Flavouring Group Evaluation 34:
One tetrahydroquinoline derivative from chemical group 28

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC)

(Question No EFSA-Q-2008-038)

Adopted on 31 January 2008

Panel Members

Summary
The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (the Panel) is asked to advise 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 Scientific Panel is asked to evaluate one flavouring substance in the Flavouring Group Evaluation FGE.34, using the procedure as referred to in the Commission Regulation (EC) No 1565/2000. This flavouring substance belongs to chemical group 28, Annex I of the Commission Regulation (EC) No 1565/2000.

The present Flavouring Group Evaluation 34 (FGE.34), deals with one tetrahydroquinoline derivative from chemical group 28, 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149]. No geometrical or optical isomers exist for this candidate substance. The flavouring substance is classified into structural class III according to the decision tree approach presented by Cramer et al. (Cramer et al., 1978).

The substance has not been reported to occur naturally in any food items.

In its evaluation, the Panel as a default used the Maximised Survey-derived Daily Intake (MSDI) approach to estimate the per capita intakes of the flavouring substances in Europe. However, when the Scientific Panel examined the information provided by the European Flavouring Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach.
In the absence of more precise information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a modified Theoretical Added Maximum Daily Intake (mTAMDI) approach based on the normal use levels reported by Industry. In those cases where the mTAMDI approach indicated that the intake of a flavouring substance might exceed its corresponding threshold of concern, the Panel decided not to carry out a formal safety assessment using the Procedure. In these cases the Panel requires more precise data on use and use levels.

According to the default MSDI approach, the flavouring substance in this group has an intake in Europe of 0.012 microgram/capita/day, which is below the threshold of concern for structural class III substances of 90 microgram/person/day.

No data on genotoxicity \((in \text{ vitro} \text{ or } in \text{ vivo})\) were available for the candidate substance or sufficiently structurally related substances.

No studies on absorption, distribution, metabolism and excretion were available for the candidate substance or sufficiently structurally related substances. Accordingly, it cannot be concluded that the candidate substance is metabolised to innocuous products.

No toxicity data were available for the candidate substance or sufficiently structurally related substances.

No No Observed Adverse Effect Level (NOAEL) exist for the candidate substance or for structurally related substances which can provide an adequate margin of safety under conditions of intended use. Therefore, additional data are required.

When the estimated intake was based on the mTAMDI approach the intake was estimated to be 400 microgram/person/day for the candidate substance. This is above the threshold of concern of 90 microgram/person/day for structural class III substances. Therefore, for this substance more reliable exposure data are required. On the basis of such additional data, this flavouring substance should be reconsidered along the steps of the Procedure. Following this procedure additional toxicological data might become necessary.

In order to determine whether the conclusion for the candidate substance, which has been evaluated using the Procedure, can be applied to the material of commerce, it is necessary to consider the available specifications.

Adequate specification including complete purity criteria and identity test for the material of commerce has been provided. However, for the candidate substance 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149], or for sufficiently structurally related substances, additional data are required.

**Key words:** Flavouring, safety, tetrahydroquinoline derivative, 1,2,3,4-tetrahydro-6-methylquinoline.
BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all others 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 2006/252/EC (EC, 2006). 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, 2000), which is broadly based on the opinion of the Scientific Committee on Food (SCF, 1999). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002 (EC, 2002b).

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

TERMS OF REFERENCE

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

ACKNOWLEDGEMENT

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food wishes to thank Jørn Gry, Henrik Frandsen, Wilfried Bursch, Vibe Beltoft, Pia Lund, Karin Nørby and Trine Klein Reffstrup for their contribution to the draft opinion.
ASSESSMENT

1. Presentation of the Substances in the Flavouring Group Evaluation 34

1.1. Description

The present Flavouring Group Evaluation, using the procedure as referred to in the Commission Regulation (EC) No 1565/2000 (EC, 2000) (The Procedure – shown in schematic form in Annex I), deals with one tetrahydroquinoline derivative, 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149], from chemical group 28, Annex I of Commission Regulation (EC) No 1565/2000 (EC, 2000). The flavouring substance under consideration, as well as its chemical Register name, FLAVIS- (FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufactures Association- (FEMA-) numbers, structure and specifications, are listed in Table 1.

No sufficiently structurally related supporting substances have been identified for the candidate substance 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149].

The candidate substance is listed in Table 1 and 2.

1.2. Stereoisomers

The candidate substance cannot exist as geometrical or optical isomers.

1.3. Natural Occurrence in Food

According to TNO, 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149] has not been reported to occur naturally in any food items (TNO, 2000).

2. Specifications

Purity criteria for the substance have been provided by the Flavouring Industry (EFFA, 2004i) (Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000), the information is adequate for the candidate substance. (see Section 1.2 and Table 1).

3. Intake Data

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

However, the Panel noted that due to year-to-year variability in production volumes, to uncertainties in the under-reporting correction factor and to uncertainties in the percentage of consumers, the reliability of intake estimates on the basis of the MSDI approach is difficult to assess.
The Panel also noted that in contrast to the generally low per capita intake figures estimated on the basis of this MSDI approach, in some cases the regular consumption of products flavoured at use levels reported by the Flavour Industry in the submissions would result in much higher intakes. In such cases, the human exposure thresholds below which exposures are not considered to present a safety concern might be exceeded.

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

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

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

3.1. Estimated Daily per Capita Intake (MSDI Approach)

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

Average per capita intake (MSDI) is estimated on the assumption that the amount added to food is consumed by 10% of the population\(^1\) (Eurostat, 1998). This is derived for candidate substances from estimates of annual volume of production provided by Industry and incorporates a correction factor of 0.6 to allow for incomplete reporting (60%) in the Industry surveys (SCF, 1999).

In the present Flavouring Group Evaluation 34 (FGE.34) the total annual production volume of the candidate substance for use as flavouring substances in Europe was reported to be 0.1 kg (EFFA, 2004m). The daily per capita intake for the substance is 0.012 microgram (Table 2).

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

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

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\(^1\) EU figure 375 millions (Eurostat, 1998). This figure relates to EU population at the time for which production data are available, and is consistent (comparable) with evaluations conducted prior to the enlargement of the EU. No production data are available for the enlarged EU.
The assumption is that a person may consume a certain amount of flavourable foods and beverages per day.

For the present evaluation of the candidate substance, information on food categories and normal and maximum use levels\(^2\),\(^3\),\(^4\) were submitted by the Flavour Industry (EFFA, 2004l; EFFA, 2007a). The candidate substance is used in flavoured food products divided into the food categories, outlined in Annex III of the Commission Regulation (EC) No 1565/2000 (EC, 2000), as shown in Table 3.1. For the present calculation of mTAMDI, the reported normal use levels were used. In the case where different use levels were reported for different food categories the highest reported normal use level was used.

<table>
<thead>
<tr>
<th>Food category</th>
<th>Description</th>
<th>Flavouring used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Dairy products, excluding products of category 2</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 2</td>
<td>Fats and oils, and fat emulsions (type water-in-oil)</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 3</td>
<td>Edible ices, including sherbet and sorbet</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 4.1</td>
<td>Processed fruits</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 4.2</td>
<td>Processed vegetables (incl. mushrooms &amp; fungi, roots &amp; tubers, pulses and legumes), and nuts &amp; seeds</td>
<td>No</td>
</tr>
<tr>
<td>Category 5</td>
<td>Confectionary</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 6</td>
<td>Cereals and cereal products, incl. flours &amp; starches from roots &amp; tubers, pulses &amp; legumes, excluding bakery</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 7</td>
<td>Bakery wares</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 8</td>
<td>Meat and meat products, including poultry and game</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 9</td>
<td>Fish and fish products, including molluscs, crustaceans and echinoderms</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 10</td>
<td>Eggs and egg products</td>
<td>No</td>
</tr>
<tr>
<td>Category 11</td>
<td>Sweeteners, including honey</td>
<td>No</td>
</tr>
<tr>
<td>Category 12</td>
<td>Salts, spices, soups, sauces, salads, protein products etc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 13</td>
<td>Foodstuffs intended for particular nutritional uses.</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 14.1</td>
<td>Non-alcoholic (&quot;soft&quot;) beverages, excl. dairy products</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 14.2</td>
<td>Alcoholic beverages, incl. alcohol-free and low-alcohol counterparts</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 15</td>
<td>Ready-to-eat savouries</td>
<td>Yes</td>
</tr>
<tr>
<td>Category 16</td>
<td>Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 1 – 15</td>
<td>Yes</td>
</tr>
</tbody>
</table>

According to the Flavour Industry the normal use level for the candidate substance is in the range of 0.1 - 2 mg/kg food, and the maximum use levels are in the range of 0.5 - 10 mg/kg (EFFA, 2002i; EFFA, 2004i).

The mTAMDI value for the candidate substance from structural class III (see Section 5) is 400 microgram/person/day.

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\(^2\) "Normal use" is defined as the average of reported usages and "maximum use" is defined as the 95th percentile of reported usages (EFFA, 2002i).

\(^3\) The normal and maximum use levels in different food categories (EC, 2000) have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004e).

\(^4\) The use levels from food category 5 “Confectionery” have been inserted as default values for food category 14.2 “Alcoholic beverages” for substances for which no data have been given for food category 14.2 (EFFA, 2007a).
For detailed information on use levels and intake estimations based on the mTAMDI approach, see Section 6 and Annex II.

4. Introduction

No studies on absorption, distribution, metabolism and excretion were available for the candidate substance. Furthermore, no sufficiently structurally related substances were available, therefore it cannot be concluded that the candidate substance is metabolised to innocuous products.

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

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

For the safety evaluation of the one candidate substance from chemical group 28 the Procedure as outlined in Annex I was applied, based on the MSDI approach. The stepwise evaluation of the substance is summarised in Table 2.

Step 1

The candidate substance is classified according to the decision tree approach by Cramer et al. (Cramer et al., 1978) into structural class III.

Step 2

Data on metabolism of the candidate substance or sufficiently structurally related substances are not available. Therefore, it cannot be concluded that the candidate substance is metabolised to innocuous products.

Step B3

The candidate substance has a European daily per capita intake from use as flavouring substance of 0.012 microgram/capita/day, which is below the threshold of concern of 90 microgram/person/day for strutural class III substances.

Step B4

No NOAEL exist for the candidate substance or for structurally related supporting substances which provide an adequate margin of safety under conditions of intended use. Therefore, additional data are required.
6. Comparison of the Intake Estimations Based on the MSDI Approach and the mTAMDI Approach

The estimated intake of the substance assigned to structural class III based on the mTAMDI is 400 microgram/person/day, which is above the threshold of concern for structural class III substances of 90 microgram/person/day. For comparison of the MSDI- and mTAMDI-values see Table 6.1.

For the candidate substance further information is required. This would include more reliable intake data and then, if required, additional toxicological data.

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>MSDI (µg/capita/day)</th>
<th>mTAMDI (µg/person/day)</th>
<th>Structural class</th>
<th>Threshold of concern (µg/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.149</td>
<td>1,2,3,4-Tetrahydro-6-methylquinoline</td>
<td>0.012</td>
<td>400</td>
<td>Class III</td>
<td>90</td>
</tr>
</tbody>
</table>

7. Considerations of Combined Intakes from Use as Flavouring Substances

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

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

However, combined intake is not relevant in this FGE, as it only concerns one candidate substance and no sufficiently structurally related substances were available.

8. Toxicity

8.1. Acute Toxicity

No data on acute toxicity are available for the candidate substance or structurally related substances.

8.2. Subacute, Subchronic, Chronic and Carcinogenicity Studies

No studies on subacute, subchronic and chronic toxicity as well as carcinogenicity are available for the candidate substance or structurally related substances.

8.3. Developmental / Reproductive Toxicity Studies

No data on developmental or reproductive toxicity are available for the candidate substance or structurally related substances.
8.4. Genotoxicity Studies

No data on genotoxicity (in vitro or in vivo) are available for the candidate substance or structurally related substances. However, this does not preclude evaluation of 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149] through the Procedure (SCF, 1999).

CONCLUSIONS

The present Flavouring Group Evaluation 34 (FGE.34), deals with one tetrahydroquinoline derivative from chemical group 28, 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149]. No geometrical or optical isomers exist for this candidate substance. The flavouring substance is classified according to the decision tree approach into structural class III. The substance has not been reported to occur naturally in any food items.

According to the default MSDI approach, the flavouring substance in this group has an intake in Europe of 0.012 microgram/capita/day, which is below the threshold of concern for structural class III substances of 90 microgram/person/day.

No data on genotoxicity (in vitro or in vivo) were available for the candidate substance or sufficiently structurally related substances.

No studies on absorption, distribution, metabolism and excretion were available for the candidate substance or sufficiently structurally related substances. Accordingly, it cannot be concluded that the candidate substance is metabolised to innocuous products.

No toxicity data were available for the candidate substance or sufficiently structurally related substances.

No NOAEL exist for the candidate substance or for structurally related substances which can provide an adequate margin of safety under conditions of intended use. Therefore, additional data are required.

When the estimated intake was based on the mTAMDI approach the intake was estimated to be 400 microgram/person/day for the candidate substance. This is above the threshold of concern of 90 microgram/person/day for structural class III substances. Therefore, for this substance more reliable exposure data are required. On the basis of such additional data, this flavouring substance should be reconsidered along the steps of the Procedure. Following this procedure additional toxicological data might become necessary.

In order to determine whether the conclusion for the candidate substance, which has been evaluated using the Procedure, can be applied to the material of commerce, it is necessary to consider the available specifications.

Adequate specification, including complete purity criteria and identity test for the material of commerce, has been provided. However, for the candidate substance 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149], or for sufficiently structurally related substances, additional data are required.
### TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 34

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>FEMA no</th>
<th>CAS no</th>
<th>Phys.form</th>
<th>Mol.formula</th>
<th>Mol.weight</th>
<th>Solubility 1)</th>
<th>Solubility in ethanol 2)</th>
<th>Boiling point, °C 3)</th>
<th>Melting point, °C</th>
<th>ID test</th>
<th>Assay minimum</th>
<th>Refrac. Index 4)</th>
<th>Spec.gravity 5)</th>
<th>Specification comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.149</td>
<td>1,2,3,4-Tetrahydro-6-methylquinoline</td>
<td><img src="image" alt="Structure" /></td>
<td>91-61-2</td>
<td>Solid</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N</td>
<td>147.22</td>
<td>Slightly soluble</td>
<td>1 ml in 1 ml</td>
<td>264</td>
<td>37</td>
<td>MS</td>
<td>95 %</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>Structural formula</th>
<th>MSDI 1) (µg/capita/day)</th>
<th>Class 2) Evaluation procedure path 3</th>
<th>Outcome on the named compound [4) or 5)]</th>
<th>Outcome on the material of commerce [6), 7), or 8)]</th>
<th>Evaluation remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.149</td>
<td>1,2,3,4-Tetrahydro-6-methylquinoline</td>
<td><img src="image" alt="Structure" /></td>
<td>0.012</td>
<td>Class III</td>
<td>B3: Intake below threshold, B4: No adequate NOAEL</td>
<td>Additional data required (6)</td>
<td>6)</td>
</tr>
</tbody>
</table>

1) EU MSDI: Amount added to food as flavor in (kg/year) x 10E9 / (0.1 x population in Europe (~ 375 x 10E6) x 0.6 x 365) = µg/capita/day.  
2) Thresholds of concern: Class I = 1800, Class II = 540, Class III = 90 µg/person/day.  
3) Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.  
4) No safety concern based on intake calculated by the MSDI approach of the named compound.  
5) Data must be available on the substance or closely related substances to perform a safety evaluation.  
6) No safety concern at estimated level of intake of the material of commerce meeting the specification of Table 1 (based on intake calculated by the MSDI approach).  
7) Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.  
8) No conclusion can be drawn due to lack of information on the purity of the material of commerce.
ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

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

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

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

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

- can the flavourings be predicted to be metabolised to innocuous products5 (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous6 (Step A4)?
- does a NOAEL exist on the flavourings or on structurally related substances (Step A5 and B4)?

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

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

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5 “Innocuous metabolic products”: Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent” (JECFA, 1997a).

6 “Endogenous substances”: Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997a).
Procedure for Safety Evaluation of Chemically Defined Flavouring Substances

Step 1.

Decision tree structural class

Step 2.

Can the substance be predicted to be metabolised to innocuous products?

Step A3.

Yes

Do the conditions of use result in an intake greater than the threshold of concern for the structural class?

No

Step A4.

Yes

Is the substance or are its metabolites endogenous?

No

Step A5.

Yes

Does a NOAEL exist for the substance which provides an adequate margin of safety under conditions of intended use, or does a NOAEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?

No

Step B3.

Yes

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

No

Step B4.

Yes

Does a NOAEL exist for the substance which provides an adequate margin of safety under conditions of intended use, or does a NOAEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?

No

Additional data required

Figure I.1 Procedure for Safety evaluation of Chemically Defined Flavouring Substances
ANNEX II: USE LEVELS / mTAMDI

II.1. Normal and Maximum Use Levels

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

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

The “normal and maximum use levels” are provided by Industry for the candidate substance in the present flavouring group (Table II.1.2).

<table>
<thead>
<tr>
<th>Food Categories</th>
<th>Normal use levels (mg/kg)</th>
<th>Maximum use levels (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>01.0</td>
<td>02.0</td>
</tr>
<tr>
<td>FL-no 14.149</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

II.2. mTAMDI Calculations

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

| Estimated amount of flavourable foods, beverages, and exceptions assumed to be consumed per person per day (SCF, 1995) |
The mTAMDI calculations are based on the normal use levels reported by Industry. The seven food categories used in the SCF TAMDI approach (SCF, 1995) correspond to the 18 food categories as outlined in Commission Regulation (EC) No 1565/2000 (EC, 2000) and reported by the Flavour Industry in the following way (see Table II.2.2):

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

The mTAMDI value (see Table II.2.3) is presented for the flavouring substance in the present Flavouring Group Evaluation, for which Industry has provided use and use levels (EFFA, 2004I). The mTAMDI value is only given for highest reported normal use.

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

<table>
<thead>
<tr>
<th>Key</th>
<th>Food category</th>
<th>Food</th>
<th>Beverages</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Dairy products, excluding products of category 02.0</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Fats and oils, and fat emulsions (type water-in-oil)</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>Edible ices, including sherbet and sorbet</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04.1</td>
<td>Processed fruit</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04.2</td>
<td>Processed vegetables (incl. mushrooms &amp; fungi, roots &amp; tubers, pulses and legumes), and nuts &amp; seeds</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>Confectionary</td>
<td>Exception a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Cereals and cereal products, incl. flakes &amp; starches from roots &amp; tubers, pulses &amp; legumes, excluding bakery</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>Bakery wares</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>Meat and meat products, including poultry and game</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>Fish and fish products, including molluscs, crustaceans and echinoderms</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Eggs and egg products</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sweeteners, including honey</td>
<td>Exception a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Salts, spices, soups, sauces, salads, protein products, etc.</td>
<td>Exception d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Foodstuffs intended for particular nutritional uses</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.1</td>
<td>Non-alcoholic (&quot;soft&quot;) beverages, excl. dairy products</td>
<td>Beverages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.2</td>
<td>Alcoholic beverages, incl. alcohol-free and low-alcoholic counterparts</td>
<td>Exception c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Ready-to-eat savouries</td>
<td>Exception b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Composite foods (e.g. casseroles, meat pies, mincemeat) - foods that could not be placed in categories 01.0 - 15.0</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mTAMDI value (see Table II.2.3) is presented for the flavouring substance in the present Flavouring Group Evaluation, for which Industry has provided use and use levels (EFFA, 2004I). The mTAMDI value is only given for highest reported normal use.

Table II.2.3 Estimated intakes based on the mTAMDI approach

<table>
<thead>
<tr>
<th>FL-no</th>
<th>EU Register name</th>
<th>mTAMDI (µg/person/day)</th>
<th>Structural class</th>
<th>Threshold of concern (µg/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.149</td>
<td>1,2,3,4-Tetrahydro-6-methylquinoline</td>
<td>400</td>
<td>Class III</td>
<td>90</td>
</tr>
</tbody>
</table>
ANNEX III: METABOLISM

No studies on absorption, distribution, metabolism and excretion were available for the candidate substance. Furthermore, no sufficiently structurally related substances were available. Therefore it cannot be concluded that the candidate substance is metabolised to innocuous products and accordingly the evaluation proceeds via the B-side of the procedure.
ANNEX IV: TOXICITY

No toxicity or genotoxicity data are available for the candidate substance 1,2,3,4-tetrahydro-6-methylquinoline [FL-no: 14.149] nor for structurally related substances.
REFERENCES:


