Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-eight meeting
Geneva, 19-28 June 2007

SUMMARY AND CONCLUSIONS

issued 12 July 2007

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 19 to 28 June 2007. The purpose of the meeting was to evaluate certain food additives, flavouring agents and contaminants.

Dr John C. Larsen, National Food Institute, Technical University of Denmark, served as Chairperson and Mrs Inge Meyland, National Food Institute, Technical University of Denmark, served as Vice-Chairperson.

Dr Annika Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization, and Dr Angelika Tritscher, International Programme on Chemical Safety, World Health Organization, served as joint secretaries.

The present meeting was the sixty-eighth in a series of similar meetings. The tasks before the Committee were (a) to elaborate principles governing the evaluation of compounds on the food additives; (b) to evaluate certain food additives, including flavouring agents, and food contaminants; and (c) to review and prepare specifications for selected food additives and flavouring agents.

The report of the meeting will be published in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances, and recommendations for future work. An annex will include detailed tables (similar to the tables in this report) summarizing the main conclusions of the Committee in terms of acceptable daily intakes (ADIs) and other toxicological and safety recommendations. Information on the specifications for the identity and purity of certain food additives and flavouring agents examined by the Committee will also be included.

The participants in the meeting are listed in Annex 1. Further information required or desired is listed in Annex 2. General considerations that contain information that the Committee would like to disseminate quickly are included in Annex 3.

Toxicological monographs or monograph addenda on most of the substances that were considered will be published in WHO Food Additives Series No.59.

New and revised specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs 4.

More information on the work of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is available at:

http://www.fao.org/ag/agn/agns/jecfa_index_en.asp

http://www.who.int/ipcs/food/jecfa/en/index.html

Toxicological recommendations and information on specifications

1. Food additives and ingredients evaluated toxicologically or assessed for dietary exposure

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Acidified sodium chlorite (ASC)		The available toxicological data were sufficient to assess the safety of ASC by setting ADIs for chlorite and chlorate. Chlorite: ADI of 0.03 mg/kg bw per day Chlorate: ADI of 0.01 mg/kg bw per day. New specifications were prepared for sodium chlorite and one of the acids used in the preparation of ASC, sodium hydrogen sulfate.
Asparaginase from *Aspergillus oryzae* expressed in *Aspergillus oryzae*	N	ADI "not specified"[b] when used in the applications specified and in accordance with good manufacturing practice.
Carrageenan and Processed Eucheuma Seaweed	R R	The group ADI "not specified"[b] for the sum of carrageenan and processed eucheuma seaweed was maintained for food additive uses in foods other than infant formula. The Committee was of the view that based on the information available, it is inadvisable to use carrageenan or processed eucheuma seaweed in infant formulas.
Cyclotetraglucose and cyclotetraglucose syrup (listed on draft agenda as cyclotetraose)	N N,T	A temporary ADI "not specified"[b] was allocated for cyclotetraglucose and cyclotetraglucose syrup pending submission of data on the identity of the bacterial strain used to produce the 6-GT/IMT enzyme preparation and evidence of its lack of pathogenicity and toxigenicity. The specifications for cyclotetraglucose syrup were made tentative pending information on the total saccharide content, the unidentified fraction and test methods.
Isoamylase from *Pseudomonas amyloderamosa*	N	ADI "not specified"[b] when used in the applications specified and in accordance with good manufacturing practice.
Magnesium sulfate	R	ADI "not specified"[b]
Phospholipase A1 from *Fusarium venetatum* produced by *Aspergillus oryzae*	S	ADI 'not specified'[b] when used in the applications specified and in accordance with good manufacturing practice.
Sodium iron(III) ethylenediaminetetraacetic acid (EDTA)	S	Sodium iron EDTA is suitable for use as a source of iron for food fortification to fulfil nutritional iron requirements, provided that the total intake of iron from all food sources including contaminants does not exceed the PMTDI of 0.8 mg/kg bw. Total intake of EDTA should not exceed acceptable levels, also taking into account the intake of EDTA from the food additive use of other EDTA compounds. An ADI of 0-2.5 mg/kg bw was previously established for the calcium disodium and disodium salts of EDTA, equivalent to up to 1.9 mg/kg bw EDTA.

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Steviol glycosides	R	The temporary ADI of 0–2 mg/kg bw for steviol glycosides, expressed as steviol was extended until 2008, pending submission of the results of the ongoing studies. The Committee considered that the newly available data did not raise additional concerns regarding the safety of steviol glycosides, but that the results of ongoing clinical studies, which more closely address the requirements specified at the sixty-third meeting, would be essential to its evaluation. The specifications were revised and the tentative assignation was removed. The method of assay includes a minimum requirement of 95% of the total of 7 steviol glycosides.

[a] N: new specifications prepared; R: existing specifications revised; S: existing specifications maintained; T: tentative specifications.

[b] ADI 'not specified' is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

2. Food additives, including flavouring agents, considered for specifications only

Food Additive		Specifications[a]
Anisyl acetone		W
Furfural		W
Ethyl maltol		R
Maltol		R
Nisin preparation		R
Pectins		R
Polyvinyl alcohol		R
Sucrose esters of fatty acids		R
Zeaxanthin-rich extract from *Tagetes erecta*		W
Flavouring agents	**JECFA No.**	**Specifications[a]**
3-Acetyl-2,5,-dimethylfuran	1482	R
Ethyl maltol	1481	R
Maltol	1480	R
Maltyl isobutyrate	1506	R
3-Methyl-2-oxobutanoic acid	631	R
3-Methyl-2-oxopentaoic acid	632	R
4-Methyl-2-oxopentanoic acid	633	R
Sodium 3-Methyl-2-oxobutanoate	631.1	R
Sodium 3-Methyl-2-oxopentaoate	632.1	R
Sodium 4-Methyl-2-oxopentanoate	633.1	R
Sodium 2-oxo-3-phenylpropionate	1479	R
2,4,5-Trimethyl-delta-oxazolin	1559	R

[a]R: existing specifications revised; W: existing specifications withdrawn.

3. Food contaminants evaluated toxicologically or assessed for dietary exposure

Food Contaminant	Tolerable intakes and other toxicological recommendations
Aflatoxins (Intake assessment from pistachios, hazelnuts, almonds, Brazil nuts and dried figs, impact of various Maximum Levels, MLs)	The Committee decided to base the assessment of the impact of different MLs for aflatoxin (AFL) exposure on data provided by producing countries, noting that these better represent the materials in commerce and result in a robust estimate of AFL dietary exposure from the tree nuts. Consumption of almonds, Brazil nuts, hazelnuts, pistachios, and dried figs contributes greater than 5% of the total AFL dietary exposure in only five of the 13 GEMS/Food cluster diets (Clusters B, C, D, E and M). If fully enforced, an ML at 20 µg/kg in hazelnuts, almonds, pistachios, Brazil nuts, and dried figs would only have an impact on the relative contribution to AFL dietary exposure in these clusters, including high-level consumers of tree nuts. This contribution is due solely to the elevated AFL level in pistachios. For tree nuts other than pistachios, the presence of an ML has no effect on AFL dietary exposure. Moreover, the Committee concluded that enforcing an ML of 15, 10, 8, or 4 µg/kg, would have little further impact on the overall dietary exposure to AFT in all five of the highest exposed population groups compared to setting an ML of 20 µg/kg. Regarding dried figs, the Committee concluded that whatever the hypothetical ML scenario applied (no ML, 4, 8, 10, 15, or 20 µg/kg) there would be no impact on the overall dietary exposure to AFL. The Committee noted that the reduction of AFL dietary exposure is an important public health goal; particularly in populations who consume high levels of any potentially AFL contaminated food.
Ochratoxin A (OTA)	The previous PTWI of 100 ng/kg bw was retained. The new data, including data on mode of action of OTA in the kidney, do not indicate any reason to modify the previous risk assessment approach taken by JECFA. The current estimate of overall dietary exposure to ochratoxin A from cereals, based mainly on European data, is about 8–17 ng/kg bw per week, based on processed cereals, compared with 25 ng/kg bw per week in the previous evaluation, based on raw cereals. The current estimates are well below the PTWI. Contamination levels in the majority of raw cereal samples were below 5 µg/kg. Due to the very small number of samples contaminated above the highest proposed limit of 20 µg/kg, such an ML would have very limited impact compared with no ML. The Committee concluded that the use of an ML of 5 or 20 µg/kg would be unlikely to have an impact on dietary exposure to ochratoxin A. The Committee was unable to reach a conclusion regarding the situation in developing countries, due to the lack of adequate data to consider.

4. Flavouring agents evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

See also General considerations on the safety evaluation of flavouring agents in Annex 3.

A. Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Ethyl-2-methyl-3,4-pentadienoate	353	S	No safety concern
Methyl 4-pentenoate	1616	N	No safety concern
2-Methylbut-2-en-1-ol	1617	N	No safety concern
Ethyl 4-pentenoate	1618	N	No safety concern
4-Pentenal	1619	N	No safety concern
3-Isopropenylpentanedioic acid	1620	N	No safety concern
trans-3-Hexenol	1621	N	No safety concern
trans-4-Hexenal	1622	N	No safety concern
5-Hexenol	1623	N	No safety concern
Methyl (Z)-3-hexenoate	1624	N	No safety concern
cis-4-Octenol	1625	N	No safety concern
Ethyl (Z)-3-hexenoate	1626	N	No safety concern
3-Octenoic acid	1627	N	No safety concern
(Z)-3-Octenyl propionate	1628	N	No safety concern
trans-4-Octenoic acid	1629	N	No safety concern
Methyl (Z)-5-octenoate	1630	N	No safety concern
cis-5-Octenoic acid	1631	N	No safety concern
Ethyl 3-octenoate	1632	N	No safety concern
cis-4-Decenol	1633	N	No safety concern
Isobutyl 10-undecenoate	1634	N	No safety concern
11-Dodecenoic acid	1635	N	No safety concern
(Z)-4-Dodecenal	1636	N	No safety concern
cis-9-Octadecenol	1637	N	No safety concern
cis-9-Octadecenyl acetate	1638	N	No safety concern
Methyl 10-undecenoate	1639	N	No safety concern
(Z)-8-Tetradecenal	1640	N	No safety concern
9-Octadecenal	1641	N	No safety concern
(E)-4-Nonenal	1642	N	No safety concern

[a]N: new specifications prepared; S: Specifications maintained.

B. Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
2,3,4-Trimethyl-3-pentanol	1643	N	No safety concern
(+/-)-2,4,8-Trimethyl-7-nonen-2-ol	1644	N	No safety concern
(E)- and (Z)-2,4,8-Trimethyl-3,7-nonadien-2-ol	1645	N	No safety concern
Nerolidol	1646	N	No safety concern
1-Phenyl-3-methyl-3-pentanol	1649	N	No safety concern
p-alpha,alpha-Trimethylbenzyl alcohol	1650	N	No safety concern
(+/-)-Ethyl 2-hydroxy-2-methylbutyrate	1651	N	No safety concern
(+/-)-Ethyl 2-hydroxy-3-methylvalerate	1652	N	No safety concern
alpha,alpha-Dimethylphenethyl alcohol	1653	N	No safety concern
alpha,alpha-Dimethylphenethyl formate	1654	N	No safety concern
alpha,alpha-Dimethylphenethyl acetate	1655	N	No safety concern
alpha,alpha-Dimethylphenethyl butyrate	1656	N	No safety concern
alpha,alpha-Dimethylbenzyl isobutyrate	1657	N	No safety concern
Structural Class II			
6-Acetoxydihydrotheaspirane	1647	N	No safety concern
6-Hydroxydihydrotheaspirane	1648	N	No safety concern

[a]N: new specifications prepared.

C. Simple aliphatic and aromatic sulfides and thiols

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Simple sulfides			
Structural Class I			
2-Methyl-1-methylthio-2-butene	1683	N	No safety concern
2,4,6-Trithiaheptane	1684	N	No safety concern
2,5-Dithiahexane	1707	N	No safety concern
Acyclic sulfides with oxidized and thiol side-chains			
Structural Class I			
Methionyl butyrate	1668	N	No safety concern
Methylthiomethylmercaptan	1675	N	No safety concern
(+/-)-Isobutyl 3-methylthiobutyrate	1677	N	No safety concern
3-(Methylthio)-2-butanone	1688	N	No safety concern
4-(Methylthio)-2-pentanone	1689	N	No safety concern
Methyl 3-(methylthio)butanoate	1690	N	No safety concern
Methyl (methylthio)acetate	1691	N	No safety concern
(+/-)-3-(Methylthio)heptanal	1692	N	No safety concern
(+/-)-3-(Ethylthio)butanol	1703	N	No safety concern
S-Allyl-L-cysteine	1710	N	No safety concern
Heterocyclic sulfides – Structural Class I			
(+/-)-2,8-Epithio-*cis*-*p*-menthane	1685	N	No safety concern
Simple thiols			
Structural Class I			
Ethanethiol	1659	N	No safety concern
1-Pentanethiol	1662	N	No safety concern
Heptane-1-thiol	1663	N	No safety concern
2-Heptanethiol	1664	N	No safety concern
Structural Class II			
(+/-)-1-Phenylethylmercaptan	1665	N	No safety concern
Thiols with oxidized side-chains			
Structural Class I			
Propyl 2-mercaptopropionate	1667	N	No safety concern
(+/-)-4-Mercapto-4-methyl-2-pentanol	1669	N	No safety concern
4-Mercapto-2-pentanone	1670	N	No safety concern
(S)-1-Methoxy-3-heptanethiol	1671	N	No safety concern
Methyl 3-mercaptobutanoate	1674	N	No safety concern
Hexyl 3-mercaptobutanoate	1704	N	No safety concern
(+/-)-3-Mercapto-1-butyl acetate	1705	N	No safety concern
3-Mercapto-3-methyl-1-butyl acetate	1706	N	No safety concern
3-Mercaptoheptyl acetate	1708	N	No safety concern
Structural Class II			
cis- and *trans*-Mercapto-*p*-menthan-3-one	1673	N	No safety concern
Structural Class III			
2-Mercaptoanisole	1666	N	No safety concern
Diisopentyl thiomalate	1672	N	No safety concern
Dithiols – Structural Class I			
Ethane-1,1-dithiol	1660	N	No safety concern
Dimercaptomethane	1661	N	No safety concern
bis(1-Mercaptopropyl)sulfide	1709	N	No safety concern
Simple disulfides			
Structural Class I			
Ethyl methyl disulfide	1693	N	No safety concern
Ethyl propyl disulfide	1694	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Methyl isopentyl disulfide	1696	N	No safety concern
Amyl methyl disulfide	1697	N	No safety concern
Butyl ethyl disulfide	1698	N	No safety concern
Diethyl disulfide	1699	N	No safety concern
Structural Class II			
Allyl propyl disulfide	1700	N	No safety concern
Trisulfides – Structural Class I			
Ethyl propyl trisulfide	1695	N	No safety concern
Diethyl trisulfide	1701	N	No safety concern
Heterocyclic disulfides – Structural Class II			
(+/-)-3,5-Diethyl-1,2,4-trithiolane	1686	N	No safety concern
Mixture of 3,6-diethyl-1,2,4,5-tetrathiane (approx. 55%) and 3,5-diethyl-1,2,4-trithiolane (approx. 45%)	1687	N	No safety concern
Thioesters and acids			
Structural Class I			
Thioacetic acid	1676	N	No safety concern
(S)-Methyl propanethioate	1678	N	No safety concern
(S)-Isopropyl 3-methylbut-2-enethioate	1679	N	No safety concern
Structural Class II			
Allyl thiohexanoate	1681	N	No safety concern
Structural Class III			
(S)-Ethyl 2-acetylaminoethanethioate	1680	N	No safety concern
Propyl propane thiosulfonate	1702	N	No safety concern

[a]N: new specifications prepared.

D. Aliphatic acyclic diols, triols, and related substances

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Structural Class I			
Dihydroxyacetone dimer	1716	N	No safety concern
1-Hydroxy-2-butanone	1717	N	No safety concern
Ethyl 3-acetoxy-2-methylbutyrate	1718	N	No safety concern
Methyl 5-acetoxyhexanoate	1719	N	No safety concern
Structural Class III			
2,4-Dimethyl-1,3-dioxolane	1711	N	No safety concern
2-Hexyl-4,5-dimethyl-1,3-dioxolane	1712	N	No safety concern
cis- and *trans*-Ethyl 2,4-dimethyl-1,3-dioxolane-2-acetate	1715	N	No safety concern

[a]N: new specifications prepared.

Five substances in this group (listed as Nos. 1720, 1721 and 1723–1725 in the Call for data; they are various fatty acid esters of glycerol and propylene glycol) had been previously evaluated by the Committee as emulsifying agents. These substances have food additive specifications and have been allocated ADIs. Although the use of these substances as flavouring agents would not be anticipated to cause a safety concern, the Committee questioned whether these substances have flavouring properties and did not evaluate them according to the Procedure for the Safety Evaluation of Flavouring Agents. In addition, the Committee questioned the flavouring function of lactylated fatty acid esters of glycerol and propylene glycol (listed as No. 1722), for which an ADI and specifications are not available, and decided not to evaluate this substance as a flavouring agent using the Procedure.

E. Aliphatic acetals

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
(+/-) 1-Acetoxy-1-ethoxyethane	1726	N	No safety concern
Acetaldehyde hexyl isoamyl acetal	1727	N	No safety concern
1,1-Dimethoxy-trans-2-hexene	1728	N	No safety concern
Acetaldehyde diisoamyl acetal	1729	N	No safety concern
Isovaleraldehyde diethyl acetal	1730	N	No safety concern
Valeraldehyde dibutyl acetal	1731	N	No safety concern
Hexanal hexyl isoamyl acetal	1735	N	No safety concern
Hexanal dihexyl acetal	1738	N	No safety concern
Nonanal dimethyl acetal	1742	N	No safety concern
Dodecanal dimethyl acetal	1746	N	No safety concern
Acetaldehyde di-*cis*-3-hexenyl acetal	1747	N	No safety concern
Structural Class III			
Isovaleraldehyde propyleneglycol acetal	1732	N	No safety concern
Isovaleraldehyde glyceryl acetal	1733	N	No safety concern
Valeraldehyde propyleneglycol acetal	1734	N	No safety concern
Hexanal octane-1,3-diol acetal	1736	N	No safety concern
Hexanal butane-2,3-diol acetal	1737	N	No safety concern
Heptanal propyleneglycol acetal	1739	N	No safety concern
2,6-Dimethyl-5-heptenal propyleneglycol acetal	1740	N	No safety concern
Octanal propyleneglycol acetal	1741	N	No safety concern
Nonanal propyleneglycol acetal	1743	N	No safety concern
Decanal propyleneglycol acetal	1744	N	No safety concern
Undecanal propyleneglycol acetal	1745	N	No safety concern
Isobutanal propyleneglycol acetal	1748	N	No safety concern
Acetaldehyde 1,3-octanediol acetal	1749	N	No safety concern

[a]N: new specifications prepared

F. Sulfur-containing heterocyclic compounds

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class II			
1-(3-Hydroxy-5-methyl-2-thienyl)ethanone	1750	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl formate	1751	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl propionate	1752	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl butanoate	1753	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl isobutyrate	1754	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl hexanoate	1755	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl octanoate	1756	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl decanoate	1757	N	No safety concern
2,5-Dimethylthiazole	1758	N	No safety concern
5-Acetyl-2,3-dihydro-1,4-thiazine	1766	N	No safety concern
Structural Class III			
2-Acetyl-2-thiazoline	1759	N	No safety concern
2-Propionyl-2-thiazoline	1760	N	No safety concern
cis- and *trans*-5-Ethyl-4-methyl-2-(2-methylpropyl)thiazoline	1761	N	No safety concern
cis- and *trans*-5-Ethyl-4-methyl-2-(1-methylpropyl)thiazoline	1762	N	No safety concern
Pyrrolidino-[1,2e]-4H-2,4-dimethyl-1,3,5-dithiazine	1763	N	No safety concern
2-Hexylthiophene	1764	N	No safety concern
3-(Methylthio)-methylthiophene	1765	N	No safety concern

[a]N: new specifications prepared

G. Aliphatic and aromatic amines and amides

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
4-Aminobutyric acid	1771	N	No safety concern
N-Gluconyl ethanolamine	1772	N	No safety concern
N-Gluconyl ethanolamine phosphate	1773	N	No safety concern
N-Lactoyl ethanolamine	1774	N	No safety concern
N-Lactoyl ethanolamine phosphate	1775	N	No safety concern
Structural Class III			
N-(Heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide	1767	N	No safety concern
N1-(2,4-Dimethoxybenzyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide	1768	N	No safety concern
N1-(2-Methoxy-4-methylbenzyl)-N2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide	1769	N	No safety concern
N1-(2-Methoxy-4-methylbenzyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide	1770	N	No safety concern
N-[(Ethoxycarbonyl)methyl)-p-menthane-3-carboxamide	1776	N	No safety concern
N-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dimethoxycinnamic acid amide	1777	N	No safety concern
N-3,7-Dimethyl-2,6-octadienyl cyclopropylcarboxamide	1779	N	No safety concern

[a]N: new specifications prepared.

H. Aliphatic alicyclic linear α,β-unsaturated di- and trienals and related alcohols, acids and esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
2,4-Hexadienyl acetate	1780	N	No safety concern
2,4-Hexadienyl propionate	1781	N	No safety concern
2,4-Hexadienyl isobutyrate	1782	N	No safety concern
2,4-Hexadienyl butyrate	1783	N	No safety concern
2,4-Heptadien-1-ol	1784	N	No safety concern
Nona-2,4,6-trienal	1785	N	No safety concern
2,4,7-Decatrienal	1786	N	No safety concern

[a]N: new specifications prepared.

Annex 1

Sixty-Eighth meeting of the
Joint FAO/WHO Expert Committee on Food Additives (JECFA)
Geneva, 19-28 June 2007

Members

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Dr Yoko Kawamura, National Institute of Health Sciences, Tokyo, Japan (FAO Expert)

Dr Yoshiko Konishi, National Institute of Health Sciences, Tokyo, Japan (WHO Temporary Adviser)

Dr Sandy Lawrie Food Standards Agency, London, United Kingdom (FAO Expert, unable to attend)

Dr Jean-Charles LeBlanc, French Food Safety Agency (AFSSA), Maisons Alfort, France (WHO Temporary Adviser)

Dr Catherine LeClercq, National Research Institute for Food and Nutrition (INRAN), Rome, Italy (FAO Expert, unable to attend)

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Annex 2

Recommendations and further information required

Carrageenan:
The Committee noted that the previous dietary exposure estimate for carrageenan was made solely using production poundage and may be outdated. The Committee therefore recommended that a new dietary exposure evaluation, employing specific food type and use level information, be undertaken, ensuring that new uses are adequately taken into consideration.

Cyclotetraglucose and cyclotetraglucose syrup:
Data on the identity of the bacterial strain used to produce the 6-GT/IMT enzyme preparation and evidence of its lack of pathogenicity and toxigenicity.
For cyclotetraglucose syrup, information on total saccharide content, the unidentified fraction and test methods.

Steviol glucosides:
Submission of the results of the ongoing toxicological and clinical studies, in particular studies addressing pharmacological effects.

Annex 3

An edited version of this section will be published in the report of the sixty-eighth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information is disseminated quickly. This draft is subject to further technical editing.

General Considerations

1. No-observed-effect level (NOEL) and no-observed-adverse effect level (NOAEL): Use in JECFA assessments

In its safety assessment of food additives and contaminants in food, the Committee identifies no-observed-effect levels (NOELs) in establishing acceptable or tolerable intakes. The Committee has until now used the term NOEL defined as follows:*

NOEL: The greatest concentration or amount of an agent, found by study or observation, that causes no detectable, usually adverse, alteration of morphology, functional capacity, growth, development, or lifespan of the target.

The Committee noted that other national and international risk assessment bodies, including the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), differentiate between the term NOAEL, to identify that an effect was considered adverse, and NOEL, for effects not considered adverse.

In the Environmental Health Criteria document 170: Assessing the human health risks of chemicals: derivation of guidance values for health-based exposure limits (WHO, 1994), these terms are defined as follows:

No-observed-adverse-effect-level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure….

No-observed-effect-level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alteration of morphology, functional capacity, growth, development, or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Taking into account common practice in other risk assessment bodies and in order to harmonize with JMPR, the Committee decided to use the term NOAEL when the relevant effect at the next higher dose is considered adverse. If such an effect is not considered adverse, then the term NOEL will be used. This includes assessments where no effects were observed at the highest dose tested. In such cases, the highest dose tested will be taken as the NOEL (see examples of the enzymes asparaginase, isoamylase and phospholipase A1 evaluated at this meeting).

The same approach will be used by the Committee with respect to the terms lowest-observed-effect level (LOEL) and lowest-observed-adverse-effect level (LOAEL).

The Committee noted that it was not possible to implement this decision for the evaluation of flavouring agents at this meeting and that the term NOEL is used according to the previous practice.

The Committee emphasized that this decision does not entail any change in its evaluation practice. It is merely harmonizing the terminology used to differentiate between observed effects and observed adverse effects. Hence, this decision has no impact on any of the previous evaluations made by this Committee.

2. Extension of an existing ADI to substances obtained from different sources and/or by different manufacturing processes

A recurring question facing the Committee is whether an ADI allocated to an additive obtained from a specific source material and/or by a specific manufacturing process can be applied to encompass similar additives obtained by other

* Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food. WHO 1987

means or from other sources. The agenda for the present meeting included some additives where this question arose. The Committee therefore considered the possibility of elaborating principles or guidelines for evaluations in this area.

At previous meetings, the Committee has evaluated several food additives containing the same chemical entity as the functional component in relation to its food additive use but obtained from different source materials and/or different manufacturing processes. One such example is colours containing beta-carotene, which may be obtained by extraction from vegetables, algae or a genetically modified microorganism or produced by chemical synthesis.†

Depending on the substance in question and information received, the Committee has reached various conclusions in its evaluations.

A guiding principle in the safety evaluation of food additives has been that the material tested toxicologically is representative of the material of commerce. To this end, specifications have been established primarily to reflect substances that have been toxicologically tested and secondarily to cover as far as possible products commercially available in the market. When additives containing the same chemical entity or entities as the functional component are produced from different sources or by different methods of manufacture, possibly leading to substantial differences in composition, it has been found necessary to prepare more than one specifications monograph, as was the case for the above-mentioned beta-carotene-containing additives.

In order to answer the question of whether it is possible to apply an existing ADI to an additive from a new source or novel method of manufacture (the "new product"), the Committee considered that it is necessary to compare the source, method of manufacture and composition of the new product with those of the product that was tested toxicologically and for which the ADI was originally allocated (the "old product").

In addition to the source, the composition of a product is commonly related to the manufacturing process. Typical methods of manufacture are chemical synthesis, extraction from natural source materials and production by a microorganism (with or without genetic modification). All of these may result in different residues and impurities that have to be taken into account.

The content of the functional component(s) is often low in products obtained by extraction of natural source materials, whereas the content is normally high in products obtained by chemical synthesis. It is evident that a product with a low content of the functional component contains significant amounts of other substances (e.g. components resulting from the source material or from an organism used in its production).

The Committee recommended that the following stepwise procedure be adopted to determine whether a new product might be included in a previously allocated ADI:

1. Information on manufacture and composition of both the new and the old products should be collated and compared, and any major differences or significant lack of information identified.

2. Data from the first step might be used to determine whether

the new product is sufficiently similar to the old product to be included in the ADI,

it is impossible to include the new product in the ADI because of substantial compositional differences between the two products, or

it may be possible to include the new product in the ADI provided that additional information is received by the Committee.

In all cases, both the nature and amount of any new by-products/solvent residues or other contaminants need to be considered. If the content of the functional component(s) of the additive is high and any new contaminants would be present in only minute amounts, consideration of the intake of the additive and consequential intake of the minor contaminant may indicate whether the presence is of safety concern.

3. The specifications should include information on source, manufacture and composition in order to reflect materials covered by the evaluation. In particular, where indicated for toxicological reasons, criteria/limits for specific components should be included in the specifications.

† Eighteenth JECFA: *beta*-Carotene (synthetic); forty-first JECFA: Carotenes (vegetable) and Carotenes (algae); fifty-seventh JECFA: *beta*-Carotene from *Blakeslea trispora.*

3. Dietary exposure assessments of flavouring agents

Introduction

JECFA employs the maximized survey-derived intake (MSDI) method as a measure of dietary exposure for use in the Procedure for the Safety Evaluation of Flavouring Agents (the Procedure), as described in Reports of the xxx meetings. The MSDI provides an estimate of the mean exposure for consumers of a flavouring agent that can then be compared with the relevant threshold of toxicological concern (TTC) for each structural class in a decision-tree approach according to the Procedure. The MSDI is based on the reported amount of the flavouring agent disappearing into the food supply per year in specific regions, currently Europe, the United States of America and Japan , and on the assumption that 10% of the relevant population would consume the foods containing the flavouring agent. The MSDI includes a correction for the proportion of the annual production volume reported. At this meeting a correction factor of 0.8 was applied to the annual production volume reported in recent surveys in Europe (EFFA, 2005) , Japan (JFFMA, 2002) and the USA (FEMA, 2006) and the populations of consumers used in the MSDI calculations were 32 x 106 in Europe, 13 x 106 in Japan and 28 x 106 in the USA.

The Committee considered issues related to the dietary exposure of flavouring agents at its forty-fourth, forty-sixth, forty-ninth, fifty-fifth, sixty-third, sixty-fifth and sixty-seventh meetings. The estimation of dietary exposures for consumers of flavouring agents based on annual production volume data was considered to be a practical and realistic approach for the average (mean) consumer, noting it includes an assumption that 10% population are consumers of the flavouring agent. Further consideration of potential health risks for high consumers of specific flavouring agents was recommended in cases where it was anticipated that there may be high use levels in specific foods, but low predicted dietary exposures when calculated by the MSDI method. The specific concern of the Committee was that the distribution of use levels for some flavouring agents may be uneven across different food categories and within food categories, and this uneven distribution cannot be taken into account in the MSDI. At its sixty-fifth meeting, the Committee proposed that an ad-hoc Working Group be convened to consider an additional estimate of exposure to complement the MSDI based on use levels recommended by the industry.

Development of the single portion exposure technique

Having examined a published analysis of data for over 800 flavouring agents, the ad-hoc Working Group noted at the sixty-seventh meeting that dietary exposures derived using use levels in foods, determined to be generally accepted as safe (GRAS) by the Flavour Extract and Manufacturers Association (FEMA) in the USA, and the PADI (Possible Average Daily Intake) or mTAMDI (modified Theoretical Added Maximum Daily Intake) methods could be several orders of magnitude higher than the MSDI. Analysis of the safety implications showed that in the great majority of cases the differences between these estimates would not have affected the conclusions reached by the Committee on those flavouring agents using the Procedure. The Committee agreed to explore an additional new method of dietary exposure assessment (since termed the Single Portion Exposure Technique, SPET) based on the daily consumption of a single portion of food containing the flavouring agent, in recognition that the alternative methods that assume daily consumption of large portions of several food categories containing the flavouring agent (PADI, TAMDI, mTAMDI) were overly conservative.

The SPET provides a dietary exposure estimate based on use levels recommended by the industry and aims to represent the chronic dietary exposure for a regular consumer who consumes daily a specific food product containing the flavouring agent of interest. The SPET identifies the single food category containing the flavouring agent of interest that is likely to contribute the highest dietary exposure based on a 'standard portion' size. The standard portion is taken to represent the mean food consumption amount for consumers of that food category, assuming daily consumption over a long period of time. The standard portion does not reflect high food consumption amounts reported in national dietary surveys for the food category and is therefore a more realistic prediction of long term consumption patterns.

Development of criteria to identify flavouring agents of potential concern

At the sixty-seventh meeting, the Committee proposed to focus on a limited number of flavouring agents having production volume data at the lower and upper ends of the distribution. The Committee noted that although the discrepancies between different methods were greatest for low reported production volume data, there was no clear cut-off value that could be used to define a 'low-production volume data' flavouring agent. An annual production volume of less than 10 kg in each specific region was selected by the Committee as a value to identify flavouring agents that might have limited food applications and for which there might be greater uncertainty about their use and distribution across various food categories.

Data on use levels for flavouring agents

Data were received by the sixty-eighth Committee from the International Organization of Flavour Industries (IOFI) for 57 of the 168 flavouring agents evaluated at the sixty eight meeting. These flavouring agents were selected from the

eight groups for further assessment of dietary exposure based on use levels recommended by the industry. One of the following two criteria was used for the selection:

(a) Flavouring agents with production volume of less than 10 kg per year; or

(b) Flavouring agents with production volume that resulted in MSDI values of more than one third of the relevant TTC value. This assumes that high consumers of such flavouring agents may possibly have dietary exposures close to the TTC. The cut off was chosen because of a known ratio, derived from national dietary surveys, of mean to high percentile food consumption amounts of one to three.

Of the 57 flavouring agents selected, 44 flavouring agents had low production volumes, 5 had high production volumes and 8 had intermediate production volumes. Overall, of the flavouring agents assessed, 42 flavouring agents were in structural class I, 6 in class II and 9 in class III.

IOFI identified companies who had submitted relevant data in recent production surveys (2004-2006) and contacted them to provide data on recommended use levels for the 57 flavourings. use levels were reported in 28 food groups and 116 food subgroups across the three regions. Weighted average use levels for each food category were calculated by IOFI from the individual responses from the different companies who produced each flavouring agent. The data received were considered to be of greater relevance than the FEMA use levels for flavouring agents for the purpose of using the SPET because they identified only those food categories where the flavouring agent was reported to be added and recommended levels of use. These types of data were not previously accessible to this Committee. A comparison of the submitted use level data for flavouring agents with published FEMA use levels indicates that use levels were in most cases similar, however, as expected flavouring agents were listed in fewer food categories than in the FEMA use levels .

Comparison of dietary exposure estimates from the SPET with the MSDI and application to the Procedure

The SPET was used to estimate dietary exposure for the 57 flavouring agents. The single food categories leading more frequently to the highest potential dietary exposure for flavouring agents from a single standard portion were non–alcoholic drinks (15 cases), fine bakery wares (9 cases), soups (7 cases), processed fruit, particularly fruit jellies (5 cases), and sauces (4 cases). For the remaining 17 flavouring agents, one of various other food categories led to the highest dietary exposure from a single standard portion, for example, either snacks, milk products, processed vegetable products, confectionary, decorations, bread or meat and fish products. No other food categories were identified as the source of the highest dietary exposure from a single food category.

In general, the estimated dietary exposure using SPET was up to several orders of magnitude higher than that calculated by the MSDI for any of the three geographic regions for which production volume data were available (Europe, Japan, US), as shown in Table 1. Although the dietary exposure estimates from the SPET and MSDI were not correlated, the ratio of SPET to MSDI was strongly correlated to the MSDI when plotted on a logarithmic scale. There was a tendency for the discrepancy between the dietary exposure estimates from the SPET and MSDI to be greater for flavouring agents with low production volume. In 4 cases however, the MSDI method provided a higher dietary exposure estimate than using the SPET (one flavouring agent with a low production volume, and 3 with high production volumes).

To assess the potential for differences in outcomes using different dietary exposure assessment methods as part of the Procedure, the higher of the dietary exposure estimates from either the MSDI or SPET calculations for each flavouring agent was compared with the TTC for each structural class. The MSDI was just above the TTC in one case (class I, high production volume); the SPET estimate was approximately two fold greater than the TTC in one case and equalled the TTC in one case (the latter two had intermediate production volumes and were class I). Only the 2 flavouring agents where the SPET estimate was equal to or exceeded the TTC would have had a different route through the Procedure ie these two compounds were further evaluated through step A4 or B4, as appropriate, rather than being judged "not expected to be of safety concern at the current levels of intake" at the previous step (as they would be if using the MSDI). Moreover, the eventual decision was the same when the margin of safety between SPET and NOEL was assessed at the further step. This analysis indicated that it would not be necessary to re-evaluate flavouring agents that have already been assessed using the Procedure.

The potential for the higher dietary exposure estimates obtained with the SPET to affect the answer at step 2 ('Can the substance be predicted to be metabolized to innocuous products?') and at step B5 ('Do the conditions of use result in an intake greater than 1.5 μg/day?') were also investigated by the Working Group. It was concluded that when a higher dietary exposure was obtained with the SPET it would not significantly affect the answer at step 2 of the Procedure, whereas it may affect the answer to question B5, noting that a very limited number of flavouring agents proceeded to this step.

Conclusion

The Committee noted that the use levels submitted by IOFI were considered to be of greater relevance than the published FEMA use levels for flavouring agents for use in the SPET dietary exposure estimate because IOFI identified

only those food categories where the flavouring agent was added while maintaining confidentiality of actual levels used by individual companies.

On the basis of the analysis undertaken for this meeting, the Committee concluded that the MSDI and SPET dietary exposure estimates provide different and complementary information. The SPET takes account of food consumption patterns and use levels of flavouring agents, and is considered to provide an estimate of dietary exposure for a regular daily consumer of a specific food product containing the flavouring agent. The MSDI is considered to provide an estimate of the dietary exposure of the flavouring agent for an average consumer, and because it is based on the reported annual production volume it cannot take use patterns into account. The Committee noted that the addition of the SPET dietary exposure estimate to the relevant step in the Procedure would be likely to lead to a more extended evaluation in only a limited number of cases. The Committee noted that this analysis indicated that it would not be necessary to re-evaluate flavouring agents that have already been assessed using the Procedure.

Prior to a final decision on the addition of the SPET dietary exposure estimate to the Procedure, the Committee agreed at this meeting to repeat the assessment of a selected number of flavouring agents using both the MSDI and SPET dietary exposure estimate for evaluation at the next meeting. It was noted that the three cases where the dietary exposure estimate exceeded the TTC (derived from MSDI or SPET) were not low production volume flavouring agents, for which concern had previously been expressed by the Committee. The Committee recognized a need to consider dietary exposures for regular consumers of intermediate and high production volume flavouring agents with different use patterns. A sample representative of different levels of production volume and use patterns reported for flavouring agents will be selected for this assessment, ensuring flavouring agents from each class and group are included, the list not limited to those scheduled for evaluation at the next meeting. Another outcome of the future work will be the further development of suitable criteria for selecting flavouring agents where additional information on added use levels recommended by the industry is required for use in the SPET, prior to evaluation.

4. Consideration of combined dietary exposure estimates for flavouring agents

At the present meeting the Committee reconsidered the justification and approach taken to consider the combined dietary exposure estimates for flavouring agents that had been evaluated as members of the same group.

Considerations of combined dietary exposures were introduced when the procedure was used for the first time at the 46th meeting to evaluate esters of allyl alcohol. Allyl esters are hydrolysed to a common toxic metabolite, allyl alcohol. Combined dietary exposure assessment was based on the total per capita estimated daily intake of allyl alcohol that would arise from the simultaneous consumption of the 21 allyl esters in the group and this estimate was compared with the ADI that had been established previously for allyl alcohol. The same meeting also undertook combined dietary exposure assessments of the esters of ethyl and isoamyl alcohols by combining the MSDI estimates of the different agents leading to the same common metabolite, ethanol or isoamyl alcohol respectively, and comparing the result with the endogenous synthesis of ethanol and the ADI for isoamyl alcohol respectively. That meeting also raised the issue of combining dietary exposure estimates from across different groups where assessment of these data and the toxicological profile warranted a combined appraisal. The groups evaluated at subsequent meetings contained more diverse structures and considerations of combined dietary exposures were usually based on addition of the dietary exposure estimates for the different agents in each structural class and comparison of the combined dietary exposure estimate with the relevant threshold for the structural class.

JECFA has now evaluated almost 1800 flavouring agents. The Committee has generally considered the combined dietary exposure estimates within each group of flavouring agents. However, a number of short chain alcohols and acids are predicted to be common metabolites from a diverse range of flavouring agents evaluated in different groups at different meetings. The present meeting evaluated additional flavouring agents for groups that had been considered at previous meetings. The combination of dietary exposure estimates for different flavouring agents evaluated at different meetings highlighted the need to reconsider the rationale for the approach that has been adopted.

The present meeting discussed the likelihood that concurrent dietary exposures might occur and the rationale for simple dose addition in the combined dietary exposure assessments.

The phrase “in the unlikely event that all foods containing all flavouring agents were consumed simultaneously on a daily basis” has been used in Reports as a caveat to allow for the low probability of simultaneous dietary exposure to all the substances in a group. The dietary exposure estimate for each flavouring agent assumes that consumers represent 10% of the total population. If each substance in a group of flavouring agents were to be present in a different food item/product, the proportion of the population that would have simultaneous dietary exposure to n substances will be 0.1^n. In reality, the proportion of the population having simultaneous dietary exposure would not be as low as this, because mixtures of flavouring agents are added to the same food/product to produce the desired flavour. Nevertheless, the likelihood of the “unlikely event” will be diminishingly small for the larger groups of flavouring agents.

Dose addition would be an appropriate approach for combined dietary exposure assessments if the individual substances share common toxicokinetics and/or toxicodynamics, as was the case for the allyl esters evaluated when the procedure was first used.

Flavouring agents are metabolized by a variety of pathways including those important in intermediary metabolism, such as β-oxidation, or by enzymes involved in foreign compound metabolism, such as esterases, alcohol and aldehyde dehydrogenases, cytochrome P450, and conjugation with glucuronic acid or glutathione. Although some pathways are saturable at high substrate concentrations, for example conjugation with glutathione or sulphate, the metabolic pathways have high capacities and would not be saturated by combined exposures to flavouring agents. In consequence, as has been stated in the various Reports, saturation of metabolism would not arise from combined dietary exposures to substances sharing the same metabolic pathway. Many groups of flavouring agents include a range of different chemical structures and molecules with multiple sites of metabolism, so that combining all substances in a group as representing the mass of potential substrates for a single metabolic pathway is not logical.

A common adverse effect could arise from simultaneous exposure to flavouring agents, due to their having the same, but unknown, site and mode of action at high doses. Flavouring agents with diverse structures would be unlikely to show common adverse effects. Dose addition would be logical for flavouring agents that produce the same common metabolite, providing that the metabolite is the active toxic entity, as is the case for esters of allyl alcohol. In most cases the common metabolite is of low potential toxicity and often is endogenous, so that dose addition would not provide an indication of possible risk. Dose addition would be logical for substances that are members of a homologous series, for example when each flavouring agent in the series has the same functional group(s) and they differ only in the length of side chains. Dose addition on a weight basis would assume that all members of the series show equal potency on a weight basis, whereas dose addition on a molar basis would allow for molecular weight differences.

The Committee recommended that the assessment of combined dietary exposure for flavouring agents at future meetings should be undertaken for:

i. Flavouring agents that share a common metabolite. The dietary exposures for up to 5 substances with the highest estimated dietary exposures should be added and expressed on the basis of the common metabolite assuming complete conversion to the common metabolite (in the absence of quantitative metabolism data). The resulting combined dietary exposure estimate should be evaluated in relation to the known toxicity of the common metabolite. In the absence of toxicity data on the common metabolites, the combined dietary exposure should be evaluated in relation to the threshold for the structural class of the common metabolite.

ii. Flavouring agents that are members of an homologous series. The dietary exposures for up to 5 flavouring agents with the highest estimated dietary exposures should be added on a molar basis and evaluated in relation to the toxicity of the most potent member of those substances combined, or in the absence of such data in relation to the most potent member of the series. In the absence of toxicity data on any member of the series, the combined dietary exposure on a weight basis should be evaluated in relation to the threshold for the relevant structural class.

5. Guidelines for the safety evaluation of enzymes produced by genetically modified microorganisms

At its sixty-fifth meeting, the Committee concluded that guidelines need to be developed on the safety evaluation of enzymes produced by genetically modified microorganisms (GMMs). These guidelines should address the information considered essential for different enzyme preparations and the details considered necessary for molecular characterization of the producing microbial strain to allow adequate assessment of its safety.

At the present meeting, the Committee reviewed comments on these considerations submitted by the Enzyme Technical Association (ETA) and the Association of Manufacturers and Formulators of Enzyme Products (Amfep). The Committee also noted the ongoing international initiatives to elaborate guidelines for the safety evaluation of enzymes (including those from GMMs) and microorganisms intended for food applications. These documents are expected to be finalized in the near future. The Committee recommended that the subject of guidelines for the safety evaluation of enzymes produced by GMMs be addressed at a future meeting.