

**MINUTES OF THE 30th PLENARY MEETING
OF THE SCIENTIFIC PANEL ON
FOOD ADDITIVES, FLAVOURINGS, PROCESSING AIDS
AND MATERIALS IN CONTACT WITH FOOD**

Held in Parma on 20-22 May 2008

Adopted on 9 July 2008 at the 31st Plenary meeting

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FOOD ADDITIVES, FLAVOURINGS, PROCESSING AIDS
AND MATERIALS IN CONTACT WITH FOOD (AFC)
Held in Parma on 20-22 May 2008**

PARTICIPANTS

Panel Members:

Fernando Aguilar, Herman Autrup, Susan Barlow (Chair), Riccardo Crebelli, Karl-Heinz Engel (Vice Chair), Nathalie Gontard, David Gott (2nd and 3rd day), Sandro Grilli (1st and 2nd day), Rainer Gürtler, John Christian Larsen (Vice Chair), Jean-Charles Leblanc, Catherine Leclercq, Xavier Malcata, Wim C. Mennes, Maria Rosaria Milana, Iona Pratt (1st and 2nd day), Paul Tobback, Fidel Toldrá (1st day)

Experts: Jørn Gry (item 7 only), Karl MacDonald (item 9.2 only)

Apologies

Laurence Castle, Wolfgang Dekant, Ivonne Rietjens

EFSA

Risk Assessment Directorate: Riitta Maijala (for item 5 only)

AFC Unit: Dimitrios Spyropoulos, Alexandre Feigenbaum, Hugues Kenigswald, Kim Rygaard Nielsen, Ana-Maria Rincon, Stavroula Tasiopoulou, Anne Theobald, (scientific staff) – Maria Correia, Maud Pâques (administrative staff)

IT department: Guisado Ferrer Ernesto (for item 5 only)

1. WELCOME; APOLOGIES FOR ABSENCE

The chair welcomed the participants and the secretariat noted apologies.

2. ADOPTION OF THE AGENDA

The agenda was adopted.

3. DECLARATIONS OF INTEREST

The declarations concerning items on the agenda of this meeting are noted under the specific item on Flavourings (item 7) and Aluminium (item 9.1).

4. MATTERS ARISING FROM THE 29TH PLENARY MEETING HELD ON 1-3 APRIL 2008

4.1. Adoption of the minutes

The draft minutes were adopted. They can be seen on:

http://www.efsa.europa.eu/en/science/afc/afc_meetings/afc_30th_meeting.html

5. GENERAL INFORMATION FROM EFSA AND THE COMMISSION

The chair's note of the April Plenary of the Scientific Committee had been circulated for information.

Riitta Maijala, Director of the Risk Assessment Directorate, explained the new procedure in EFSA regarding:

- the quality control of published opinions or scientific reports. The procedure is to be implemented following the Scientific Committee's advice on the issue. It is mainly the responsibility of the Secretariat of the Panel to ensure that the procedure is correctly implemented.
- the submission and placing on the EFSA website of declarations of interest (DoI). A new IT tool has been developed giving the possibility to the experts to fill in their DoI online. Each expert will have access through a unique code to the EFSA's extranet and will update their annual DoI each time that a new interest arises and, in any event, at least once a year. Specific DoI submitted online will have to be updated at the meeting if the agenda has changed.

A short presentation of the electronic platform was given.

6. NUTRIENT SOURCES

6.1. Selenium yeasts

(EFSA-Q-2005-078, EFSA-Q-2005-119, EFSA-Q-2005-186, EFSA-Q-2006-215, EFSA-Q-2006-216, EFSA-Q-2006-217)

The rapporteur presented the draft opinion. It was discussed and changes were suggested. As clarification of some issues is still outstanding with some of the applicants, the draft opinion will be re-discussed at the next Plenary meeting.

6.2. Amino-acid chelates

(EFSA-Q-2005-035, EFSA-Q-2005-133, EFSA-Q-2005-034, EFSA-Q-2005-038, EFSA-Q-2005-166, EFSA-Q-2005-033, EFSA-Q-2005-132, EFSA-Q-2005-036, EFSA-Q-2005-130)

The rapporteur presented the draft opinion. It was discussed and a number of revisions of the text were agreed. The opinion was adopted.

The Panel concluded that the use of copper bisglycinate chelate as source for copper added for nutritional purposes to food supplements, and of calcium bisglycinate chelate and magnesium bisglycinate chelate as sources for respectively calcium and magnesium added for nutritional purposes to foods for particular nutritional uses and food supplements, and of zinc bisglycinate chelate when used as a source for zinc in foods intended for the general population (including food supplements) and foods for particular nutritional uses, is not of safety concern.

However, due to lack of information on the specific structure of the active ingredients for chromium glycinate nicotinate the Panel was unable to reach a conclusion on the safety of the source and the bioavailability of chromium from this source.

6.3. Aspartate sources

(EFSA-Q-2005-129, EFSA-Q-2006-260, EFSA-Q-2005-215, EFSA-Q-2005-101, EFSA-Q-2006-253, EFSA-Q-2006-294, EFSA-Q-2005-109, EFSA-Q-2006-282, EFSA-Q-2006-283, EFSA-Q-2006-284, EFSA-Q-2006-285, EFSA-Q-2006-305, EFSA-Q-2006-254, EFSA-Q-2005-161, EFSA-Q-2006-259)

Due to lack of time the discussion of the draft opinion was deferred to the next Plenary meeting.

7. FLAVOURINGS

J.C. Larsen declared an interest for camphor, FGE 57, 85, 86, 87 and 89 because he had participated in the evaluation of these substances by the Joint Expert Committee on Food Additives (JECFA). It was not considered as a conflict of interest and he was invited to participate in the discussions.

S. Grilli declared an interest for coumarin as he had advised an Italian distribution company regarding use of coumarin in cosmetics. It was not considered as a conflict of interest and he was invited to participate in the discussions.

7.1. Coumarin

The Draft Opinion on Coumarin was referred back to the Working Group for clarification of new available information.

7.2. Camphor

The European Food Safety Authority (EFSA) was asked to advise the Commission on the implications for human health of the presence of *d*-camphor in the diet. Dietary exposure to

camphor arises from the consumption of foods flavoured by using herbs, their essential oils or the chemically defined flavouring substance *d*-camphor.

The rapporteur presented the Draft Opinion on Camphor, where the current EU regulatory status and the background of previous scientific evaluations were given, and the exposure data and available data on toxicity were presented.

General remarks to the Draft Opinion were given. The Panel went through the document, which was discussed, and changes to the text were proposed.

The Panel concluded as follows. The available data on toxicity of camphor are limited and thus a Tolerable Daily Intake (TDI) cannot be derived. However, based on the available toxicity data and the Panel's conservative estimate of chronic exposure (15 mg/day, equivalent to 250 µg/kg body weight (bw)/day), calculated using the maximum limits for food suggested by the Council of Europe, the Panel considered that there would be no safety concern regarding chronic toxicity.

The Panel considered that safety aspects of camphor in terms of acute toxicity needed to be addressed. All reported acute toxicity data on adults and children arise mostly from accidental ingestion of camphor-containing medications. The probable lethal oral bolus dose has been reported to be in the range of 50 to 500 mg/kg bw. No acute toxicity was reported after doses lower than 2 mg/kg bw and clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher, whereas clinically manifest toxicity in sensitive persons would require doses higher than 30 mg/kg bw.

Potential acute exposure related to the consumption of large amounts of certain foods consumed on a single day in different age groups was estimated by the Panel. It was lowest in adults (from 0.14 to 0.34 mg/kg bw according to the food commodity) and highest in children under 6 (from 0.41 to 0.83 mg/kg bw according to the food commodity). The commodity leading to the highest potential acute exposure was fresh cheese in any age group.

The acute exposure estimates for children and adults are about 60–120 times and 150-360 times, respectively, lower than the probably lowest acute lethal bolus dose of 50 mg/kg bw. The acute exposure estimates for children and adults are about 2-5 times and 6-14 times, respectively, lower than the dose of 2 mg/kg bw below which no acute effects have been reported in human case studies.

Although these margins might appear to be low, the large number of cases describing the dose-response relationship suggests that the data sufficiently cover inter-individual variability in sensitivity. Therefore, the Panel concluded that it is unlikely that acute effects may occur in relation to consumption of foods providing less than 2 mg/kg bw in one large portion.

The acute exposure estimates considered by the Panel are based on observed high consumption in only one Member State and on maximum limits suggested by the Council of Europe. However, Maximum Permitted Levels for camphor are not currently set in the EU legislation and there is uncertainty on its actual upper use levels in foods and beverages currently on the market and on the high consumption of food flavoured with camphor all over Europe.

The Panel therefore suggests that maximum limits should be set to ensure that exposure to camphor does not exceed 2 mg/kg bw on a single day in any age group.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3. Flavouring Group Evaluations (FGE)

7.3.1. *FGE.29*

Substances from the Priority list from chemical groups 30 and 31.

By Commission Decision (EC) No 1999/217/EC certain flavouring substances received priority in the evaluation programme (Commission Regulation (EC) No 1565/2000), 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".

By the amendment from 2002 to the Commission Decision the list contains 43 flavouring substances with this remark. Of these 43 substances, one is suggested for deletion from the Register, 12 have been evaluated in other Flavouring Group Evaluations (FGEs), and 22 have been evaluated by the JECFA, of which 20 of these JECFA evaluated substances have been or will be considered by EFSA too.

The remaining eight substances are considered in the following FGEs:

FGE.29a: One aromatic hydrocarbon, vinylbenzene [F1-no: 01.015].

FGE.29b: Three quinine salts, quinine hydrochloride [FL-no: 14.011], quinine sulphate [FL-no: 14.152], quinine monohydrochloride dihydrate [FL-no: 14.155].

FGE.29c: Two triterpene glycosides, glycyrrhizic acid [FL-no: 16.012], glycyrrhizic acid, ammoniated [FL-no: 16.060].

FGE.29d: Two xanthine alkaloids, caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032].

7.3.2. *FGE.29a*

Substance from the Priority list: Vinylbenzene.

The rapporteur presented the Draft Opinion on Vinylbenzene (styrene) and the evaluation and regulation status were given.

Vinylbenzene [FL-no: 01.015] is currently being assessed under the EC Programme on Risk Assessment of Existing Substances (EC, 1993). A draft Risk Assessment Report (RAR) on the substance (draft dated November 2007) is currently being considered by the Scientific Committee on Health and Environmental Risks (SCHER).

General remarks to the Draft Opinion were given. The Panel noted that vinylbenzene has been assessed previous by the SCF as a food contact material (SCF, 2005) and the conclusion was that the concentration in food should be as low as possible. The evaluation of vinylbenzene as a flavouring substance is therefore postponed pending the finalisation of the final RAR on vinylbenzene.

The Panel went through the document and changes to the text were proposed. The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.3. **FGE.29b**

Three Quinine salts from the Priority list.

The rapporteur presented the Draft Opinion on Quinine salts. Evaluation and regulation status was discussed.

General remarks to the Draft Opinion were given. The Panel is aware that existing evaluations of quinine (SCF,1988; JECFA, 1993) were finalised more than 15 years ago and that more recent warnings have been issued about persons who may be particularly sensitive to the effects of quinine (BfR, 2008). The Panel therefore recommends that re-evaluation of quinine should be undertaken as a single substance.

For quinine hydrochloride [FL-no: 14.011] and quinine sulphate [FL-no: 14.152] use levels are required.

The Panel went through the document and changes to the text were proposed. The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on: http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.4. **FGE.29c**

Two Triterpene Glycosides from the Priority list.

The rapporteur presented the Draft Opinion on glycyrrhizic acid [FL-no: 16.012] and glycyrrhizic acid, ammoniated [FL-no: 16.060].

The Panel agrees with the evaluation by the SCF and emphasizes the need for further information on use levels and intake that were requested by the SCF in its opinion from 2003 (see Annex II). The mTAMDI of 210 mg/person/day exceeds by a factor of two the intake of 100 mg/person/day considered by the SCF to offer a sufficient level of protection. Therefore, refined use levels and intake data are needed.

The Panel went through the document and changed wording to the text were proposed. The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.5. **FGE.29d**

Xanthin Alkaloids from the Priority list.

The rapporteur presented the Draft Opinion on caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032]. Evaluation and regulation status was discussed. Editorial changes proposed.

Caffeine and theobromine cannot be evaluated using the Procedure as information on production volumes has not been submitted. Furthermore, data on normal and maximum use levels are also

lacking. The Panel is also aware that further toxicological data on caffeine have been published since the review by SCF in 2003. These data also need to be taken into account.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.6. **FGE.31**

One Epoxide from chemical group 32.

The rapporteur presented the Draft Opinion. Editorial changes were proposed.

The present FGE deals with one aliphatic terpene oxide, carvone-5,6-oxide [FL-no: 16.042], which is an epoxide. The epoxide ring is considered a structural alert for genotoxicity. In the absence of experimental evidence on the genotoxic potential of this candidate substance, it is not considered justified to evaluate this substance through the Procedure.

Thus, for carvone-5,6-oxide [FL-no: 16.042] the Panel concluded that there was a possible genotoxic potential, and therefore the Procedure could not be applied to this candidate substance until adequate genotoxicity data become available.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.7. **FGE.47**

Bicyclic secondary alcohols, ketones and related esters from chemical group 8.

The rapporteur presented the Draft Opinion, which was discussed. Minor changes to the text were proposed.

The four candidate substances are one bicyclic ketone [FL-no: 07.171] and three esters of bicyclic secondary alcohols [FL-no: 09.584, 09.848 and 09.888].

It is considered that on the basis of the default MSDI approach the four candidate substances would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

Information on chirality is missing for one substances [FL-no: 09.888] and for all four substances [FL-no: 07.171, 09.584, 09.848 and 09.888], identity tests are missing.

Thus, the final evaluation of the materials of commerce cannot be performed for the four substances [FL-no: 07.171, 09.584, 09.848 and 09.888], pending further information on specifications.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.8. **FGE.57**

Consideration of four substances structurally related to pulegone evaluated by JECFA (55th meeting).

The Draft Opinion was presented and issues for major consideration were raised. The documents was discussed and it was decided that a revised version of the Draft Opinion should be submitted for the next Plenary in July.

7.3.9. **FGE.85**

Consideration of miscellaneous nitrogen-containing substances evaluated by JECFA (65th meeting).

At the 29th Plenary it was agreed to make a revision of the text and consider a revised Draft Opinion at the 30th Plenary.

The revised Draft Opinion was presented and discussed. Editorial changes were proposed.

The Panel has considered 16 substances in the JECFA flavouring group of miscellaneous nitrogen-containing substances and concluded that no corresponding FGE is available.

For three substances [FL-no: 14.014, 14.029 and 14.070] the MSDI values are only based on US production figures. EU production figures are needed in order to finalise the evaluation of these substances.

Information on the stereoisomeric composition is lacking for two substances [FL-no: 13.039 and 13.115] and for one substance [FL-no: 12.193] an identity test is missing.

Thus, for six substances [FL-no: 12.193, 13.039, 13.115, 14.014, 14.029 and 14.070] the Panel has reservations (only USA production volumes available and/or missing data on specification or stereoisomerism). For the remaining 10 of the 16 evaluated miscellaneous nitrogen-containing substances [FL-no: 12.025, 12.030, 12.102, 12.107, 13.091, 13.112, 13.118, 13.154, 13.169 and 13.195] the Panel concluded that they would be of no safety concern when used at their estimated levels of intake as flavouring substances based on the MSDI approach.

The Draft Opinion was adopted and the complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.10. **FGE.86**

Consideration of aliphatic and aromatic amines and amides evaluated by JECFA (65th meeting).

The rapporteur presented the Draft Opinion and the major issues of concern to be discussed were highlighted, i.e. amide hydrolysis and amine nitrosation. A report on nitrosation is attached (Annex 1) to the minutes. The document was discussed and editorial changes were proposed.

The Panel has considered 35 substances in the JECFA flavouring group of aliphatic and aromatic amines and amides. The Panel concluded that no corresponding FGE is available.

For two substances [FL-no: 11.006 and 16.053] EU production figures are needed in order to finalise the evaluation of these substances.

For one substance [FL-no: 16.013] information on the stereoisomeric composition is lacking and for one substance [FL-no: 11.017] composition of mixture has to be specified. For one substance [FL-no: 14.064] data on solubility is needed, and for three substances [FL-no: 11.017, 14.168 and 16.094] identity tests are missing

Thus, for seven substances [FL-no: 11.006, 11.017, 14.064, 14.168, 16.013, 16.053 and 16.094] the Panel has reservations (no European production volumes available, and/or missing data on specifications and/or information on stereoisomerism/composition).

For six of the 35 evaluated substances the Panel does not agree with the JECFA application of the Procedure as additional toxicity data are required for the substances [FL-no: 11.014, 14.003, 16.091, 16.093 and 16.094] and the substance [FL-no: 16.049] cannot be evaluated through the Procedure due to concern with respect to genotoxicity/carcinogenicity.

For the remaining 23 of the 35 JECFA evaluated aliphatic and aromatic amines and amides [FL-no: 11.001, 11.002, 11.003, 11.004, 11.005, 11.007, 11.009, 11.015, 11.016, 11.018, 11.020, 11.021, 11.023, 11.025, 11.026, 14.010, 14.080, 14.133, 14.141, 14.167, 16.006, 16.052 and 16.092] the Panel concluded that they would be of no safety concern when used at their estimated levels of intake as flavouring substances based on the MSDI approach.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.11.FGE.87

Consideration of bicyclic secondary alcohols, ketones and related esters evaluated by the JECFA (65th meeting).

The rapporteur presented the Draft Opinion, which was discussed and minor changes to the text were proposed.

The Panel concluded that all the 15 substances in the JECFA flavouring group of bicyclic secondary alcohols, ketones and related esters are structurally related to the group of four bicyclic secondary alcohols, ketones and related evaluated by EFSA in the Flavouring Group Evaluation 47 (FGE.47).

The Panel agrees with the application of the Procedure as performed by the JECFA for the 15 bicyclic secondary alcohols, ketones and related esters.

For two substances [FL-no: 09.153 and 09.319] the MSDI values are only based on US production figures. EU production figures are needed in order to finalise the evaluation of these substances.

Information on stereoisomerism composition of mixture is lacking for eight substances [FL-no: 02.016, 02.038, 07.159, 09.017, 09.131, 09.153, 09.176 and 09.218].

Thus, for nine substances [FL-no: 02.016, 02.038, 07.159, 09.017, 09.131, 09.153, 09.176, 09.218, and 09.319] the Panel has reservations (no European production volumes available and/or information on the composition of mixture is lacking data are missing on stereoisomerism).

For the remaining 6 of the 15 JECFA evaluated bicyclic secondary alcohols, ketones and related esters [FL-no: 02.059, 07.153, 09.082, 09.269, 09.456 and 09.457] the Panel concluded that they would be of no safety concern when used at their estimated levels of intake as flavouring substances based on the MSDI approach.

The Draft Opinion was adopted subject to the proposed changes. The complete Opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm.

7.3.12. **FGE.89**

Consideration of phenyl-substituted aliphatic tertiary alcohols and related aldehydes and esters evaluated by JECFA (63rd and 68th meetings).

Not discussed because of lack of time. The Draft Opinion will be on the agenda at the 31st Plenary in July 2008.

7.3.13. **FGE.19**

A plan for action regarding this FGE is still ongoing.

8. FOOD CONTACT MATERIALS

8.1. Recycling of Plastics: Guidelines to assist applicants in the preparation and submission of applications - Outcome of the public consultation

The draft opinion was discussed in the light of comments received from the public consultation which was closed on 6 March. Changes were proposed to take account of these comments and, subject to these changes, the opinion was adopted.

The opinion as well as the comments received during the public consultation and the answers given to these comments were published on:

http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178717811412.htm

8.2. Natural Mineral Waters treatment with metal oxyhydroxides

The opinion was discussed and changes were agreed. The amended draft opinion was adopted by written procedure.

The opinion will be published on:

http://www.efsa.europa.eu/EFSA/ScientificPanels/AFC/efsa_locale-1178620753812_Opinions425.htm

8.3. Evaluation of substances for the 20th list of monomers and additives:

The draft opinions on the following substances were deferred to the next Plenary meeting due to lack of time.

- Ref. No. 91530, sulphosuccinic acid, alkyl (C4-C20) or cyclohexyl diesters, sodium salts and
- Ref. No. 91815, sulphosuccinic acid mono-alkyl (C10-C16) polyethyleneglycol esters, sodium salts
- Ref. No. 80510, Poly(3-nonyl-1,1-dioxo-1-thiopropene-1,3-diyl)-block-poly(x-oley1-7-hydroxy-1,5-diiminooctane-1,8-diyl), process mixture with x=1 and/ or 5, neutralised with dodecylbenzenesulfonic acid
- Ref. No. 81870, N,N''-1,3-propanediylbis(N'-octadecylurea)

9. OTHERS AREAS WITHIN THE REMIT OF THE AFC PANEL

9.1. Aluminium

S. Barlow, J.C. Larsen, J.-C. Leblanc and C. Leclercq declared that they had been present in the JECFA meeting when this substance was discussed and C. Leclercq declared she had been a drafting expert for the monograph. It was found that this was not a conflict and they were invited to participate in the discussions.

R. Gürtler declared that he in the past had prepared a statement on aluminium for his institute, but that he had not been involved in the recent statement from BfR on aluminium. It was found that this was not a conflict and he was invited to participate in the discussions.

S. Grilli declared an interest for this substance as he had advised an Italian distribution company regarding use of aluminium compounds in cosmetics. It was not considered as a conflict of interest and he was invited to participate in the discussions.

M.R. Milana declared an interest as she had provided technical advice for her institute. It was not considered as a conflict of interest and she was invited to participate in the discussions.

The draft opinion was discussed and changes were noted. Subject to these changes the opinion was adopted.

The Panel noted that several compounds containing aluminium have the potential to produce neurotoxicity (mice, rats) and to affect the male reproductive system (dogs). In addition, after maternal exposure they have shown embryotoxicity (mice) and have affected the developing nervous system in the offspring (mice, rats). The Panel also noted that there are very few specific toxicological data for food additives containing aluminium. Thus the Panel considered it prudent to take the above-mentioned effects into account when setting a tolerable intake for all dietary sources. The available studies have a number of limitations and do not allow any dose-response relationships to be established. The Panel therefore based its evaluation on the combined evidence from several studies in mice, rats and dogs that used dietary administration of aluminium compounds.

Using the lower end of the lowest-observed-adverse-effect levels (LOAELs) of 50 mg aluminium/kg bw per day for neurodevelopmental toxicity in mice and applying the default uncertainty factor of 100 to allow for inter- and intra species variations and an additional factor of 3 for using a LOAEL instead of a no-observed-adverse-effect level (NOAEL), the Panel derived a tolerable daily intake (TDI) of 0.17 mg aluminium/kg bw. The Panel noted that in the case of the study providing this LOAEL, another study performed by the same group of researchers with administration of aluminium lactate from conception throughout the whole lifespan, a dose level of 100 mg/kg bw/day in the same strain of mice showed no clear signs of neurotoxicity. The Panel concluded therefore that the additional factor of 3 used for using a LOAEL instead of a NOAEL was sufficiently large.

Using the lowest NOAEL of 10 mg aluminium/kg bw per day for neurodevelopmental toxicity in mice and applying the default uncertainty factor of 100 to allow for inter- and intra species variations, the Panel calculated a tolerable daily intake (TDI) of 0.10 mg aluminium/kg bw.

The Panel noted several deficiencies and uncertainties in the overall database. The available data do not permit a direct comparison of the half-lives for aluminium in the blood of humans and rodents, but the Panel considered that the default uncertainty factor for inter-species differences in toxicokinetics would not adequately cover potential differences between humans and animals, the half-life being longer in humans than in mice. On the other hand, the bioavailability of aluminium from aluminium lactate or aluminium chloride, used in the pivotal studies, is considered to be generally higher than the bioavailability of aluminium from the aluminium compounds used as food additives and the forms in which aluminium occurs naturally in food. Overall, The Panel considered that an additional uncertainty factor was not needed for uncertainties in the database. In view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a tolerable daily intake (TDI). When the LOAEL approach is used this would result in a TWI of 1.2 mg/kg bw per week, whereas the use of the NOAEL approach would result in a TWI of 0.7 mg/kg bw. However, given the lack of clear dose-response relationships from the available studies and the consequent uncertainties in defining reliable NOAELs and LOAELs for the toxicity of aluminium, the Panel concluded that a value of 1 mg aluminium/kg bw per week, representing an average value between the TWIs provided by the LOAEL and NOAEL approaches, should be established as the TWI.

The estimated mean daily dietary exposure of adults to aluminium in several European countries was estimated to be between 1.6 and 13 mg aluminium per day, corresponding to an exposure of approximately 0.2 to 1.5 mg/kg bw per week from water and food. In children and young people the estimated exposure at the 97.5th percentile in the UK and France ranged from 0.7 to 2.3 mg aluminium/kg bw per week.

The TWI of 1 mg/kg bw is therefore likely to be exceeded in a significant part of the European population. Cereals and cereal products, vegetables, beverages and certain infant formulae appear to be the main contributors to the dietary aluminium exposure.

Aluminium in drinking water represents another, minor, source of exposure. Additional exposures may arise from the use of aluminium compounds in pharmaceuticals and consumer products.

The Panel also noted that due to the design of the human dietary studies and the analytical methods used, which only determine the total aluminium content in food, and not the individual aluminium compounds or species present, it was not possible to conclude on the specific sources contributing to the aluminium content of a particular food, such as the amount inherently present, the contributions from use of food additives, and the amounts released to the food during processing and storage from aluminium-containing foils, containers, or utensils. Thus a detailed breakdown by exposure source was not possible.

9.2. Food enzymes

The draft guidelines were discussed and many changes were noted. The document has to be redrafted and come back for discussion by the new Panel on food contact materials, enzymes, flavourings and processing aids (CEF).

10. ANY OTHER BUSINESS

10.1. Bisphenol A

The US NTP (National Toxicology Program) draft brief and the draft Risk Assessment report as well as the Risk Management Scope document from Canada on bisphenol A were published in April. Some concern is expressed there especially for effects on fetuses and neonates. Because of this, the Canadian Authorities, taking a precautionary approach, have proposed a ban on polycarbonate feeding bottles for babies.

Following these reports and the proposed measures from Canada the Commission has sent a new mandate to EFSA to assess any possible age-dependent toxicokinetics of bisphenol A in animals and humans and their implication for the risk assessment of the substance.

The mandate is published on the EFSA website on:

http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178710299186.htm

The members were informed that EFSA's scientific staff, with the assistance of other experts, has already started reviewing all the relevant scientific studies. The Panel wished to have the draft statement presented for discussion at the next Panel meeting in July.

11. ANNEX 1 TO THE MINUTES OF THE 30TH MEETING OF THE AFC PANEL

7.3.10. FGE.86

Consideration of potential nitrosation of flavouring substances that are nitrosable secondary amines, tertiary amines, amides, or other nitrogen compounds

In connection with its evaluation of Flavouring group 84 (FGE.84) at its 29th Meeting and of Flavouring group 86 (FGE.86) at this meeting the Panel performed an assessment of the potential formation of nitrosamines from reaction of salivary nitrite with ingested flavourings compounds that are secondary amines. This issue required special attention because several nitrosamines are known to be genotoxic and carcinogenic in laboratory animals. The assessment was based on the assumption that the nitrosation of these compounds follow the same reaction kinetics as have been described for formation of dimethylnitrosamine (DMNA) (Mirvish 1975).

$$R \text{ (mol/L/sec)} = k_2[\text{amine}] [\text{nitrite}]^2$$

In this formula R represents the formation rate of the nitrosamine, k_2 is a reaction constant and [amine] and [nitrite] are the intragastric concentrations of the respective secondary amine and nitrite.

The rate constants for the various secondary amines are not known, but these can be estimated from the rate constant of DMA if the pK_A for the amine under consideration is known. For DMA the rate constant k_2 has been found to be $0.0017 \text{ (M}^{-2} \text{ sec}^{-1}\text{)}$ for the optimum pH of 3.4 and the pK_A for DMA is 10.7. For other secondary amines k_2 values for nitrosation can then be calculated relative to the rate constant for nitrosation of DMA as follows:

If the pK_A for the amine is e.g. xx, the k_2 would be $0.0017 \times 10^{10.7-xx}$. Thus for a pK_A of 8.7 a rate constant (k_2) of $0.17 \text{ M}^{-2} \text{ sec}^{-1}$ can be calculated.

In humans, endogenously produced nitrite is constantly being excreted in the saliva. In 2 hours 62.5 to 125 ml saliva is being swallowed (daily saliva flow: 750 to 1500 ml). From a background concentration of 0.09 mM nitrite in saliva (Wagner et al. 1983) a nitrite production in 2 hours of 0.0056 to 0.0112 mmoles have been calculated (RIVM 2005).

For the present assessment, the Panel assumed that in 2 hours 0.0112 mmoles of nitrite would end up in a total of 0.3 L stomach juice (together with the ingested secondary amine) providing a nitrite concentration of $3.7 \times 10^{-5} \text{ M (mol/L)}$. The Panel further assumed that the whole MSDI of X $\mu\text{g/person per day}$ of the amine under evaluation would be ingested within the same two hours and end up in the same 0.3 L of gastric use, providing a concentration of: $Y = 3.3 * X * 10^{-6} / (\text{molecular weight of the amine}) \text{ M (mol/L)}$.

Following these considerations, the potential daily formation of a nitrosamine from the secondary amine can be estimated from the reaction rate equation:

$$R = k_2[\text{amine}] [\text{nitrite}]^2 = k_2[Y] [3.3 \times 10^{-5}]^2 = k_2 * Y * 10 \times 10^{-10} \text{ (mol/L/sec)}$$

During the reaction time of 2 hours $7200 * k_2 * Y * 10 \times 10^{-10} * 0.3 = k_2 * Y * 2.16 \times 10^{-6}$ moles of the nitrosated product will be formed, providing a daily dose of:

$$Z = (k_2 * Y * 2.16 \times 10^{-6}) * (\text{Molecular weight of the N-NO compound formed}) / 60 \text{ g/kg bw per day}$$

or

$$k_2 * Y * 3.6 \times 10^{-14} * (\text{Molecular weight of the N-NO compound formed}) \mu\text{g/kg bw per day.}$$

A margin of exposure (MOE) can be calculated by assuming that the nitrosamine formed has a carcinogenic potency equal to that of dimethylnitrosamine (DMNA), for which a BMDL_{10}^1 of 62

¹ Lower 95% confidence limit of the dose that would result in a 10% increase in tumour incidence in the animals in the bioassay.

µg/kg body weight per day has been calculated for liver carcinogenesis in male rats (O'Brien et al., 2006):

$$\text{MOE} = 1.7 \times 10^{15} / (\text{Molecular weight of the N-NO compound formed}) * k_2 * Y.$$

The Panel examined the potential nitrosamine formation and associated cancer risk from daily ingestion of 100 µg/person of dimethylamine (DMA; not used as flavouring substance) and pyrrolidine (PYR; from FGE.86), both representing secondary amines with high pK_A values and relatively low molecular weights, and of methyl-N-methylantranilate (MMA; from FGE.84) representing a secondary amine with a low pK_A and a relatively high molecular weight.

Dimethylamine

DMA has a k₂ of 0.0017 (M⁻² sec⁻¹), a pK_A of 10.7, and a molecular weight of 45 D. Dimethylnitrosamine (DMNA) has a molecular weight of 74 D.

Using the equations outlined above the reaction rate for nitrosamine formation from 100 µg DMA in 0.3 L of stomach juice would be 1.25x10⁻¹⁸ mol/L/sec.

The calculated exposure to the corresponding nitrosamine (DMNA) would then be 3.34x10⁻¹⁵ µg/kg bw per day and the corresponding MOE can be calculated to be 1.9x10¹⁵.

Pyrrolidine

The k₂ for nitrosation of PYR, which has a pK_A of 11.3, can be calculated to be 0.0017 x 10^{10.7-11.3} i.e. 0.000538 M⁻² sec⁻¹. PYR has a molecular weight of 71 D and N-nitroso-pyrrolidine (NPYR) has a molecular weight of 100 D.

Using the equations outlined above, the reaction rate for nitrosamine formation from 100 µg PYR in 0.3 L of stomach juice would be 2.5x10⁻¹⁹ mol/L/sec.

The calculated exposure to the corresponding nitrosamine (NPYR) would then be 9.0x10⁻¹⁵ µg/kg bw per day and the corresponding MOE (relative to NDMA) can be calculated to be 6.9x10¹⁵.

Methyl-N-methylantranilate

The k₂ for nitrosation of MMA, for which the Panel estimated a pK_A of 4.5, can be calculated to be 0.0017 x 10^{10.7-4.5} i.e. 2694,3 M⁻² sec⁻¹. MMA has a molecular weight of 165 D and N-nitroso-methyl-N-methylantranilate (NMMA) has a molecular weight of 194 D.

Using the equations outlined above, the reaction rate for nitrosamine formation from 100 µg MMA in 0.3 L of stomach juice would be 5.4x10⁻¹³ mol/L/sec.

The calculated exposure to the corresponding nitrosamine (NMMA) would then be 3.8×10^{-8} $\mu\text{g}/\text{kg}$ bw per day and the corresponding MOE (relative to DMNA) can be calculated to be 1.6×10^9 .

Evaluation

The EFSA Scientific Committee in its opinion on risk assessment of substances which are both genotoxic and carcinogenic (EFSA, 2005; Barlow et al., 2006) proposed that a margin of exposure (MOE) of 10,000 or higher, based on a BMDL10 from an animal study, would be of low concern from a public health point of view.

The Panel considered the estimated MOEs of 1.6×10^9 - 1.9×10^{15} for the NO-compounds representing the spectrum of nitrosamines that may be formed from the flavouring substances being secondary amines to be very large and representing negligible cancer risks. The exposure scenario used in calculations was 100 μg amine per person per day, which is higher than the estimated MSDI values for pyrrolidine and methyl-N-methylantranilate (0.12 and 51 μg per person per day, respectively). Even if mTAMDI values were to be used the estimated MOEs would still represent negligible cancer risks. In addition, the Panel used an estimate of the peak level of nitrite in the stomach, which would not be constantly present on a long-term, daily basis. The Panel also noted that the assumption that NPYR and NMMA have carcinogenic potency equal to that of DMNA is conservative as any carcinogenic potency of these nitrosamines would be expected to be lower than that of DMNA.

In conclusion the Panel concluded that the potential formation of nitrosamines from flavouring substances being secondary amines would represent a negligible risk at the current estimated exposures using the MSDI approach.

Although the rate of N-nitroso compound formation from several of groups of amides seems to be similar to or in some cases even higher than that from secondary amines (Mirvish 1975), the Panel concluded that their formation from flavouring compounds would also represent a negligible cancer risk at the current estimated exposures using either the MSDI or the mTAMDI approach. In addition, the Panel noted that the rate of nitrosamine formation from tertiary amines appears to be much slower than that from secondary amines (Mirvish 1975) and the formation of nitrosamines from such flavouring compounds would therefore also represent a negligible cancer risk.

References

- Barlow, S., Renwick, A.G., Kleiner, J. et al. (2006). Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International Conference organized by EFSA and WHO with support of ILSI Europe. *Food and Chemical Toxicology*, 44, 1636-1650.
- EFSA (2005). Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (Request No. EFSA Q-2004-020). Adopted on 18 October 2005. The European Food Safety Authority, Parma, Italy. Available from:
http://www.efsa.europa.eu/EFSA/Scientific_Opinion/sc_op_ej282_gentox_en3,0.pdf.
- Mirvish, S.S. (1975). Formation of N-nitroso compounds: Chemistry, Kinetics, and *in vivo* occurrence. *Toxicology and Applied Pharmacology*, 31, 325-352.
- O'Brien, J., Renwick, A.G., Constable, A. et al. (2006). Approaches to the risk assessment of genotoxic carcinogens in food: A critical appraisal. *Food and Chemical Toxicology*, 44, 1613-1635.
- RIVM (2005). Expert evaluation of hypothetical cancer risk assessment connected to supposed nitrosation of Neotame. Zeilmaker, M., Speijers, G.J., and Mennes, W. National Institute for Public Health and the Environment, Bilthoven, The Netherlands. Document submitted to the EFSA-AFC Panel.
- Wagner, D.A., Schultz, D.S, Deen, W.M., Young, V.R. and Tannenbaum, S.R. (1983). Metabolic fate of an oral dose of ¹⁵N-labeled nitrate representing a negligible risk in humans: Effect of diet supplementation with ascorbic acid. *Cancer Res.*, 43, 1921-1925.