_2CH_2O)_2C_2H_5]_2$	1M HCl, 20°C	~ 18 min	
n- $C_3H_7CH[O(CH_2CH_2O)_2C_2H_5]_2$	1M HCl, 20°C	~ 17 min	
$CH_3CH[O(CH_2CH_2O)_2C_3H_7]_2$	1M HCl, 20°C	~ 27 min	
n- $C_4H_9CH[O(CH_2CH_2O)_3CH_3]_2$	1M HCl, 20°C	~ 17 min	
n- $C_5H_{11}CH[O(CH_2CH_2O)_3CH_3]_2$	1M HCl, 20°C	~ 19 min	
n- $C_4H_9CH[O(CH_2CH_2O)_4CH_3]_2$	1M HCl, 20°C	~ 17 min	

ANNEX IV: TOXICITY

Oral acute toxicity data are available for four candidate substances of the present Flavouring Group Evaluation from chemical groups 1, 2 and 4, and for two supporting substances evaluated by Council of Europe (CoE, 1992). The supporting substances are listed in brackets.

TABLE IV.1: ACUTE TOXICITY

Chemical Name [FL-no]	Species	Sex	Route	LD_{50} (mg/kg bw)	Reference
(1,1-Dipropoxyethane [06.034])	Rat	NR	Oral	5000	(Opdyke, 1979e)
(1,1-Dibutoxyethane [06.033])	Rat	NR	Oral	8790	(Smyth et al., 1954)
Diethoxymethane [06.064]	Rabbit	NR	Oral	2600	(Knoefel et al., 1932)
Dimethoxymethane [06.074]	Rat	F	Oral	7950	(Dow Chemical Company, 1987)
	Rabbit	NR	Oral	5708	(Knoefel et al., 1932)
1-Ethoxy-1-hexyloxyethane [06.082]	Rat	NR	Oral	13300	(Kynoch et al., 1978)
	Rat	NR	Oral	5000	(Moreno, 1980b)
Triethoxymethane [06.096]	Rat	NR	Oral	7060	(Smyth et al., 1951a)

TABLE IV.2: SUBACUTE / SUBCHRONIC / CHRONIC / CARCINOGENICITY STUDIES

No subacute, subchronic, chronic, carcinogenicity toxicity studies are available for any candidate of the present flavouring group evaluation from chemical groups 1, 2 and 4 or for supporting substances evaluated by JECFA at the 57th (JECFA, 2002a) and by CoE (CoE, 1992).

TABLE IV.3: DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental and reproductive toxicity data are available for the candidate substances of the present flavouring group evaluation from chemical groups 1, 2 and 4 or for supporting substances evaluated by JECFA at the 57th (JECFA, 2002a) and by CoE (CoE, 1992).

In vitro mutagenicity/genotoxicity data are available for three candidate substances of the present Flavouring Group Evaluation.

TABLE IV.4: GENOTOXICITY (*IN VITRO*)

Chemical Name [FL-no]	Test System	Test Object	Concentration	Result	Reference	Comments
Dimethoxymethane [06.074]	Ames test	*S.typh.* TA98, TA 100 S.typh, TA 1535, TA 1537, TA 1538	667-10000 microgram/plate 667-10000 microgram/plate	Neg.* / Pos.** Neg.*/** See footnote 1)	(Hoechst-Celanese Corp., 1989b)	In compliance with GLP and OECD guideline 471 (1983).
	HGPRT assay	CHO cells	0.5 to 5 mg/l	Neg.*/** See footnote 2)	(Hoechst-Celanese Corp., 1990a)	In compliance with GLP and OECD guideline 476 (1984).
Diethoxymethane [06.064]	Ames test	*S.typh.* TA98, TA 100, TA 1535, TA 1537, TA 1538	100-10000 microgram/plate	Neg.*/** See footnote 3)	(Cameron, 1995)	Quality of studies cannot be evaluated.
	Mouse lymphoma TK assay	L5178Y (TK+/TK-)	3000 – 5000 microgram/ml 250 – 1500 microgram/ml	Neg.** Pos.* See footnote 3)	(Cameron, 1995)	Quality of studies cannot be evaluated.
Triethoxymethane [06.096]	Ames test	*S.typh.* TA97, TA98, TA 100	8 – 5000 microgram/plate	Neg.*/** See footnote 3)	(Huels, 1992)	Quality of studies cannot be evaluated.

**With metabolic activation*

***Without metabolic activation*

1) Dimethoxymethane [06.074] (purity not reported) was tested in a bacterial reversion assay (Ames test) with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with and without exogenous metabolic activation (liver S9 mix from rats pretreated with Aroclor 1254), following the preincubation method. A dose range-finding experiment was performed with strain TA100 at doses from 10 to 10000 microgram/plate (one plate per dose). The main experiment was conducted at five doses from 667 to 10000 microgram/plate. All doses were tested in triplicate. Water was used as solvent.

Result: A weak positive response was observed with strain TA100 in the absence of microsomal enzymes (2.4-fold maximum increase in revertant colonies in the dose range-finding experiment and 2.1-fold maximum increase in the main study at 10000 microgram/plate, respectively). A positive response was also observed with strain TA98 in the absence of microsomal enzymes (3.9-fold maximum increase at 10000 microgram/plate). These effects were dose-related. No positive responses were observed with any of the other strains and activation conditions. No bacteriotoxicity was observed up to 10000 microgram/plate in the presence and absence of microsomal enzymes. Precipitations were not observed.

2) Dimethoxymethane [06.074] (purity not reported) was tested in a gene mutation assay at the HPRT locus in the CHO-K1-BH_4 Chinese Hamster Ovary (CHO) cell line with and without exogenous metabolic activation (liver S9 mix from rats pretreated with Aroclor 1254). A dose range-finding experiment was performed with 10 concentrations from 0.0098 to 5.0 mg/ml. One main experiment was performed with six dose levels from 0.5 to 5.0 mg/ml. Duplicate cell cultures were used for each experimental point. Water was used as solvent.

Result: The test substance produced slight toxicity at concentrations above 1.0 mg/ml in the assays with and without metabolic activation. One treated culture each with and without metabolic activation had a mutant frequency that was statistically elevated over the mutant frequencies of the concurrent vehicle control cultures. Adjacent dose levels with similar levels of toxicity showed no indication of a mutagenic response. The significant mutant frequencies were within the normal range for background mutant frequency variation which was 0 to 15 x 10-6. The test substance was considered negative for inducing forward mutations at the HPRT locus in CHO cells.

3) There are data on genotoxicity for diethoxymethane [06.064] and triethoxymethane [06.096]. While diethoxymethane [06.064] is reported to be negative in a bacterial reversion assay (Ames test) it is reported to be positive in a gene mutation assay at the TK locus in mammalian cells in the presence of metabolic activation (Cameron, 1995). Triethoxymethane [06.096] is reported to be negative in a bacterial reversion assay (IUCLID data base of the European Chemicals Bureau, referring on Huels Report No. AM-92/20, 1992 (unpublished) (Report is not available)). However, from these studies, details are not available with respect to methods and results, respectively. Thus, the quality of these studies cannot be evaluated.

In vivo *mutagenicity/genotoxicity data are only available for one candidate substance of the present Flavouring Group Evaluation.*

TABLE IV.5: GENOTOXICITY (*IN VIVO*)

Chemical Name	Test System	Test Object	Route	Dose	Result	Reference	Comments
Dimethoxymethane [06.074]	Micronucleus assay	Mouse	I.p.	400 – 4000 mg/kg bw	Neg. See footnote 1)	(Hoechst-Celanese Corp., 1990b)	In compliance with GLP and OECD guideline 474 (1983).

1) Dimethoxymethane [06.074] (purity not reported) was tested in the micronucleus test in bone marrow cells of ICR mice. Based on the results of a previously conducted dose range-finding study, groups of five males and five females were exposed to the test substance at doses of 400, 1333, and 4000 mg/kg body weight by intraperitoneal injection (I.P.) (0.9% sodium chloride was used as vehicle). The animals were sacrificed 24, 48 and 72 hours after dosing. Micronuclei were scored in 1000 PCEs per animal. The PCE/NCE ratio was determined by scoring the number of NCEs while scoring 1000 PCEs.

Result: Within one minute of dosing mice at the 4000 mg/kg dose became prostrate with dyspnea and mice at 1333 mg/kg showed uncoordinated movement. Most mice recovered in one hour. The PCE/NCE ratio was reduced in single groups (e.g. 0.59 at 4000 mg/kg after 24 hours in males), however, the PCE/NCE ratio was not clearly dose-related. The test substance did not induce a significant increase in micronucleated bone marrow PCEs.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids Chemical Abstract Service
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
DBM	Di-(1-butoxy)methane
22DED	2,2-Diethoxypropane
DEE	1,1-Diethoxyethane
DEEP	1,2-Di[(1'-ethoxy)ethoxy]propane
DEM	Diethoxymethane
DEOH	2,2-Diethoxyethanol
11DEP	1,1-Diethoxypropane
DDO	8,8-Dimethoxy-2,6-dimethyl-2-octanol
DME	Dimethoxyethane
DMM	Dimethoxymethane
DMPP	1,1-Dimethoxy-2-phenylpropane
DNA	Deoxyribonucleic acid
D1PM	Di-(1-propoxy)methane
D2PM	Di-(2-propoxy)methane
EC	European Commission
EEMMD	4-(1'-Ethoxy)ethoxymethyl-2-methyl-1,3-dioxolane
EFFA	European Flavour and Fragrance Association
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 (FL)	Flavour Information System (database)
HPRT	Hypoxanthine phosphoribosyltransferase
ID	Identity
IM	Intra muscular
IOFI	International Organization of the Flavour Industry
IP	Intraperitoneal
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives

LD_{50}	Lethal Dose, 50%; Median lethal dose
MPD	4-Methyl-2-phenyl-1,3-dioxolane
MS	Mass spectrometry
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
No	Number
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Program
PEEP	Potassium 2-(1'-ethoxy)ethoxypropanoate
PO	Peroral
SCE	Sister Chromatid Exchange
SCF	Scientific Committee on Food
SMART	Somatic Mutation and Recombination Test
TAMDI	Theoretical Added Maximum Daily Intake
TEEP	1,2,3-Tris((1'-ethoxy)-ethoxy)propane
TeEE	1,1,2,2-Tetraethoxyethane
TEM	Triethoxymethane
TMT	2,4,6-Trimethyl-1,3,5-trioxane
TrEE	1,1,2-Triethoxyethane
UDS	Unscheduled DNA Synthesis
WHO	World Health Organisation