EFSA ; Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1): Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1):

Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting)[1]

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

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) to provide scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The present consideration concerns 34 aliphatic and aromatic amines and amides evaluated by the JECFA (65th meeting). The Panel concluded that no corresponding FGE is available.

Further two substances were evaluated by the JECFA in this group, but these are not in the Register (1-amino-2-propanol and acetamide; JECFA-no: 1591 and 1592, respectively). A third substance evaluated by the JECFA is an alpha,beta-unsaturated ketone [FL-no: 14.168] considered with respect to genotoxicity in FGE.223, corresponding to subgroup 5.1 of FGE.19, for which a final conclusion regarding its genotoxic properties could not be reached and additional data were requested. This consideration therefore only deals with 34 flavouring substances.

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1 On request from the Commission, Question No EFSA-Q-2010-01261, adopted on 25 November 2010.

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The Panel agreed with the application of the Procedure as performed by the JECFA for 27 of the 34 substances. The JECFA concluded on five substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094] at step B4, but the Panel did not agree that appropriate studies are available for deriving NOAELs and accordingly the Panel in FGE.86 concluded that additional toxicity data are required for these five substances.

The flavouring Industry has in response to the requested toxicity data in FGE.86 submitted additional data for three of the five substances [FL-no: 16.091, 16.093 and 16.094]. The following information has been submitted:

Ames test and acute oral toxicity test have been submitted by Industry on [FL-no: 16.093]. The Industry suggests that these data also can support the evaluation of [FL-no: 16.091 and 16.094]. These studies do not fulfil the suggested minimum requirement to provide an adequate NOAEL for flavourings in the Procedure, which is considered to be a 90-day study. The minimum requirement has not been met by the new toxicity data submitted by Industry for the substances in FGE.86 therefore additional toxicity data is still requested.

Further has Industry submitted Ames test and a 28 day study on substance [FL-no: 16.095] (evaluated in FGE.94 (EFSA, 2010i)) to support the evaluation of [FL-no: 16.091, 16.093 and 16.094]. The Panel did not consider [FL-no: 16.095] sufficiently structurally related to be used as supporting substance for this FGE.

In addition to the five substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094] for which the Panel did not agree that appropriate studies are available for deriving NOAELs, butyramide [FL-no: 16.049] cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicity. For N-isopentylidene isopentylamine [FL-no: 11.017] the Panel concluded that this substance can be metabolised to innocuous products and accordingly evaluated along the A-side of the Procedure (while the JECFA evaluated [FL-no: 11.017] along the B-side). Like the JECFA the Panel concluded that [FL-no: 11.017] is of no safety concern at estimated level of intake, based on the MSDI approach. So, the Panel did not agree with the application of the Procedure as performed by the JECFA for 7 of the 34 substances.

For 22 substances evaluated by the JECFA through the Procedure use levels have been provided by the Industry [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049, 16.052, 16.091, 16.092, 16.093 and 16.094]. The mTAMDI figures calculated for the substances in structural class I are 340 microgram/person/day, except for [FL-no: 16.092], for which the mTAMDI is 15000 microgram/person/day, exceeding the threshold of 1800 microgram/person/day for structural class I. The mTAMDI figures for the structural class II substances range from 200 to 340 microgram/person/day, except for [FL-no: 14.141] for which the figure is 600 microgram/person/day, exceeding the threshold of 540 microgram/person/day for structural class II. For the substances [FL-no: 11.014, 16.052, 16.091, 16.093 and 16.094] in structural class III the figures range from 200 to 1900 microgram/person/day, exceeding the threshold of concern of 90 microgram/person/day for structural class III. Thus, for seven substances [FL-no: 11.014, 14.141, 16.052, 16.091, 16.092, 16.093 and 16.094] the intakes, estimated on the basis of the mTAMDI approach, exceed the threshold for their structural classes. Therefore more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be considered using the Procedure. Subsequently, additional data might become necessary.

For the remaining 12 substances [FL-no: 11.001, 11.003, 11.006, 11.009, 11.017, 14.003, 14.010, 14.064, 14.167, 16.006, 16.013 and 16.053] use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 34 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications

including complete purity criteria and identity are available for 33 of the 34 JECFA evaluated substances. For one substance [FL-no: 16.013] information on the stereoisomeric composition is lacking.

Thus, for one substance [FL-no: 16.013] the Panel has reservation (information on stereoisomeric composition is requested).

For seven of the 34 evaluated substances the Panel did not agree with the JECFA application of the Procedure and additional toxicity data are required for five of the seven substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094]. One substance cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicity [FL-no: 16.049] and one substance [FL-no: 11.017] is evaluated along the A-side, while the JECFA evaluated it along the B-side.

Overall, for 27 of the 34 JECFA evaluated aliphatic and aromatic amines and amides [FL-no: 11.001, 11.002, 11.003, 11.004, 11.005, 11.006, 11.007, 11.009, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.010, 14.064, 14.080, 14.133, 14.141, 14.167, 16.006, 16.052, 16.053 and 16.092] the Panel agreed with the JECFA conclusion "no safety concern at estimated levels of intake as flavouring substances" based on the MSDI approach.

KEY WORDS

Flavourings, safety, aliphatic amines, aliphatic amides, aromatic amines, JECFA, 65th meeting.

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BACKGROUND

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

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

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

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

TERMS OF REFERENCE

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

In addition, in letter of 19 May 2009 the Commission requested EFSA to carry out a re-evaluation of flavouring substances [FL-no: 16.091, 16.093 and 16.094] in accordance with Commission Regulation (EC) No 1565/2000:

"The European Commission requests the European Food Safety Authority to carry out a risk assessment on 2,4-Decadienamide, N-(2-methylpropyl)-, (2E,4E)- ([FL-no: 16.091]), N-Cyclopropyl (2E,6Z)-nonadienamide ([FL-no: 16.093]) and N-Ethyl (2E,6Z)-nonadienamide ([FL-no: 16.094]) in accordance with Commission Regulation (EC) No 1565/2000, if possible by the end of the evaluation programme, if not within nine month from finalisation of that programme".

The deadline of the Terms of Reference was negotiated to 31 December 2010.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), hereafter named the "EFSA Procedure". This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999a), which has been derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996a; JECFA, 1997a; JECFA, 1999b), hereafter named the "JECFA Procedure". The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring

substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be put through the EFSA Procedure.

The following issues are of special importance.

Intake

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

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

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

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

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

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

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

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

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

Genotoxicity

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

Specifications

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

Structural Relationship

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

HISTORY OF THE EVALUATION OF THE SUBSTANCES IN THE PRESENT FGE

In FGE.86, which considered 35 aliphatic and aromatic amines and amides, the Panel concluded that for five substances no applicable NOAEL was available for the substance itself or for a structurally related substance and accordingly further data are required.

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
86	22 May 2008	http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902197654.htm	35
86Rev1	25 November 2010		34

The present Revision of Flavouring Group Evaluation 86, Revision 1 (FGE.86Rev1) concerns the re-consideration of three JECFA-evaluated substances considered in FGE.86.

Additional data (Ames test, acute oral toxicity test) have been submitted by Industry on [FL-no: 16.093]. The Industry suggests that these data also can support the evaluation of [FL-no: 16.091 and 16.094].

Further has Industry submitted additional data (Ames test and a 28 day study) on substance [FL-no: 16.095] (evaluated in FGE.94 (EFSA, 2010i)) to support the evaluation of [FL-no: 16.091, 16.093 and 16.094].

Industry has also submitted additional information needed on stereoisomeric composition [FL-no: 16.013], composition of mixture [FL-no: 11.017], specifications (data on solubility [FL-no: 14.064 and 14.168]), missing ID-tests [FL-no: 11.017, 14.168 and 16.094] and EU production figures [FL-no: 11.006 and 16.053].

[FL-no: 14.168], which contains an alpha,beta-unsaturated ketone structure has been withdrawn from this consideration and transferred to FGE.223 for evaluation with respect to genotoxic potential.

After publication of FGE.86, the JECFA has re-evaluated flavouring substances for which estimated intake was originally based on anticipated poundage data (JECFA, 2009c), but for which new tonnage data were submitted to the JECFA by Industry. These new tonnage figures are included in the present FGE for [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049 and 16.052.

Furthermore in FGE.86 two substances [FL-no: 11.006 and 16.053] could not be evaluated using the Procedure, as no EU production figures were available. In February 2010, the Industry provided EU production figures for these two substances together with similar data on approximately 100 other substances from 27 different FGEs. In order to avoid unnecessary delay, these substances were evaluated in FGE.96 (EFSA, 2010aj). The outcome of the evaluations have also been included in the current revision of FGE.86.

1. Presentation of the Substances in the JECFA Flavouring Group

1.1. Description

1.1.1. JECFA Status

The JECFA has evaluated a group of 37 flavouring substances consisting of aliphatic and aromatic amines and amides at the 65th meeting (JECFA, 2006d).

1.1.2. EFSA Considerations

Two of the 37 flavouring substances evaluated by the JECFA in the group named "aliphatic and aromatic amines and amides" are not in the Register (1-amino-2-propanol and acetamide; JECFA-no: 1591 and 1592, respectively). A third substance evaluated by the JECFA contains an alpha,beta-unsaturated ketone moiety and has been considered with respect to genotoxicity in FGE.223, corresponding to subgroup 5.1 of FGE.19 (EFSA, 2008b), for which a final conclusion regarding its genotoxic properties could not be reached and additional data were requested. This consideration therefore only deals with 34 flavouring substances.

The Panel concluded that no corresponding FGE is available.

1.2. Isomers

1.2.1. JECFA Status

The following six substances [FL-no: 11.005, 11.014, 11.020, 14.133, 16.013 and 16.092] in the group of JECFA evaluated aliphatic and aromatic amines and amides have one or more chiral centres. Four substances [FL-no: 14.003, 16.091, 16.093 and 16.094] can exist as geometrical isomers.

1.2.2. EFSA Considerations

In FGE.86, information is lacking about stereoisomerism for one substance [FL-no: 16.013]. After publication of FGE.86, Industry has informed that it is a mixture of diastereoisomers (EFFA, 2010a). However, information on the ratios of the diastereoisomers is needed. See Table 1.

1.3. Specifications

1.3.1. JECFA Status

The JECFA specifications are available for all 34 substances (JECFA, 2005d). See Table 1.

1.3.2. EFSA Considerations

The available specifications are considered adequate for 33 substances. For one substance [FL-no: 16.013] additional information on the stereoisomeric mixture is needed (See Section 1.2).

2. Intake Estimations

2.1. JECFA Status

For all 34 substances evaluated through the JECFA Procedure intake data are available for the EU. (See Table 3.1).

After publication of FGE.86, the JECFA has re-evaluated flavouring substances for which estimated intake was originally based on anticipated poundage data (JECFA, 2009c), but for which new tonnage (production) data were submitted to the JECFA by Industry. These new tonnage figures are included in the present FGE for [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049 and 16.052.

2.2. EFSA Considerations

For seven substances [FL-no: 11.006, 14.167, 16.053, 16.091, 16.092, 16.093 and 16.094] the Industry has submitted production figure for EU to EFSA (EFFA, 2004ao; Flavour Industry, 2004e; Flavour Industry, 2004f). These data have been used in this consideration (see Table 2.2.2 and 3.1).

New tonnage (production) figures are included in the present FGE for [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049 and 16.052 (See Section 2.1).

For 22 substances [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049, 16.052, 16.091, 16.092, 16.093 and 16.094], the Industry has submitted use levels for normal and maximum use (EFFA, 2005c; Flavour Industry, 2004f; EFFA, 2007a) (see Table 2.2.1). Based on these normal use levels mTAMDI figures can be calculated (see Table 2.2.2), (EFSA, 2004d).

Table 2.2.1 Normal and Maximum use levels (mg/kg) available for JECFA evaluated substances in FGE.86

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
11.002	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.004	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.005	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.007	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	1	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	5	-	5	5	1
11.014	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.015	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.016	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.018	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.020	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.021	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.023	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.025	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2

Table 2.2.1 Normal and Maximum use levels (mg/kg) available for JECFA evaluated substances in FGE.86

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**
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
11.026	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
14.080	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
14.133	0,4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
14.141	4	0,1	0,4	0,4	-	1	0,2	2	0,2	0,2	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	10	1	1	-	-	0,5	1	-	5	5	1
16.049	0,4	0,1	0,4	0,4	-	1	0,2	1	0,1	0,1	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	5	0,4	0,4	-	-	0,5	1	-	5	5	1
16.052	0,4	0,1	0,4	0,4	-	1	0,2	1	0,1	0,1	-	-	0,1	0,2	-	1	1	0,2
	2	0,5	2	2	-	5	1	5	0,4	0,4	-	-	0,5	1	-	5	5	1
16.091	0,02	0,02	0,2	-	-	2	-	0,2	0,02	0,02	-	-	0,02	-	2	2	0,02	0,02
	1	1	10	-	-	100	-	10	1	1	-	-	1	-	100	100	1	1
16.092	0,4	0,4	0,4	-	-	40	-	4	0,4	0,4	-	-	0,4	-	40	40	0,4	0,4
	4	4	4	-	-	400	-	40	4	4	-	-	4	-	400	400	4	4
16.093	0,05	0,05	0,5	-	-	5	1	0,5	0,05	0,05	-	-	0,05	-	5	5	0,05	0,05
	0,5	0,5	5	-	-	50	10	5	0,5	0,5	-	-	0,5	-	50	50	0,5	0,5
16.094	0,05	0,05	0,5	-	-	5	1	0,5	0,05	0,05	-	-	0,05	-	5	5	0,05	0,05
	0,5	0,5	5	-	-	50	10	5	0,5	0,5	-	-	0,5	-	50	50	0,5	0,5

Table 2.2.2 Estimated intakes based on the MSDI approach and the mTAMDI approach

FL-no	EU Register name	MSDI – EU (µg/*capita*/day)	MSDI – USA (µg/*capita*/day)	mTAMDI (µg/person/day)	Structural class	Threshold of concern (µg/person/day)
11.001	3-Methylbutylamine	24	0.07		Class I	1800
11.002	Isobutylamine	0.012	0.09	340	Class I	1800
11.003	Butylamine	89	0.01		Class I	1800
11.004	Propylamine	0.012	0.02	340	Class I	1800
11.005	sec-Butylamine	0.012	2	340	Class I	1800
11.009	Trimethylamine	130	70		Class I	1800
11.015	Ethylamine	0.012	0.2	340	Class I	1800
11.016	Hexylamine	0.024	0.007	340	Class I	1800
11.018	Isopropylamine	0.012	0.02	340	Class I	1800
11.020	2-Methylbutylamine	0.012	0.02	340	Class I	1800
11.021	Pentylamine	0.037	0.2	340	Class I	1800
11.023	Triethylamine	0.073	0.9	340	Class I	1800
11.025	Trimethylamine oxide	2.3	0.09	340	Class I	1800
11.026	Tripropylamine	0.012	0.02	340	Class I	1800
16.092	N,N-Dimethyl menthyl succinamide	61	88	15000	Class I	1800
11.006	Phenethylamine	0.075	0.05		Class II	540
11.007	2-(4-Hydroxyphenyl)ethylamine	0.012	0.02	340	Class II	540
14.010	Piperidine	88	96		Class II	540
14.064	Pyrrolidine	0.12	2		Class II	540
14.080	2-Acetyl-1-pyrroline	0.012	0.1	340	Class II	540
14.133	2-Methylpiperidine	0.012	0.002	340	Class II	540
14.141	Piperazine	0.012	0.002	600	Class II	540
14.167	1-Pyrroline	0.012	0.4		Class II	540
16.049	Butyramide	0.012	0.002	200	Class II	540
16.013	N-Ethyl-2-isopropyl-5-methylcyclohexane carboxamide	0.4	127		Class III	90
16.053	2-Isopropyl- N,2,3-trimethylbutanamide	24	1054		Class III	90
11.014	N,N-Dimethylphenethylamine	0.012	0.09	340	Class III	90
11.017	N-Isopentylidene isopentylamine	0.012	0.01		Class III	90
14.003	Piperine	20	0.07		Class III	90
16.006	N-Nonanoyl 4-hydroxy-3-methoxybenzylamide	6.0	0.07		Class III	90
16.052	1,6-Hexalactam	0.012	0.002	200	Class III	90
16.091	Deca-(2E,4E)-dienoic acid isobutyl-amide	6.1	83	770	Class III	90
16.093	N-Cyclopropyl (2E,6Z)-nonadienamide	61	40	2000	Class III	90
16.094	N-Ethyl (2E,6Z)-nonadienamide	61	88	2000	Class III	90

3. Genotoxicity Data

3.1. Genotoxicity Studies – Text Taken[4] from the JECFA (JECFA, 2006d)

In vitro

No mutagenicity was found in the standard Ames assay when various strains of *Salmonella typhimurium* (TA97a, TA98, TA100, TA102, TA1535, TA1537, TA1538, TA1530, TA1531, TA1532 and TA1964) were incubated with up to 10000 microgram/plate of ethylamine [FL-no: 11.015], isopropylamine [FL-no: 11.018], butylamine [FL-no: 11.003], isobutylamine [FL-no: 11.002], pentylamine [FL-no: 11.021], acetamide (No. 1592, not in Register), 2-isopropyl-N,2,3-trimethylbutyramide [FL-no: 16.053], N-isobutyl (E,E)-2,4-decadienamide [FL-no: 16.091], piperine [FL-no: 14.003], piperidine [FL-no: 14.010], pyrrolidine [FL-no: 14.064], trimethylamine [FL-no: 11.009], triethylamine [FL-no: 11.023] or piperazine [FL-no: 14.141] with or without metabolic activation (Green & Savage, 1978; Haworth et al., 1978; Andrews et al., 1980; Florin et al., 1980; Haworth et al., 1983; Mortelmans et al., 1986; Zeiger et al., 1987; Karekar et al., 1996; King, 2003).

In a host-mediated assay in which *S. typhimurium* strain TA1950, TA1951, TA1952 or TA1964 was injected intraperitoneally into mice followed by an intramuscular injection of 800 mg/kg bw of piperidine or pyrrolidine, no mutagenicity was observed (Green & Savage, 1978).

There was no evidence of DNA damage when *Escherichia coli* 343/591 uvrB-/recA-/lac+ or uvrB+/recA+/lac+ was incubated with up to 1080 mM (63793 microgram/ml) of acetamide (No. 1592, not in Register) or up to 33.7 mM (2870 microgram/ml) of piperidine [FL-no: 14.010] (Hellmér & Bolcsfoldi, 1992a). In the SOS Chromotest with *E. coli* PQ37, the N-nitroso derivative of tyramine [FL-no: 11.007] gave positive results (Ohshima et al., 1989).

Assays in mammalian cell lines have been performed with tyramine [FL-no: 11.007], acetamide (No. 1592, not in Register), 2-isopropyl-N,2,3-trimethylbutyramide [FL-no: 16.053], and piperidine [FL-no: 14.010]. Unscheduled DNA synthesis was not increased when WI-38 human cells were incubated with 125 - 2000 microgram/ml of 2-isopropyl-N,2,3-trimethylbutyramide (Skinner, 1978). No single-strand DNA breaks were reported when 0.03 - 1000 mM (2 - 59068 microgram/ml) of acetamide or 0.03 - 3 mM (2.6 to 255 microgram/ml) of piperidine were incubated with rat hepatocytes (Sina et al., 1983). Mixed results have been reported with tyramine and piperidine in the mouse lymphoma forward mutation assay: positive results were reported for both compounds when tested at up to 823 and 688 microgram/ml, respectively, in L5178Y mouse lymphoma cells with and without metabolic activation, but only at cytotoxic doses (Wangenheim & Bolcsfoldi, 1988). No mutagenic effects were reported when tyramine and 2-isopropyl-N,2,3-trimethylbutyramide were tested at concentrations of up to 3500 and 1000 microgram/ml, respectively, in L5178Y mouse lymphoma cells (Kirby et al., 1978; McGregor et al., 1988c). No mutagenic effects were observed when piperidine was tested at concentrations of up to 512 microgram/ml without metabolic activation in L5178Y mouse lymphoma cells; however, equivocal results were noted when metabolic activation was added (Garberg et al., 1988).

In vivo

In male and female C57B1/6, male CBA, male CD_1 and male BDF_1 mice, a single dose of acetamide (No. 1592, not in Register) of up to 5000 mg/kg bw did not induce micronuclei in the bone marrow or peripheral blood when administered by gavage or intraperitoneal injection (Mirkova, 1996; Morita et al., 1997). Micronuclei were found in the bone marrow of female C57B1/6 mice given 3.39 mmol/kg bw (approximately 200 mg/kg bw) of acetamide by gavage 30 and 6 h before termination; however, no dose-response relation was seen, as only a single dose was used (Chieli et al., 1987).

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

Piperine [FL-no: 14.003] did not induce micronuclei in the bone marrow of male Swiss mice given a single dose of 10 or 20 mg/kg bw by gavage (Karekar et al., 1996) or two intraperitoneal doses (at 0 and 24 h) for a total dose of up to 4 mg/kg bw (Muralidhara & Narasimhamurthy, 1990).

Male and female $1C3F_1$ mice were given a single dose of 1000 mg/kg bw of 1,6-hexalactam [FL-no: 16.052] by gavage, and bone marrow was sampled from groups of 10 animals after 24, 30 and 48 h. Colchicine was administered to the mice 1 h before sacrifice. No chromosomal aberrations were seen (Adler & Ingwersen, 1989). The Comet assay was used to quantify DNA damage in cells from organs of male ddy mice given either acetamide (No. 1592, not in Register) or 1,6-hexalactam [FL-no: 16.052]. No DNA damage was reported in mice given a single dose of 2000 mg/kg bw 1,6-hexalactam by gavage; however, DNA damage was reported in the stomach, colon, lungs and bone marrow of male mice given a single intraperitoneal injection of acetamide at 2,000 mg/kg bw (Sasaki et al., 2000).

1,6-Hexalactam [FL-no: 16.052] did not induce replicative DNA synthesis in rat or mouse hepatocytes after treatment *in vivo* or *in vitro* at a dose of 350 or 700 mg/kg bw or 250 or 500 mg/kg bw, respectively (Uno et al., 1994; Miyagawa et al., 1995). In the mouse spot test, a single [route not stated but assumed to be intraperitoneal] injection of 1,6-hexalactam at a dose of up to 500 mg/kg bw significantly increased the frequency of spots over those in controls (Neuhäuser-Klaus & Lehmacher, 1989); however, statistically significant effects were observed in only one of three or four trials. It has been suggested that the colour spots observed were indicative of mitotic recombination and not mutation (Fahrig, 1989). Moreover, administration of 700 mg/kg bw in one trial did not significantly increase the frequency of spots over that in controls (Neuhäuser-Klaus & Lehmacher, 1989).

Female *Drosophila melanogaster* larvae fed up to 20 mmol/l (2263 microgram/ml) of 1,6-hexalactam [FL-no: 16.052] showed sex-linked recessive lethal mutations and somatic mutation-mitotic recombination, whereas male larvae fed up to 5 mmol/l (566 microgram/ml) did not have sex-linked recessive lethal mutations (Vogel, 1989).

Piperidine [FL-no: 14.010] and pyrrolidine [FL-no: 14.064] were tested for promoting activity in male Wistar rats given a single dose of 100 mg/kg bw of the test substance by gavage in dimethyl sulphoxide or 1 % Tylose. The number of mitoses in the adrenal cortex was examined 36 h after dosing. Only administration of pyrrolidine in dimethyl sulphoxide caused a statistically significant increase (approximately two-fold) in the number of mitoses over that in controls (Danz & Urban, 1979).

Piperine [FL-no: 14.003] and piperidine [FL-no: 14.010] did not cause mutations in male germ cells, as assessed by sperm shape abnormality and tests for dominant lethal mutations in mice and hamsters. Mice given piperine at doses of up to 75 mg/kg bw/day by gavage or up to 4 mg/kg bw per day by intraperitoneal injection for 5 days showed no sperm shape abnormalities or dominant lethal mutations (Muralidhara & Narasimhamurthy, 1990; Karekar et al., 1996; Daware et al., 2000). In another study, an oral dose of 400 mg/kg bw/day of piperidine for 40-100 days did not induce sperm shape abnormalities in mice or hamsters (Bempong & Scully, 1983).

Conclusion on genotoxicity

Negative results were reported in bacterial assays for reverse mutation with 15 aliphatic and aromatic amine and amide derivatives: ethylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, pentylamine, acetamide, 2-isopropyl-N,2,3-trimethylbutyramide, N-isobutyl (E,E)-2,4-decadienamide, piperine, piperidine, pyrrolidine, trimethylamine, triethylamine and piperazine.

Two substances, tyramine and piperidine, gave both positive and negative results in the mouse lymphoma assay, particularly at cytotoxic concentrations, while nitrosated tyramine gave positive results in the SOS Chromotest with *E. coli*.

Piperine and piperidine consistently gave negative results in a variety of studies *in vivo*, whereas acetamide, 1,6-hexalactam and pyrrolidine gave mainly negative results with some positive findings.

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

3.2. EFSA Considerations

The only valid positive *in vivo* genotoxicity studies cited by the JECFA are related to acetamide, which the JECFA considered inappropriate to be used as a flavouring substance due to its reported carcinogenicity in both rats and mice, and consequently it was not evaluated using the Procedure.

As butyramide [FL-no: 16.049] is structurally related to acetamide the Panel concluded not to evaluate butyramide through the Procedure.

N-nonanoyl 4-hydroxy-3-methoxybenzylamide [FL-no: 16.006] (Nonivamide, pelargonyl vanillylamide (PAVA)) is structurally related to capsaicin. Capsaicin has been evaluated by SCF in 2002 (SCF, 2002h) and concluded to have shown genotoxic effects *in vitro* and *in vivo* and accordingly deleted from the Register. However, N-nonanoyl 4-hydroxy-3-methoxybenzylamide has more recently been evaluated by the UK Committee on Toxicity of Chemicals in Food in 2004 (COT, 2004) and concluded not to be an *in vivo* mutagen. The Panel agrees with this conclusion made by COT in 2004, based on the negative results of a bone marrow cytogenetic assay (COT, 2002) and an *in vivo* liver unscheduled DNA synthesis assay (Clay, 2003). Accordingly N-nonanoyl 4-hydroxy-3-methoxybenzylamide [FL-no: 16.006] can be evaluated through the Procedure along the B-side, which is also done by the JECFA.

For 1,6-hexalactam [FL-no: 16.052] the Panel noted an increased frequency of spots in only one of three or four trials in the mouse spot tests. In addition, sex-linked recessive lethal mutations and somatic mutations were reported in female *Drosophila* larvae fed 1,6-hexalactam. However, 1,6-hexalactam did not show carcinogenic effects in male and female mice and rats following daily administration for two years of up to 2250 mg/kg bw (mice) or up to 350 mg/kg bw (rats).

Otherwise, the Panel agreed with the JECFA that the available studies on genotoxicity did not preclude the evaluation of the aliphatic and aromatic amines and amides by using the Procedure.

For N-cyclopropyl (2E,6Z)-nonadienamide [FL-no: 16.093] additional genotoxicity data have been submitted by EFFA (Bowles, 2003). The substance was tested in a bacterial reverse mutation test using *S. typhimurium* strains TA98, TA100, TA1535, 1537 and *E. Coli* strain WP2uvrA with and without metabolic activation (see Table 2.2). It was concluded to be negative regarding the induction of mutagenicity.

4. Application of the Procedure

4.1. Application of the Procedure to 34 Aliphatic and Aromatic Amines and Amides by JECFA (JECFA, 2006d)

After publication of FGE.86, the JECFA has re-evaluated flavouring substances for which estimated intake was originally based on anticipated poundage data (JECFA, 2009c). New annual production volumes were submitted to the JECFA by the Flavour Industry for [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049 and 16.052]. The JECFA concluded that there was “no safety concern” for these substances.

No new monograph was prepared, so all text about anticipated poundage in Section 4.1 below should not be taken into account.

Step 1.

In applying the Procedure for the safety evaluation to these flavouring substances, the Committee assigned 15 substances [FL-no: 11.001, 11.002, 11.003, 11.004, 11.005, 11.009, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026 and 16.092] to structural class I, nine flavouring substances [FL-no: 11.006, 11.007, 14.010, 14.064, 14.080, 14.133, 14.141, 14.167, and 16.049] to structural class II and the remaining ten flavouring substances [FL-no: 11.014, 11.017, 14.003, 16.006, 16.013, 16.052, 16.053, 16.091, 16.093 and 16.094] to structural class III.

Step 2.

Twenty-four flavouring substances in this group, namely all those in structural classes I and II [FL-no: 11.001, 11.002, 11.003, 11.004, 11.005, 11.006, 11.007, 11.009, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.010, 14.064, 14.080, 14.133, 14.141, 14.167, 16.049 and 16.092] are predicted to be metabolised to innocuous products. The evaluation of these substances therefore proceeded via the A-side of the Procedure.

For the ten flavouring substances in structural class III, namely the medium chain saturated and unsaturated aliphatic and alicyclic amides [FL-no: 11.017, 14.003, 16.006, 16.013, 16.052, 16.053, 16.091, 16.093 and 16.094] and N,N-dimethylphenethylamine [FL-no: 11.014], limited metabolic data were available, and evaluation of these substances therefore proceeded via the B-side of the Procedure.

Step A3.

The estimated daily *per capita* exposures to all 15 flavouring substances in structural class I are below the threshold of concern (1800 microgram/person/day for class I). Three of these 15 substances [FL-no: 11.001, 11.003 and 11.009] are reported to be currently used as flavouring substances, and, according to the Procedure, the current use and exposure levels of these three substances raise no safety concern. The other 12 substances [FL-no: 11.002, 11.004, 11.005, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026 and 16.092] are proposed for use as flavouring substances. Although, according to the Procedure, the use of these 12 substances raises no safety concern at the exposure estimated from anticipated volumes of production, less uncertain estimates are needed. The estimated daily per capita exposure to all nine flavouring substances in structural class II is below the threshold of concern (540 microgram/day). Three of these nine substances [FL-no: 11.006, 14.010 and 14.064] are reported to be used as flavouring substances, and, according to the Procedure, their use raises no safety concern at current estimated level of exposure. The other six substances [FL-no: 11.007, 14.080, 14.133, 14.141, 14.167 and 16.049] are proposed for use as flavouring substances. Although, according to the Procedure, use of these six substances raises no safety concern at the exposure levels estimated from anticipated volumes of production, less uncertain exposure estimates are needed.

Step B3.

The estimated *per capita* exposures to eight of the flavouring substances in structural class III [FL-no: 11.014, 11.017, 14.003, 16.006, 16.052, 16.091, 16.093 and 16.094] are below the threshold of concern (90 microgram/person/day). One of these substances [FL-no: 14.003] is reported to be used as a flavouring substance in Europe and the USA, one [FL-no: 16.006] is reported to be used in Europe and to be proposed for use in the USA, and six [FL-no: 11.014, 11.017, 16.052, 16.091, 16.093 and 16.094] are proposed for use in both regions. For those eight substances proposed for use in flavours in one or more region [FL-no: 11.014, 11.017, 14.003, 16.006, 16.052, 16.091, 16.093 and 16.094], less uncertain exposure estimates are needed. In accordance with the Procedure, evaluation of these eight flavouring substances proceeded to Step B4.

The *per capita* exposures in the USA of the two remaining flavouring substances in structural class III, 2-isopropyl-N-2,3-trimethylbutyramide ([FL-no: 16.053]; exposure, 1054 microgram/day) and N-ethyl-2-isopropyl-5-methylcyclohexane carboxamide ([FL-no: 16.013]; exposure, 127 microgram/day), exceed the threshold of concern for their structural class (90 microgram/person/day). In accordance with the Procedure, data must be available on these substances or closely related substances for a safety evaluation. For [FL-no: 16.053], which is proposed for use as a flavouring substance, a less uncertain exposure estimate is needed.

Step B4.

The No Observed Effect Level (NOEL) of 750 mg/kg bw/day for 1,6-hexalactam [FL-no: 16.052] in a 90-day feeding study in rats (NTP, 1982a) is at least 2.5 x 10^{10} times higher than the estimated exposure from its proposed use as a flavouring substance in Europe (0.00002 microgram/kg bw/day) and in the USA (0.00003 microgram/kg bw/day).

The NOEL of 572 mg/kg bw/day for the structurally related substance, N-isobutyl-2,6,8-decatrienamide [FL-no: 16.121] (Moore, 2002), is applicable to N-ethyl (2E,6Z)-nonadienamide [FL-no: 16.094], N-cyclopropyl (2E,6Z)-nonadienamide [FL-no: 16.093] and deca-(2E,4E)-dienoic acid isobutylamide [FL-no: 16.091], as they follow similar pathways of metabolism. This NOEL is 600000 times the estimated exposure to N-ethyl (2E,6Z)-nonadienamide [FL-no: 16.094] from its proposed use as a flavouring substance in the USA (1 microgram/kg bw/day) and is more than 800000 times the estimated exposure to N-cyclopropyl (2E,6Z)-nonadienamide [FL-no: 16.093] from its proposed use as flavouring substance in the USA (0.7 microgram/kg bw/day) and at least 600000 times the estimated exposure to deca-(2E,4E)-dienoic acid isobutylamide [FL-no: 16.091] from its proposed use as flavouring substance in Europe and in the USA (both 1 microgram/kg bw/day).

The NOEL of 8.4 mg/kg bw/day for N-nonanoyl 4-hydroxy-3-methoxybenzylamide [FL-no: 16.006] (Posternak et al., 1969) is more than 70000 times the estimated exposure from its proposed use as a flavouring substance in Europe (0.1 microgram/kg bw/day) and 8.4 x 10^6 times that in the USA (0.001 microgram/kg bw/day).

The NOEL of 20 mg/kg bw/day for piperine [FL-no: 14.003] (Bhat & Chandrasekhara, 1986b) is 50000 times the estimated exposure to piperine from its reported use as a flavouring substance in Europe (0.4 microgram/kg bw/day) and 2 x 10^7 times that in the USA (0.001 microgram/kg bw/day).

The NOEL of 115 mg/kg bw/day for the structurally related substance sec-butylamine [FL-no: 11.005] (Gage, 1970) is applicable to N-isopentylidene isopentylamine [FL-no: 11.017] and is at least 5.75 x 10^8 times the estimated intake to N-isopentylidene isopentylamine from its proposed use as flavouring substance in Europe (0.0001 microgram/kg bw/day) and in the USA (0.0002 microgram/kg bw/day).

The NOEL of 247 ppm in a study in rats treated by inhalation (equivalent to an oral dose of 157 mg/kg bw/day) for the structurally related substance triethylamine [FL-no: 11.023] is applicable to N,N-dimethylphenethylamine [FL-no: 11.014] and is at least 1 x 10^8 times the estimated exposure to N,N-dimethylphenethylamine from its proposed use as flavouring substance in Europe (0.001 microgram/kg bw/day) (Lynch et al., 1990; JECFA, 2006b).

Consideration of flavour substances with high exposure, evaluated via the B-side of the Procedure

In accordance with the Procedure, more data on toxicity were considered to evaluate the safety of 2-isopropyl-*N*-2,3-trimethylbutyramide [FL-no: 16.053] and *N*-ethyl-2-isopropyl-5-methylcyclohexane carboxamide [FL-no: 16.013], as the estimated exposure levels from proposed use [FL-no: 16.053] and reported use [FL-no: 16.013] as flavouring substances were determined to exceed the threshold of concern for structural class III (90 microgram per person per day).

The results of three studies in Sprague-Dawley (CD®) rats treated by gavage were available on 2-isopropyl-*N*-2,3-trimethylbutanamide [FL-no: 16.053]: a 14-day study in groups of six rats of each sex

at a dose of 0, 5, 25 or 50 mg/kg bw in corn oil twice daily (Nixon & Alden, 1978); a 14-week study in groups of 30 rats of each sex at a dose of 0, 10, 50 or 100 mg/kg bw in corn oil once daily (Pence, 1980a); and a 14-week study in groups of 30 rats of each sex at a dose of 0, 1, 2, 5, 10 or 50 mg/kg bw in corn oil once daily (Cheng, 1982). The studies showed treatment-related hepatic and renal toxicity at doses of 10 mg/kg bw and higher. The NOEL was 5 mg/kg bw/day, on the basis of histopathological lesions in the kidneys of male rats in the 14-week study (Cheng, 1982). A study of reproductive and teratogenic toxicity in rats at a dose of 0, 10, 50 or 100 mg/kg bw showed no reproductive effects or fetal abnormalities (Pence, 1980b). The NOEL of 5 mg/kg bw/day is 280 times the estimated daily exposure to 2-isopropyl-*N*-2,3-trimethylbutyramide [FL-no: 16.053] when used as a flavouring substance in the USA (18 microgram/kg bw/day).

Two studies were conducted on N-ethyl-2-isopropyl-5-methylcyclohexane carboxamide [FL-no: 16.013] in rats treated by gavage: a 28-day study in groups of six Crj:CD(SD) rats of each sex at a dose of 0, 8, 40, 200 or 1000 mg/kg bw/day (Miyata, 1995) and a 22-week study in groups of 15 Sprague-Dawley (CFY) rats of each sex at a dose of 0, 100, 300 or 725 mg/kg bw/day. Mild toxicity in the liver and kidneys was observed at doses of 40 mg/kg bw and above. Two further studies were conducted in beagle dogs given gelatine capsules: a 28-day study in groups of one male and one female given a dose of 0, 600, 1000 or 1500 mg/kg bw/day and a 52-week study in groups of three animals of each sex given a dose of 0, 100, 300 or 1000 mg/kg bw/day (James, 1974). These studies showed mild toxic effects in the liver at all doses. The NOEL of 8 mg/kg bw/day in these studies is 1000000 times the estimated daily exposure to N-ethyl-2-isopropyl-5-methylcyclohexanecarboxamide when used as a flavouring substance in Europe (0.008 microgram/kg bw/day) and 4000 times that in the USA (2 microgram/kg bw/day).

The additional toxicity data indicate that 2-isopropyl-*N*-2,3-trimethylbutyramide [FL-no: 16.053] and N-ethyl-2-isopropyl-5-methylcyclohexane carboxamide [FL-no: 16.013] would not be expected to raise safety concerns at their estimated levels of exposure when used as flavouring substances. For one of these substances [FL-no: 16.053], however, less uncertain exposure estimates are needed, as the existing estimate was based on anticipated poundage.

In conclusion, the JECFA evaluated all 34 substances as to be of no safety concern at the estimated levels of intake as flavouring substances based on the MSDI approach.

The evaluations of the 34 aliphatic and aromatic amines and amides are summarised in Table 3.1: Summary of Safety Evaluation of 34 Aliphatic and Aromatic Amines and Amides (JECFA, 2006d).

4.2. EFSA Considerations

After the publication of FGE.86 Industry has submitted additional data (toxicity data and mutagenicity data) on substance [FL-no: 16.095] (evaluated in FGE.94 (EFSA, 2010i)) to support the evaluation of [FL-no: 16.091, 16.093 and 16.094]. However, for the present evaluation the Panel consider the substance [FL no: 16.095] not to be sufficiently structurally related to candidate substances [FL-no: 16.091, 16.093 and 16.094] owing to the configuration of the amide bond and different characteristics of possible hydrolysis products (e.g. cyclopropyl amine and unsaturated carboxylic acid for [FL-no: 16.093] vs. cyclopropyl carboxylic acid and unsaturated amine for [FL-no: 16.095]; no cyclopropyl group in [FL-no: 16.091 and 16.094]. Due to these structural differences, routes of metabolism will also be different and also differences in toxicity must be anticipated.

The Panel agrees with the application of the Procedure as performed by the JECFA for 25 of the 34 substances in the group. Furthermore, for two more substances [FL-no: 11.006 and 16.053] the EU volumen has been provided since the publication of FGE.86. Based on the submitted EU production volumes, the Panel could also agree with the application of the Procedure as performed by the JECFA for these two substances. Further details can be found in FGE.96 (EFSA, 2010aj).

N-isopentylidene isopentylamine [FL-no: 11.017] is anticipated to be completely hydrolysed to isopentylamine and isopentylaldehyde, which are further metabolised to innocuous products. Accordingly [FL-no: 11.017] can be anticipated to be metabolised to innocuous products and evaluated along the A-side of the Procedure. The JECFA evaluated [FL-no: 11.017] along the B-side. As the estimated European *per capita* intake of 0.0073 microgram is below the treshold of concern for structural class III substances of 90 microgram/person/day, the Panel concluded (as did the JECFA) that there was no safety concern of the estimated level of intake of [FL-no: 11.017] based on the MSDI approach.

For butyramide [FL-no: 16.049] the Panel, contrary to the JECFA, concluded that this substance cannot be evaluated through the Procedure due to structural relationship to acetamide for which the Panel has concern with respect to carcinogenicity and a genotoxic mechanism which cannot be discounted.

In contrast to butyramide [FL-no: 16.049] the other amides in the present FGE are amides of alkylamines.

The JECFA derives a No Observed Adverse Effect Level (NOAEL) of 572 mg/kg bw/day for N-isobutyl-2,6,8-decatrienamide [FL-no: 16.121] from a 28-day feeding study with groups of 10 rats given different amounts of an extract of unknown purity from gold root (*Halopsis longiper*) with an estimated concentration of 50 % of N-isobutyl-2,6,8-decatrienamide (Moore, 2002). This study is also considered in FGE.303, in which N-isobutyl-2,6,8-decatrienamide [FL-no: 16.121] is the candidate substance. The Panel did not agree with the JECFA that the study is appropriate for deriving a NOAEL to be used at step B4 of the Procedure for the three substances [FL-no: 16.091, 16.093 and 16.094], and accordingly additional data are required.

The JECFA derives a NOAEL of 20 mg/kg bw/day for piperine [FL-no: 14.003] from a 56-day feeding study in groups of six rats given different doses of black pepper or oleoresin corresponding to up to approximately 20 mg/kg bw/day or 100 mg piperine/kg feed corresponding to up to approximately 10 mg/kg bw/day. No histopathology was performed. The Panel did not agree with the JECFA that the study is appropriate for deriving a NOAEL to be used at step B4 of the Procedure for piperine [FL-no: 14.003], and accordingly additional data are required.

The JECFA derives a NOAEL of 157 mg/kg bw/day from an inhalation study in groups of 100 rats exposed to 25 or 247 ppm triethylamine per day for up to 120 days, estimate to correspond to 25 to 157 mg/kg bw/day, respectively (Lynch et al., 1990). The Panel did not agree with the JECFA that the study is appropriate for deriving a NOAEL to be used at step B4 of the Procedure for N,N-dimethylphenethylamine [FL-no: 11.014] (JECFA, 2006b) and accordingly additional data are required.

The Panel considered further the possible consequences of nitrosation after ingestion of the secondary and tertiary amine and secondary amide candidate substances according to the approach described in the Annex to the minutes of the 30th AFC Panel meeting, May 2008 (EFSA, 2008e). From these considerations, the Panel concluded that extremely large margins of exposure could be calculated (>> 10^9) for nitrosated products possibly formed from amines used as flavouring substances in foods. Such large margins of exposure indicate that a risk of carcinogenicity resulting from such possible nitrosation products is virtually absent.

The Panel also noted that this conclusion is not applicable for foods preserved with nitrites, because for such foods the conditions for nitrosation, either in the foods themselves or after consumption in the stomach, may differ substantially from the worst-case conditions on which the calculations in the above mentioned Annex were based.

5. Conclusion

The Panel has considered 34 of 37 substances in the JECFA flavouring group of aliphatic and aromatic amines and amides. The Panel concluded that no corresponding FGE is available.

A further two substances were evaluated by the JECFA in this group, but these are not in the Register (1-amino-2-propanol and acetamide; JECFA-no: 1591 and 1592, respectively). A third substance evaluated by the JECFA is an alpha,beta-unsaturated ketone [FL-no: 14.168] considered with respect to genotoxicity in FGE.223, corresponding to subgroup 5.1 of FGE.19, for which a final conclusion regarding its genotoxic properties could not be reached and additional data were requested. This consideration therefore only deals with 34 flavouring substances.

The Panel agreed with the application of the Procedure as performed by the JECFA for 27 of the 34 substances. The JECFA concluded on five substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094] at step B4, but the Panel did not agree that appropriate studies are available for deriving NOAELs and accordingly the Panel in FGE.86 concluded that additional toxicity data are required for these five substances.

The flavouring Industry has in response to the requested toxicity data in FGE.86 submitted additional data for three of the five substances [FL-no: 16.091, 16.093 and 16.094]. The following information has been submitted:

Ames test and acute oral toxicity test have been submitted by Industry on [FL-no: 16.093]. The Industry suggests that these data also can support the evaluation of [FL-no: 16.091 and 16.094]. These studies do not fulfil the suggested minimum requirement to provide an adequate NOAEL for flavourings in the Procedure, which is considered to be a 90-day study. The minimum requirement has not been met by the new toxicity data submitted by Industry for the substances in FGE.86 therefore additional toxicity data is still requested.

Further has Industry submitted Ames test and a 28 day study on substance [FL-no: 16.095] (evaluated in FGE.94 (EFSA, 2010i)) to support the evaluation of [FL-no: 16.091, 16.093 and 16.094]. The Panel did not consider [FL-no: 16.095] sufficiently structurally related to be used as supporting substance for this FGE.

In addition to the five substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094] for which the Panel did not agree that appropriate studies are available for deriving NOAELs, butyramide [FL-no: 16.049] cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicity. For N-isopentylidene isopentylamine [FL-no: 11.017] the Panel concluded that this substance can be metabolised to innocuous products and accordingly evaluated along the A-side of the Procedure (while the JECFA evaluated [FL-no: 11.017] along the B-side). Like the JECFA the Panel concluded that [FL-no: 11.017] is of no safety concern at estimated level of intake, based on the MSDI approach. So, the Panel did not agree with the application of the Procedure as performed by the JECFA for 7 of the 34 substances.

For 22 substances evaluated by the JECFA through the Procedure use levels have been provided by the Industry [FL-no: 11.002, 11.004, 11.005, 11.007, 11.014, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.080, 14.133, 14.141, 16.049, 16.052, 16.091, 16.092, 16.093 and 16.094]. The mTAMDI figures calculated for the substances in structural class I are 340 microgram/person/day, except for [FL-no: 16.092], for which the mTAMDI is 15000 microgram/person/day, exceeding the threshold of 1800 microgram/person/day for structural class I. The mTAMDI figures for the structural class II substances range from 200 to 340 microgram/person/day, except for [FL-no: 14.141] for which the figure is 600 microgram/person/day, exceeding the threshold of 540 microgram/person/day for structural class II. For the substances [FL-no: 11.014, 16.052, 16.091, 16.093 and 16.094] in structural class III the figures range from 200 to 1900 microgram/person/day, exceeding the threshold of concern of 90 microgram/person/day for structural class III. Thus, for seven substances [FL-no: 11.014, 14.141, 16.052, 16.091, 16.092, 16.093 and 16.094] the intakes, estimated on the basis of the

mTAMDI approach, exceed the threshold for their structural classes. Therefore more reliable exposure data are required. On the basis of such additional data, these flavouring substances should be considered using the Procedure. Subsequently, additional data might become necessary.

For the remaining 12 substances [FL-no: 11.001, 11.003, 11.006, 11.009, 11.017, 14.003, 14.010, 14.064, 14.167, 16.006, 16.013 and 16.053] use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 34 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications. Specifications including complete purity criteria and identity are available for 33 of the 34 JECFA evaluated substances. For one substance [FL-no: 16.013] information on the stereoisomeric composition is lacking.

Thus, for one substance [FL-no: 16.013] the Panel has reservation (information on stereoisomeric composition is requested).

For seven of the 34 evaluated substances the Panel did not agree with the JECFA application of the Procedure and additional toxicity data are required for five of the seven substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094]. One substance cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicity [FL-no: 16.049] and one substance [FL-no: 11.017] is evaluated along the A-side, while the JECFA evaluated it along the B-side.

Overall, for 27 of the 34 JECFA evaluated aliphatic and aromatic amines and amides [FL-no: 11.001, 11.002, 11.003, 11.004, 11.005, 11.006, 11.007, 11.009, 11.015, 11.016, 11.017, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.010, 14.064, 14.080, 14.133, 14.141, 14.167, 16.006, 16.052, 16.053 and 16.092] the Panel agreed with the JECFA conclusion “no safety concern at estimated levels of intake as flavouring substances” based on the MSDI approach.

TABLE 1: SPECIFICATION SUMMARY

Table 1: Specifications Summary for the JECFA Evaluated Substances in the Present Group (JECFA, 2005d)

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic and Aromatic Amines and Amides (JECFA, 2005d)

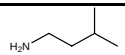
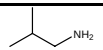
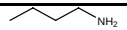
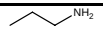
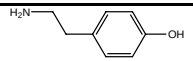
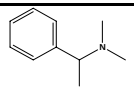
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
11.001 1587	3-Methylbutylamine		3219 512 107-85-7	Liquid $C_5H_{13}N$ 87.16	Soluble Soluble	95-97 NMR 98 %	1.405-1.411 0.747-0.753	
11.002 1583	Isobutylamine		513 78-81-9	Liquid $C_4H_{11}N$ 73.14	Soluble Soluble	68 MS 95 %	1.391-1.397 0.731-0.737	
11.003 1582	Butylamine		3130 524 109-73-9	Liquid $C_4H_{11}N$ 73.14	Soluble Soluble	78 NMR 99 %	1.398-1.404 0.732-0.740	
11.004 1580	Propylamine		601 107-10-8	Liquid C_3H_9N 59.11	Soluble Soluble	48 MS 95 %	1.384-1.390 0.714-0.720	
11.005 1584	sec-Butylamine		707 13952-84-6	Liquid $C_4H_{11}N$ 73.14	Soluble Soluble	63 MS 95 %	1.387-1.393 0.715-0.721	Racemate.
11.006 1589	Phenethylamine		3220 708 64-04-0	Liquid $C_8H_{11}N$ 121.18	Soluble Soluble	194-195 NMR 95 %	1.526-1.532 (25°) 0.961-0.967	
11.007 1590	2-(4-Hydroxyphenyl)ethylamine		709 51-67-2	Solid $C_8H_{11}NO$ 137.18	Soluble Soluble	 165 MS 95 %	n.a. n.a.	
11.009 1610	Trimethylamine		3241 10497 75-50-3	Gas C_3H_9N 59.11	Soluble Soluble	3-4 - NMR 98 %	n.a. 0.667-0.675 (4°)	
11.014 1613	N,N-Dimethylphenethylamine		19342-01-9	Liquid $C_{10}H_{15}N$ 149.24	Soluble Soluble	183 MS 95 %	1.500-1.506 0.898-0.904	Register name to be changed to (R)-N,N-Dimethylphenethylamine.
11.015 1579	Ethylamine		10477	Gas C_2H_7N	Soluble Soluble	17 -81	n.a. 0.682-0.686	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic and Aromatic Amines and Amides (JECFA, 2005d)

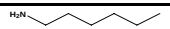
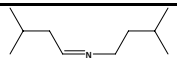
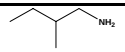
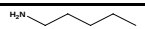
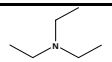
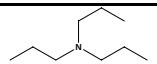
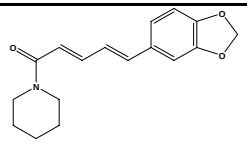
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
			75-04-7	45.08		MS 95 %	(10°)	
11.016 1588	Hexylamine		10478 111-26-2	Liquid $C_6H_{15}N$ 101.19	Soluble Soluble	130 MS 95 %	1.415-1.421 0.761-0.767	
11.017 1606	N-Isopentylidene isopentylamine		3990 35448-31-8	Liquid $C_{10}H_{21}N$ 155.29	Insoluble Soluble	145-148 MS 98 %	1.422-1.428 0.768-0.774	
11.018 1581	Isopropylamine		10480 75-31-0	Liquid C_3H_9N 59.11	Soluble Soluble	34 MS 95 %	1.367-1.373 0.687-0.693	
11.020 1586	2-Methylbutylamine		10484 96-15-1	Liquid $C_5H_{13}N$ 87.16	Soluble Soluble	96 MS 95 %	1.417-1.423 0.777-0.779	Racemate.
11.021 1585	Pentylamine		11734 110-58-7	Liquid $C_5H_{13}N$ 87.16	Soluble Soluble	103 MS 95 %	1.418-1.424 0.750-0.759	
11.023 1611	Triethylamine		10496 121-44-8	Liquid $C_6H_{15}N$ 101.19	Soluble Soluble	88 MS 95 %	1.395-1.401 0.724-0.730	
11.025 1614	Trimethylamine oxide		10494 1184-78-7	Solid C_3H_9NO 75.11	Soluble Soluble	 213 MS 95 %	n.a. n.a.	
11.026 1612	Tripropylamine		10495 102-69-2	Liquid $C_9H_{21}N$ 143.27	Soluble Soluble	156 MS 95 %	1.411-1.417 0.754-0.760	
14.003 1600	Piperine		2909 492 94-62-2	Solid $C_{17}H_{19}O_3N$ 285.34	Very slightly soluble Soluble	 128-130 NMR 97 %	n.a. n.a.	CASrn in the Register refers to the (E,E)-isomer. Register name to be changed to (E,E)-piperidine.
14.010 1607	Piperidine		2908 675 110-89-4	Liquid $C_5H_{11}N$ 85.15	soluble Soluble	106 IR 98 %	1.450-1.454 0.858-0.862	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic and Aromatic Amines and Amides (JECFA, 2005d)

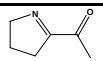
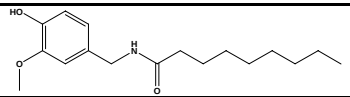
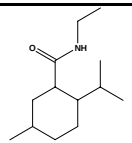
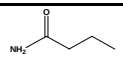
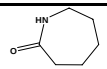
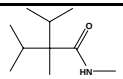
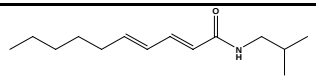
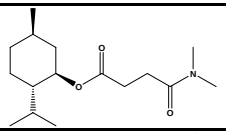
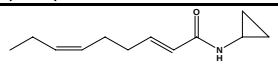
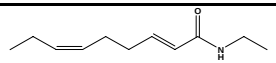
FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
14.064 1609	Pyrrolidine		3523 10491 123-75-1	Liquid C_4H_9N 71.12	Soluble Freely soluble	87-89 IR NMR 95 %	1.440-1.446 0.847-0.853	
14.080 1604	2-Acetyl-1-pyrroline		 99583-29-6	Solid C_6H_9NO 111.14	Soluble Soluble	 19 MS 95 %	n.a. n.a.	
14.133 1608	2-Methylpiperidine		 109-05-7	Liquid $C_6H_{13}N$ 99.18	Soluble Soluble	118 MS 95 %	1.442-1.448 0.838-0.844	Racemate
14.141 1615	Piperazine		 110-85-0	Solid $C_4H_{10}N_2$ 86.14	Soluble soluble	 109 MS 95 %	n.a. n.a.	
14.167 1603	1-Pyrroline		 5724-81-2	Liquid C_4H_7N 69.10	Soluble Soluble	87-89 NMR 99 %	1.440-1.446 0.849-0.855	
16.006 1599	N-Nonanoyl 4-hydroxy-3-methoxybenzylamide		2787 590 2444-46-4	Solid $C_{17}H_{27}O_3N$ 293.41	Slightly soluble Soluble	 124-128 NMR 96 %	n.a. n.a.	
16.013 1601	N-Ethyl-2-isopropyl-5-methylcyclohexane carboxamide		3455 2298 39711-79-0	Solid $C_{13}H_{25}ON$ 211.35	Insoluble Soluble	 91-93 NMR 98 %	n.a. n.a.	Mixture of diastereoisomers (EFFA, 2010a). Range should be given. CASrn in Register does not specify stereoisomeric composition.
16.049 1593	Butyramide		 541-35-5	Solid C_4H_9NO 87.12	Soluble Soluble	 115 NMR MS 95 %	n.a. n.a.	
16.052 1594	1,6-Hexalactam		 105-60-2	Solid $C_6H_{11}NO$ 113.16	Soluble Soluble	 70 NMR MS 95 %	n.a. n.a.	
16.053 1595	2-Isopropyl-N,2,3-trimethylbutanamide		3804 10459 51115-67-4	Solid $C_{10}H_{21}ON$ 171.28	insoluble Soluble	 56-64 NMR 99 %	n.a. n.a.	

Table 1: Specification Summary of the Substances in the JECFA Flavouring Group of Aliphatic and Aromatic Amines and Amides (JECFA, 2005d)

FL-no JECFA-no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility 1) Solubility in ethanol 2)	Boiling point, °C 3) Melting point, °C ID test Assay minimum	Refrac. Index 4) Spec.gravity 5)	EFSA comments
16.091 1598	Deca-(2E,4E)-dienoic acid isobutyl-amide		18836-52-7	Solid $C_{14}H_{23}NO$ 223.36	Insoluble Soluble	82-90 IR NMR MS 95 %	n.a. n.a.	
16.092 1602	N,N-Dimethyl menthyl succinamide		544714-08-1	Liquid $C_{16}H_{30}O_2N_2$ 282.43	Slightly soluble Soluble	380 IR NMR 95 %	1.522-1.530 0.965-0.975	Register name to be changed to (1R,2S,5R) N,N-Dimethyl menthyl succinamide.
16.093 1597	N-Cyclopropyl (2E,6Z)-nonadienamide		608514-55-2	Solid $C_{12}H_{19}NO$ 193.29	Sparingly soluble Soluble	33-37 IR NMR 95 %	n.a. n.a.	
16.094 1596	N-Ethyl (2E,6Z)-nonadienamide		608514-56-3	Liquid $C_{11}H_{19}NO$ 181.28	Sparingly soluble Soluble	120 (0.8 hPa) IR NMR MS 96 %	1.484-1.493 0.910-0.920	

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

TABLE 2: GENOTOXICITY DATA

Table 2.1: Genotoxicity Data (in vitro / in vivo) for 34 Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

Table 2.1: Summary of Genotoxicity Data of 34 Aliphatic and Aromatic Amines and Amides evaluated by JECFA

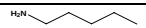
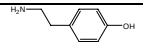
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
In vitro							
11.015 1579	Ethylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100 to 10,000 µg/plate	Negative[1]	(Mortelmans et al., 1986)
11.018 1581	Isopropylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	10 to 10,000 µg/plate	Negative[1]	(Zeiger et al., 1987)
11.003 1582	Butylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3.3 to 3,333 µg/plate	Negative[1]	(Zeiger et al., 1987)
			Reverse Mutation	*S. typhimurium* TA100	3 µmol/plate (219 µg/plate)[2]	Negative[1]	(Florin et al., 1980)
11.002 1583	Isobutylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	33 to 10,000 µg/plate	Negative[1]	(Mortelmans et al., 1986)
11.005 1584	sec-Butylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	10 to 3,333 µg/plate	Negative[1]	(Zeiger et al., 1987)
11.021 1585	Pentylamine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	33 to 3,333 µg/plate	Negative[1]	(Mortelmans et al., 1986)
11.007 1590	2-(4-Hydroxyphenyl)ethylamine		Forward Mutation	Mouse lymphoma L5178Y cells	500 to 3,500 µg/ml	Negative	(McGregor et al., 1988c)
			Forward Mutation	Mouse lymphoma L5178Y cells	0.08, 0.80, 2.0, 4.0 or 6.0 mM (11, 109, 274, 548 and 823 µg/ml)[3,4]	Positive [5,6]	(Wangenheim & Bolcsfoldi, 1988)
			Forward Mutation	Mouse lymphoma L5178Y cells	0.40, 0.80, 1.60, 2.39 or 3.20 mM (55, 109, 220, 327 and 439 µg/ml)[3,4]	Positive [6,7]	(Wangenheim & Bolcsfoldi, 1988)
1592	Acetamide (not in Register)		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100 to 10,000 µg/plate	Negative[1]	(Haworth et al., 1983)
			DNA Repair	*Escherichia coli* 343/591 *uvr*B$^-$/*rec*A$^-$/*lac*$^+$ and *uvr*B$^+$/*rec*A$^+$/*lac*$^+$	Up to 1,080 mM (63,793 µg/ml)[8]	Negative[1]	(Hellmér & Bolcsfoldi, 1992a)
			Single Strand DNA Breaks	Rat hepatocytes	0.03, 0.3, 3, 10, 30, 100, 300, or 1,000 mM (2, 18, 177, 591, 1,772,	Negative	(Sina et al., 1983)

Table 2.1: Summary of Genotoxicity Data of 34 Aliphatic and Aromatic Amines and Amides evaluated by JECFA

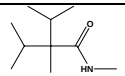
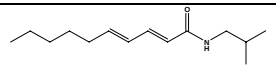
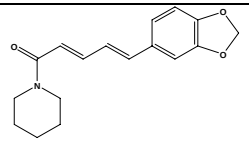
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
					5,907, 17,720, or 59,068 µg/ml)[8]		
16.053 1595	2-Isopropyl- N,2,3-trimethylbutanamide		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	200, 1,000, 5,000, 10,000 or 20,000 µg/plate	Negative[1]	Haworth *et al.* (1978)
			Forward Mutation	Mouse lymphoma L5178Y cells	0.01 to 1,000 µg/ml	Negative[1]	Kirby *et al.* (1978)
			Unscheduled DNA Synthesis	WI-38 cells (human)	125 to 2,000 µg/ml[9]	Negative[1]	Skinner (1978)
16.091 1598	Deca-(2E,4E)-dienoic acid isobutylamide		Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537	5 to 1,500 µg/plate[10]	Negative[5]	King (2003)
			Reverse Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537	5 to 5,000 µg/plate[11]	Negative[7]	King (2003)
14.003 1600	Piperine		Reverse Mutation	*S. typhimurium* TA97a, TA98, TA100, TA102	0.01, 0.5 or 10 µmol/plate (3, 143 and 2,853 µg/plate)[12]	Negative[1]	(Karekar et al., 1996)
			Reverse Mutation (pre-incubation)	*S. typhimurium* TA97a, TA98, TA100, TA102	0.005, 0.05, 0.5 or 5 µmol/plate (1, 14, 143 and 1,427 µg/plate)[12,13]	Negative[1]	(Karekar et al., 1996)
			Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1,000 µg	Negative[1]	(Andrews et al., 1980)
14.010 1607	Piperidine		Reverse Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol/plate (255 µg/plate)[14]	Negative[1]	(Florin et al., 1980)
			Reverse Mutation	*S. typhimurium* TA1530, TA1531, TA1532, TA1964	1 to 5 mg/plate (1,000 to 5,000 µg/plate)[14]	Negative	(Green & Savage, 1978)
			Reverse Mutation (microsomal assay)	*S. typhimurium* TA1530, TA1531, TA1532, TA1964	0.15 M (12,772 µg/ml)[14,15]	Negative	(Green & Savage, 1978)
			Reverse Mutation (host-mediated, mice)	*S. typhimurium* TA1950, TA1951, TA1952, TA1964	800 mg/kg bw[16]	Negative	(Green & Savage, 1978)
			Forward Mutation	Mouse lymphoma L5178Y cells	3.03, 4.04, 5.05, 6.06 or 7.07 mM (258, 344, 430, 516 and 602 µg/ml)[14]	Positive [5,6]	(Wangenheim & Bolcsfoldi, 1988)
			Forward Mutation	Mouse lymphoma L5178Y cells	4.04, 5.05, 6.06, 7.07 or 8.08 mM (344, 430, 516, 602 and 688 µg/ml)[14]	Negative[7]	(Wangenheim & Bolcsfoldi, 1988)
			Forward Mutation	Mouse lymphoma L5178Y cells	2.0, 4.01, or 6.01 mM (170, 341 and 512 µg/ml)[14]	Negative[5]	(Garberg et al., 1988)
			Forward Mutation	Mouse lymphoma	2.0, 4.01, 6.01 or 8.02	Equivocal	(Garberg et al., 1988)

Table 2.1: Summary of Genotoxicity Data of 34 Aliphatic and Aromatic Amines and Amides evaluated by JECFA

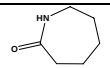
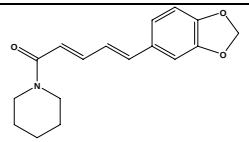
FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
				L5178Y cells	mM (170, 341, 512 and 683 µg/ml)[14]	[7,17]	
			DNA Repair	*Escherichia coli* 343/591 *uvr*B$^-$/*rec*A$^-$/*lac*$^+$ and *uvr*B$^+$/*rec*A$^+$/*lac*$^+$	33.7 mM (2,870 µg/ml)[14,18]	Negative[5]	(Hellmér & Bolcsfoldi, 1992a)
			DNA Repair	*Escherichia coli* 343/591 *uvr*B$^-$/*rec*A$^-$/*lac*$^+$ and *uvr*B$^+$/*rec*A$^+$/*lac*$^+$	101 mM (8,600 µg/ml)[14,18]	Negative[5]	(Hellmér & Bolcsfoldi, 1992a)
			Single Strand DNA Breaks	Rat hepatocytes	0.03, 0.3 or 3 mM (2.6, 26 and 255 µg/ml)[14]	Negative	(Sina et al., 1983)
14.064 1609	Pyrrolidine		Reverse Mutation	*S .typhimurium* TA100	Up to 3 µmol/plate (213 µg/plate)[19]	Negative[1]	(Florin et al., 1980)
			Reverse Mutation	*S .typhimurium* TA1530, TA1531, TA1532, TA1964	1 to 5 mg/plate (1,000 to 5,000 µg/plate)[3]	Negative	(Green & Savage, 1978)
			Reverse Mutation (microsomal assay)	*S. typhimurium* TA1530, TA1531, TA1532, TA1964	0.5 M (35,561 µg/ml)[19]	Negative	(Green & Savage, 1978)
			Reverse Mutation (host-mediated, mice)	*S .typhimurium* TA1950, TA1951, TA1952, TA1964	800 mg/kg bw[16]	Negative	(Green & Savage, 1978)
11.009 1610	Trimethylamine		Reverse Mutation	*S .typhimurium* TA98, TA100, TA1535, TA1537	10 to 1,000 µg/plate	Negative[1]	(Mortelmans et al., 1986)
11.023 1611	Triethylamine		Reverse Mutation	*S .typhimurium* TA98, TA100, TA1535, TA1537	10 to 10,000 µg/plate	Negative[1]	(Zeiger et al., 1987)
14.141 1615	Piperazine		Reverse Mutation	*S .typhimurium* TA98, TA100, TA1535, TA1537	33 to 3,167 µg/plate	Negative[1]	(Haworth et al., 1983)
In vivo							
1592	Acetamide (not in Register)		DNA Damage (Comet assay)	Male ddy mice	2,000 mg/kg bw[20]	Positive [21]	(Sasaki et al., 2000)
			Micronuclei (bone marrow)	C57B1/6 mice	2,500 or 5,000 mg/kg bw[22]	Negative	(Mirkova, 1996)
			Micronuclei (bone marrow)	Male CBA mice	5,000 mg/kg bw[22]	Negative	(Mirkova, 1996)
			Micronuclei (bone marrow and peripheral blood)	Male CD1 mice	500 to 5,000 mg/kg bw[23]	Negative	(Morita et al., 1997)
			Micronuclei (bone marrow and peripheral blood)	Male BDF1 mice	1,250 to 5,000 mg/kg bw[23]	Negative	(Morita et al., 1997)
			Micronuclei (bone marrow)	Female C57B1/6 mice	3.39 mmol/kg bw (200 mg/kg bw)[24,25]	Positive	(Chieli et al., 1987)
16.052 1594	1,6-Hexalactam		DNA Damage (Comet assay)	Male ddy mice	2,000 mg/kg bw[22]	Negative	(Sasaki et al., 2000)
			Replicative DNA Synthesis	Male F344 rats	350 or 700 mg/kg bw[26]	Negative	(Uno et al., 1994)
			Replicative DNA Synthesis	Male B6C3F$_1$ mice	250 or 500 mg/kg bw[22]	Negative	(Miyagawa et al., 1995)

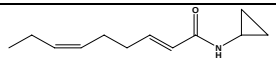
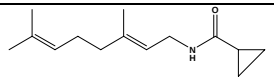
Table 2.1: Summary of Genotoxicity Data of 34 Aliphatic and Aromatic Amines and Amides evaluated by JECFA

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference
			Mammalian Spot	(C57B1xT)F_1 mouse embryos	400 or 500 mg/kg bw[22]	Positive [27]	(Fahrig, 1989)
			Mammalian Spot	(TxHT)F_1 mouse embryos	500 mg/kg bw[28]	Positive [29]	(Neuhäuser-Klaus & Lehmacher, 1989)
			Mammalian Spot	(TxHT)F_1 mouse embryos	700 mg/kg bw[28]	Negative	(Neuhäuser-Klaus & Lehmacher, 1989)
			Sex-Linked Recessive Lethals	Male *Drosophila melanogaster* larvae	5.0 mM[30] (566 µg/ml)[31]	Negative	(Vogel, 1989)
			Sex-Linked Recessive Lethals	Female *Drosophila melanogaster* larvae	5.0 or 20.0 mM[30] (566 or 2,263 µg/ml)[31]	Positive	(Vogel, 1989)
			Somatic Mutation/Mitotic Recombination	Female *Drosophila melanogaster* larvae	2.5, 5.0, 10.0 or 20.0 mM[30] (283, 566, 1,132 and 2,263 µg/ml)[31]	Positive	(Vogel, 1989)
			Chromosomal Aberrations (bone marrow)	Male and female 1C3F_1 mice	1,000 mg/kg bw[22]	Negative	(Adler & Ingwersen, 1989)
14.003 1600	Piperine		Micronuclei (bone marrow)	Male Swiss mice	10 or 20 mg/kg bw[22]	Negative	(Karekar et al., 1996)
			Micronuclei (bone marrow)	Male Swiss mice	1, 2 or 4 mg/kg bw[32]	Negative	(Muralidhara & Narasimhamurthy, 1990)
			Sperm Morphology	Male Swiss mice	10 or 50 mg/kg bw/day[33]	Negative	(Karekar et al., 1996)
			Sperm Morphology	Male Swiss mice	35, 50 or 75 mg/kg bw/day[34]	Negative	(Daware et al., 2000)
			Sperm Morphology	Male Swiss mice	1, 2 or 4 mg/kg bw/day[35]	Negative	(Muralidhara & Narasimhamurthy, 1990)
			Dominant Lethal Mutations	Male and Female Swiss mice	10 or 50 mg/kg bw[22]	Negative	(Karekar et al., 1996)
			Dominant Lethal Mutations	Male Swiss mice	4 mg/kg bw/day[35]	Negative	(Muralidhara & Narasimhamurthy, 1990)
14.010 1607	Piperidine		Mitosis in Adrenocortical Cells	Male Wistar rats	100 mg/kg bw in DMSO[22]	Negative	(Danz & Urban, 1979)
			Mitosis in Adrenocortical Cells	Male Wistar rats	100 mg/kg bw in 1% Tylose[22]	Negative	(Danz & Urban, 1979)
			Sperm Morphology	Male hybrid mice	400 mg/kg bw/day[36]	Negative	(Bempong & Scully, 1983)
			Sperm Morphology	Male golden Syrian hamsters	400 mg/kg bw/day[36]	Negative	(Bempong & Scully, 1983)
14.064 1609	Pyrrolidine		Mitosis in Adrenocortical Cells	Male Wistar rats	100 mg/kg bw in 1% Tylose[22]	Negative	(Danz & Urban, 1979)
			Mitosis in Adrenocortical Cells	Male Wistar rats	100 mg/kg bw in DMSO[22]	Positive	(Danz & Urban, 1979)

[1] With and without S9.
[2] Calculated using the molecular weight of butrylamine (73.14 g/mol).
[3] Calculated using the molecular weight of tyramine (137.18 g/mol).
[4] Actual compound used in this study was tyramine hydrochloride at concentrations of 0.101 to 7.59 mM (18 to 1,318 µg/ml) without metabolic activation, and 0.506 to 4.05 mM (88 to 703 µg/ml) with metabolic activation.
[5] Without metabolic activation.

[6] Significant increases in mutation frequency were observed only at cytotoxic doses.
[7] With metabolic activation.
[8] Calculated using the molecular weight of acetamide (59.07 g/mol).
[9] Cytotoxic at 2,000 µg/ml.
[10] Toxic and precipitates at 1,500 µg/plate.
[11] Toxic and precipitates at 5,000 µg/plate.
[12] Calculated using the molecular weight of piperine (285.34 g/mol).
[13] Toxic at 5 µmol/plate without metabolic activation.
[14] Calculated using the molecular weight of piperidine (85.15 g/mol).
[15] Highest non-cytotoxic concentration.
[16] Intraperitoneal injection of *S. typhimurium* strain with intramuscular injection of test material.
[17] Results observed did not meet the criteria for positive or negative classification.
[18] Concentration at which a significant reduction in the number of colonies of each strain was observed; however, the highest concentration of piperidine tested was 1,010 mM.
[19] Calculated using the molecular weight of pyrrolidine (71.12 g/mol).
[20] Administered via a single intraperitoneal injection.
[21] Increase in DNA damage was observed in the stomach, colon, lungs and bone marrow of mice.
[22] Administered via a single gavage dose.
[23] Single, double, or quadruple intraperitoneal injections, separated by 24 hours, were administered.
[24] Administered by gavage at 30 and 6 hours prior to sacrifice.
[25] Calculated using the molecular weight of acetamide (59.07 g/mol).
[26] Administered via a single subcutaneous injection.
[27] Frequency of spots of genetic relevance was significantly increased relative to controls only in 1 out of 3 trials, and only at the highest dose (500 mg/kg bw).
[28] Administered at a single dose (route not specified).
[29] Significant increase in spots of genetic relevance was observed only in 1 out of 4 groups receiving 500 mg/kg body weight.
[30] Administered in the diet.
[31] Calculated using the molecular weight of 1,6-hexalactam (113.16 g/mol).
[32] Intraperitoneal injection in 2 installments at 0 and 24 hours.
[33] Administered via gavage for 5 days.
[34] Administered orally for 5 consecutive days.
[35] Administered intraperitoneally for 5 days, followed by a 35-day maintenance period.
[36] Piperidine was administered orally to mice for 100 days. However, on day 40 and every subsequent 5 days, 3 mice were killed for examination of sperm morphology.

Table 2.2: Additional genotoxicity data submitted by the Industry

FL-no JECFA-no	EU Register name JECFA name	Structural formula	End-point	Test system	Concentration	Results	Reference	Comments
In vitro								
16.093 1597	N-Cyclopropyl (2E,6Z)-nonadienamide		Reverse Mutation	*S.typhimurium* TA98, TA100, TA1535, TA1537	Up to 5000 µg/plate	Negative[1]	(Bowles, 2003)	
			Reverse Mutation	*E.coli WP2 uvrA*$^-$	Up to 5000 µg/plate	Negative[1]	(Bowles, 2003)	
16.095 1779	N-3,7-Dimethyl-2,6-octadienyl cyclopropylcarboxamide		Reverse Mutation	*S.typhimurium* TA97a, TA1535	Up to 2000 µg/plate	Negative	(Next Century Incorporated, 2004)	Cytotoxic at different concentration with and without S9.
			Reverse Mutation	*S.typhimurium* TA98, TA100	Up to 5000 µg/plate	Negative	(Next Century Incorporated, 2004)	
			Reverse Mutation	*Escherichia coli WP2 uvrA (328)*	Up to 2000 µg/plate	Negative	(Next Century Incorporated, 2004)	

[1] With and without S9.

TABLE 3: SUMMARY OF SAFETY EVALUATIONS

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

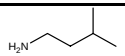
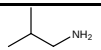
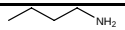
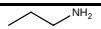
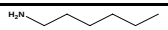
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
11.001 1587	3-Methylbutylamine		24 0.07	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.002 1583	Isobutylamine		0.012 0.09	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.003 1582	Butylamine		89 0.01	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.004 1580	Propylamine		0.012 0.02	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.005 1584	sec-Butylamine		0.012 2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	Racemate. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.009 1610	Trimethylamine		130 70	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.015 1579	Ethylamine		0.012 0.2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.016 1588	Hexylamine		0.024 0.007	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

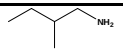
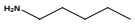
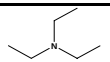
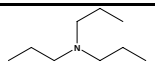
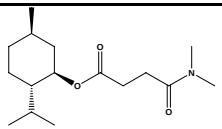
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
11.018 1581	Isopropylamine		0.012 0.02	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.020 1586	2-Methylbutylamine		0.012 0.02	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	Racemate. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.021 1585	Pentylamine		0.037 0.2	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.023 1611	Triethylamine		0.073 0.9	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.025 1614	Trimethylamine oxide		2.3 0.09	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.026 1612	Tripropylamine		0.012 0.02	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
16.092 1602	N,N-Dimethyl menthyl succinamide		61 88	Class I A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	Register name to to be changed to (1R,2S,5R)-N,N-Dimethyl menthyl succinamide. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

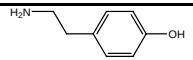
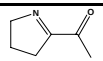
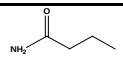
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
11.006 1589	Phenethylamine		0.075 0.05	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at the estimated level of intake based on the MSDI approach.
11.007 1590	2-(4-Hydroxyphenyl)ethylamine		0.012 0.02	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.010 1607	Piperidine		88 96	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.064 1609	Pyrrolidine		0.12 2	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.080 1604	2-Acetyl-1-pyrroline		0.012 0.1	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.133 1608	2-Methylpiperidine		0.012 0.002	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	Racemate. No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.141 1615	Piperazine		0.012 0.002	Class II A3: Intake below threshold	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.167 1603	1-Pyrroline		0.012 0.4	Class II A3: Intake below threshold	4)	EU MSDI is available No safety concern at estimated level of intake as flavouring substance based on the MSDI approach	EU MSDI is available No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
16.049 1593	Butyramide		0.012 0.002	Class II A3: Intake below threshold	4)	The Panel concluded that the substance cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicit	The Panel concluded that the substance cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicit

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

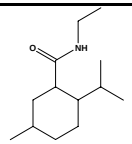
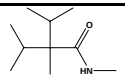
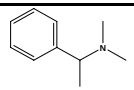
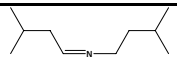
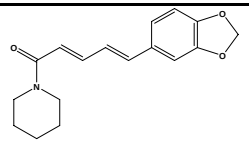
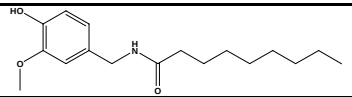
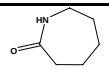
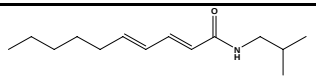
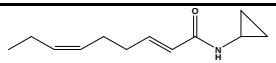
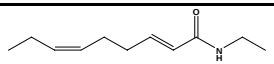
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
						y	y.
16.013 1601	N-Ethyl-2-isopropyl-5-methylcyclohexane carboxamide		0.4 127	Class III B3: Intake above threshold	Data must be available 5) Data were available indicate that the substance would not be expected to raise safety concern.	Additional data indicate that the substance would not be expected to raise safety concerns at its estimated level of intake when used as flavourings	Composition of stereoisomeric mixture to be specified. Additional data indicate that the substance would not be expected to raise safety concern at its estimated level of intake when used as flavourings.
16.053 1595	2-Isopropyl- N,2,3-trimethylbutanamide		24 1054	Class III B3: Intake above threshold	Data must be available 5) Data were available indicate that the substance would not be expected to raise safety concern.	No safety concern at the estimated level of intake based on the MSDI approach. EFSA concluded at step B4: Yes, an adequate NOAEL could be established	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
11.014 1613	N,N-Dimethylphenethylamine		0.012 0.09	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Additional toxicity data required	Additional toxicity data required. Name to be changed to (R)-N,N-Dimethylphenethylamine.
11.017 1606	N-Isopentylidene isopentylamine		0.012 0.01	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
14.003 1600	Piperine		20 0.07	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Additional toxicity data required	CASrn in the Register refers to the trans, trans isomer Register name to be changed to (E,E)-piperidine. Additional toxicity data required.
16.006 1599	N-Nonanoyl 4-hydroxy-3-methoxybenzylamide		6.0 0.07	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.
16.052 1594	1,6-Hexalactam		0.012 0.002	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	No safety concern at the estimated level of intake based on the MSDI approach	No safety concern at estimated level of intake as flavouring substance based on the MSDI approach.

Table 3.1: Summary of Safety Evaluation of Aliphatic and Aromatic Amines and Amides (JECFA, 2006d)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI 1) US MSDI (µg/*capita*/day)	Class 2) Evaluation procedure path 3)	Outcome on the named compound [4) or 5)]	EFSA conclusion on the named compound (Procedure steps, intake estimates, NOAEL, genotoxicity)	EFSA conclusion on the material of commerce
16.091 1598	Deca-(2E,4E)-dienoic acid isobutyl-amide		6.1 83	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Additional toxicity data required	Additional toxicity data required.
16.093 1597	N-Cyclopropyl (2E,6Z)-nonadienamide		61 40	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Additional toxicity data required	Additional toxicity data required.
16.094 1596	N-Ethyl (2E,6Z)-nonadienamide		61 88	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	4)	Additional toxicity data required	Additional toxicity data required.

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.

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ABBREVIATIONS

BW	Body Weight
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CHO	Chinese hamster ovary (cells)
CoE	Council of Europe
COT	Committee on Toxicity of Chemicals in Food
DMSO	Dimethyl Sulphoxide
DNA	Deoxyribonucleic acid
EFSA	The European Food Safety Authority
EPA	United States Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practice
ID	Identity
Ip	Intraperitoneal
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
NCE	Normochromatic erythrocyte
No	Number
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
PCE	Polychromatic erythrocyte

SCE	Sister chromatic exchange
SCF	Scientific Committee on Food
WHO	World Health Organisation