Flavouring Group Evaluation 49, (FGE.49): Xanthin alkaloids from the Priority list from chemical group 30

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA-Q-2003-172D)

Adopted on 22 May 2008

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 Panel is asked to evaluate two flavouring substances in the Flavouring Group Evaluation 49 (FGE.49), using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These two flavouring substances belong to chemical group 30, Annex I of the Commission Regulation (EC) No 1565/2000.

The two flavouring substances, caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032], cannot be evaluated using the Procedure as information on production volumes in order to calculate a Maximised Survey-Derived Daily Intake (MSDI) has not been submitted. Furthermore, data on normal and maximum use levels are also lacking. The Panel is also aware that further toxicological data have been published on caffeine since the review by the SCF in 2003. These will also need to be taken into account.

KEYWORDS

Flavourings, safety, caffeine, theobromine.
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BACKGROUND

Regulation (EC) No 2232/96 of the European Parliament and the Council (EC, 1996) lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the EU. In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC (EC, 1999a), as last amended by Commission Decision 2008/478/EC (EC, 2008). Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

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

After the completion of the evaluation programme the 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). By Commission Decision 1999/217/EC certain flavouring substances received priority in the evaluation programme, since concerns about the safety of the health of consumers were expressed by some Member States. In the Register, these substances received the following remark: 3. “Substance to be given priority evaluation”.


<table>
<thead>
<tr>
<th>FL-no</th>
<th>Name</th>
<th>Status in the FLAVIS database, May 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.015</td>
<td>Vinylbenzene</td>
<td>FGE.29 – Priority substance.</td>
</tr>
<tr>
<td>08.017</td>
<td>Malic acid</td>
<td>JECFA-no: 619.</td>
</tr>
<tr>
<td>08.041</td>
<td>Octadeca-9,12-dienoic acid</td>
<td>JECFA-no: 332.</td>
</tr>
<tr>
<td>13.018</td>
<td>Furfural</td>
<td>EFSA Opinion adopted 2004. ADI of 0.5 mg/kg bw. FGE.19 - EFSA evaluation of alpha,beta-unsaturated aldehydes and ketones under evaluation.</td>
</tr>
<tr>
<td>13.035</td>
<td>Menthofuran</td>
<td>FGE.57 – EFSA consideration of JECFA evaluated substances - under evaluation.</td>
</tr>
<tr>
<td>13.126</td>
<td>Furfural diethyl acetal</td>
<td>EFSA Opinion adopted 2004. ADI of 0.5 mg/kg bw. FGE.19 - EFSA evaluation of alpha,beta-unsaturated aldehydes and ketones under evaluation.</td>
</tr>
<tr>
<td>16.002</td>
<td>Diammonium sulfide</td>
<td>Not allocated any evaluation – suggested for deletion by DG SANCO.</td>
</tr>
</tbody>
</table>
Of the 43 substances in Table A, one is suggested for deletion from the Register, 12 have been evaluated in other FGEs, and 22 have been evaluated by the JECFA (20 of these JECFA evaluated substances are also considered by EFSA).

The remaining eight substances, vinylbenzene [FL-no: 01.015], quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152], quinine monohydrochloride dihydrate [FL-no: 14.155], glycyrrhizic acid [FL-no: 16.012], glycyrrhizic acid, ammoniated [FL-no: 16.060], caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] are considered in the following Flavouring Group Evaluations:

FGE.29: Aromatic hydrocarbon: vinylbenzene [FL-no: 01.015].
FGE.36: Triterpene glycosides: glycyrrhizic acid [FL-no: 16.012], glycyrrhizic acid, ammoniated [FL-no: 16.060].


**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, 2000a).

**ASSESSMENT**

1. **Presentation of the Substances in the Flavouring Group Evaluation 49**

1.1. **Description**

The present Flavouring Group Evaluation 49 (FGE.49), 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 two xanthin alkaloids, caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032], from EU chemical group 30, Annex I of Commission Regulation (EC) No 1565/2000 (EC, 2000). The two flavouring substances under consideration, as well as their chemical Register names, FLAVIS- (FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufacturers Association- (FEMA-) numbers, structure and specifications, are listed in Table 1.

1.2. **Stereoisomers**

The candidate substances cannot exist as geometrical or optical isomers.

1.3. **Natural Occurrence in Food**

The caffeine [FL-no: 16.016] contents in a series of plant foods (seed, leaf and bark) on dry food weight basis have been reported (Andersson et al., 2004). In coffee beans the caffeine content is about 1-2 %, in some cases up to 3 %; in tea leaves about 2-4 %, in some cases significantly higher levels; in guarana seeds about 2-6 %; in cola nuts about 1-3 %; in maté leaves about 0.4-2 % and yoco bark about 3 %.

In these six plant foods the theobromine [FL-no: 16.032] levels are much lower, from traces and up to 1 %. In cocoa beans theobromine is the dominating methylxanthine with lower levels of caffeine. In fermented, not roasted cocoa beans there are about 2-3 % theobromine and less than 1 % of caffeine, and in powdered fermented, roasted and de-fatted cocoa beans about 2-4 % theobromine and traces or up to 1 % caffeine (Andersson et al., 2004).

2. **Specifications**

Purity criteria for the two substances have been provided by the Flavour Industry (Table 1).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000 (EC, 2000), the information is adequate for the two candidate substances (see Section 1.3 and Table 1).
3. Intake Data

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

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

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

Considering that the MSDI model may underestimate the intake of flavouring substances by certain groups of consumers, the SCF recommended also taking into account the results of other intake assessments (SCF, 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 in most consumers because it is based on the assumption that the consumer regularly eats and drinks several food products containing the same flavouring substance at the upper use level.

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

3.1. Estimated Daily per Capita Intake (MSDI Approach)

The 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\(^2\) (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).

\(^2\) 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.
No annual production volumes and no normal and maximum use levels as flavouring substances have been reported for the two candidate substances.

### Table 3.1 Estimated intakes based on the MSDI approach and the mTAMDI approach

<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>16.016</td>
<td>Caffeine</td>
<td></td>
<td></td>
<td>Class III</td>
<td>90</td>
</tr>
<tr>
<td>16.032</td>
<td>Theobromine</td>
<td></td>
<td></td>
<td>Class III</td>
<td>90</td>
</tr>
</tbody>
</table>

#### 4. Evaluation/Regulatory Status

Caffeine [FL-no: 16.016] has previously been evaluated in relation to its presence in “energy” drinks (SCF, 1999; SCF, 2003c). An amendment to the EC labelling Directive (European Council Directive 2000/13/EC) requires that beverages, other than those based on coffee or tea, containing more than 150 mg caffeine should be labelled “high caffeine content” and the exact amount present indicated on the label (Hooks et al., 1992; EC, 2002c). Annex II provides more details on the outcome of these evaluations.

#### 5. Conclusions

Caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] cannot be evaluated using the Procedure as information on production volumes in order to calculate an MSDI has not been submitted. Furthermore, data on normal and maximum use levels are also lacking. The Panel is also aware that further toxicological data have been published on caffeine since the review by the Scientific Committee for Food (SCF) in 2003. These will also need to be taken into account.
### TABLE 1: SPECIFICATION SUMMARY OF THE SUBSTANCES IN THE FLAVOURING GROUP EVALUATION 49

<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 4)</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>16.016</td>
<td>Caffeine</td>
<td><img src="image" alt="Caffeine" /></td>
<td>2224</td>
<td>11741</td>
<td>Solid</td>
<td>C₈H₁₀N₄O₂</td>
<td>194.19</td>
<td>Soluble</td>
<td>Soluble</td>
<td>235-238 IR 98 %</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>16.032</td>
<td>Theobromine</td>
<td><img src="image" alt="Theobromine" /></td>
<td>3591</td>
<td>83-67-0</td>
<td>Solid</td>
<td>C₇H₈N₄O₂</td>
<td>180.17</td>
<td>Slightly soluble</td>
<td>Soluble</td>
<td>357 IR 98 %</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Sublimes at 290-295 °C.</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.
ANNEX I: PROCEDURE FOR THE SAFETY EVALUATION

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000 (EC, 2000a), named the “Procedure”, is shown in schematic form in Figure I.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 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 products3 (Step 2)?
- do their exposures exceed the threshold of concern for the structural class (Step A3 and B3)?
- are the flavourings or their metabolites endogenous4 (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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3 “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).

4 “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.
Do the conditions of use result in an intake greater than the threshold of concern for the structural class?

No

Yes

Step A4.
Is the substance or are its metabolites endogenous?

No

Yes

Step A5.
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

Yes

Step B3.
Do the conditions of use result in an intake greater than the threshold of concern for the structural class?

No

Yes

Step B4.
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

Yes

Additional data required
Figure I.1 Procedure for Safety Evaluation of Chemically Defined Flavouring Substances
ANNEX II: EVALUATION/REGULATION STATUS

Caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032]

SCF Opinion of the Scientific Committee on Food on additional information on “energy” drinks (SCF, 2003c)

The Committee was asked to review additional information submitted on energy drinks and indicate if the conclusions in its Opinion of 21 January 1999 needed to be modified.

Conclusion by the SCF:

“Based on the submission of further data and developments in EU, the Committee’s earlier Opinion on caffeine remains unchanged.”

In the SCF Opinion from 1999 it was concluded:

“For caffeine, it was concluded that the contribution of “energy” drinks to overall caffeine intake was not a matter of concern for non-pregnant adults. For children who do not normally consume much tea or coffee, and who might substitute “energy” drinks for cola or other soft drinks, consumption of “energy” drinks might represent an increase in daily caffeine exposure compared with their previous intake. The Committee considered that this could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety. For pregnant adults, the Committee concluded that while intakes of caffeine up to 300 mg/day appeared to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300 mg/day remained open. This suggested that moderation of caffeine intake, from whatever source, was advisable during pregnancy” (SCF, 2003c).


There is an amendment to the EC labelling directive (European Council Directive 2000/13/EC), which came into effect by July 2004 (Commission Directive 2002/67/EC (EC, 2002c), requiring that beverages, other than those based on coffee or tea, containing more than 150 mg caffeine/l should be labelled “high caffeine content” and the exact amount present indicated on the label (EC, 2002c).
REFERENCES:


SCIENTIFIC PANEL MEMBERS


ACKNOWLEDGEMENT

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food wishes to thank Jørn Gry, Vibe Beltoft, Pia Lund and Karin Nørby for their contribution to the draft Opinion.