Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-ninth meeting
Rome, Italy, 17-26 June 2008

SUMMARY AND CONCLUSIONS

issued 4 July 2008

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 17 to 26 June 2008. The purpose of the meeting was to evaluate certain food additives and flavouring agents.

Mrs Inge Meyland, National Food Institute, Technical University of Denmark, served as Chairperson and Dr John C. Larsen, 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-ninth 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 (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. 60.

New and revised specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs 5.

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
Asparaginase from *Aspergillus niger* expressed in *A. niger*	N	**ADI "not specified"**[b] when used in the applications specified and in accordance with good manufacturing practice.
Ethyl lauroyl arginate	N	**ADI of 0–4 mg/kg bw for Ethyl-N$^{\alpha}$-lauroyl-L-arginate** based on a NOAEL of 442 mg/kg bw per day in two reproductive toxicity studies and a safety factor of 100. The Committee noted that some of the estimates of high exposure (greater than 95th percentile) exceeded the ADI, but recognized that these estimates were highly conservative and that actual intakes were likely to be within the ADI.
Calcium lignosulfonate (40-65) The suffix (40-65) reflects the weight-average molecular weight range (40 000–65 000) to distinguish it from other calcium lignosulfonates in commerce	N	**ADI of 0–20 mg/kg bw** based on a NOEL of 2000 mg/kg bw per day from a 90-day toxicity study and a safety factor of 100. The maximum potential dietary exposure to calcium lignosulfonate (40–65) was low and not expected to exceed 7 mg/kg bw per day from use as a carrier of fat-soluble vitamins and carotenoids in food and supplements.
Paprika extract Since the source material and the manufacturing process differ for paprika preparations used as a spice and as a food colour, the name "paprika extract" was adopted for use as a food colour, leaving the term "paprika oleoresin" for use as a spice.	N,T	The Committee did **not allocate an ADI**. Concern was expressed as to whether the material tested in the 90-day and long-term studies was representative of all commercial production of paprika extract used as food colour. The fact that the material tested contained less than 0.01% capsaicin and the fact that the Committee did not receive adequate data to establish a limit for capsaicin in the specifications for paprika extract added to this concern. New tentative specifications were prepared, pending receipt of additional information on paprika extract used as food colour, including concentrations of capsaicin (to differentiate from materials used as flavours) and additional information about the composition of batches of extract produced by a variety of manufacturers.
Phospholipase C expressed in *Pichia pastoris*	N	**ADI "not specified"**[b] when used in the applications specified and in accordance with good manufacturing practice.

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Phytosterols, phytostanols and their esters	N	**Group ADI of 0–40 mg/kg bw for phytosterols, phytostanols and their esters, expressed as the sum of phytosterols and phytostanols in their free form**, based on an overall NOAEL of 4200 mg/kg bw per day to which a safety factor of 100 was applied. The overall NOAEL was identified using the combined evidence from several studies of short-term (90 day) toxicity. The Committee considered the margin between this overall NOAEL and the lowest LOAEL from the 90 day toxicity studies of 9000 mg/kg bw per day as adequate for this overall NOAEL to be used as the basis for establishing an ADI. This conclusion is supported by the results of the available studies of reproductive toxicity, Based on available data the Committee concluded that dietary exposure to phytosterols and -stanols would typically be within the ADI.
Polydimethylsiloxane (PDMS)	R	**Temporary ADI of 0–0.8 mg/kg bw for PDMS,** based on the previous ADI and **applying an additional safety factor of 2**. The previously established ADI of 0–1.5 mg/kg bw was withdrawn. Results of studies to elucidate the mechanism and relevance of ocular toxicity observed in the submitted toxicology studies, as well as data on actual use levels in foods should be provided before the end of 2010. The temporary ADI applies to PDMS that meets the revised specifications prepared.
Steviol glycosides	R	**ADI of 0–4 mg/kg bw expressed as steviol**, based on a NOEL of 970 mg/kg bw per day from a long-term experimental study with stevioside (383 mg/kg bw per day expressed as steviol) and a safety factor of 100. The results of the new studies presented to the Committee showed no adverse effects of steviol glycosides when taken at doses of about 4 mg/kg bw per day, expressed as steviol, for up to 16 weeks by individuals with type 2 diabetes mellitus and individuals with normal or low-normal blood pressure for 4 weeks. Some estimates of high-percentile dietary exposure to steviol glycosides exceeded the ADI, particularly when assuming complete replacement of caloric sweeteners with steviol glycosides. The Committee recognized that these estimates were highly conservative and that actual intakes were likely to be within the ADI.
Sulfites Dietary exposure assessment		The main contributors to total dietary exposure to sulfites differ between countries owing to differing patterns of use of sulfites in foods and of consumption of foods to which sulfites may be added. Thus dried fruit, sausages and nonalcoholic beverages were the main contributors of sulfites in some countries, while in other countries these foods are generally produced without the use of sulfites. In countries where wine is regularly consumed, it was one of the main contributors to dietary exposure in adults. Dietary exposure in high regular consumers of wine (97.5th

		percentile) was shown to exceed the ADI for sulfites (0-0.7 mg/kg bw) based either on MLs in Codex GSFA, on MLs in national legislation or on the average concentration determined analytically (about 100 mg/l). In children and teenagers, a significant contribution to mean exposure to sulfites could come from fruit juices and soft drinks (including cordial), sausages, various forms of processed potatoes, dried fruit and nuts. Other significant contributions to dietary exposure in the adult population come from dried fruit, sausages and beer. The Committee provided recommendation on further relevant actions to be considered by countries and the Codex Alimentarius Commission (see Annex 2).

[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]
Canthaxanthin	R
Carob bean gum and carob bean gum (clarified)	R
Chlorophyllin, copper complexes sodium and potassium salts	R
Carbohydrase from *Aspergillus niger var.*	W
Estragole	W
Fast Green FCF	R
Guar gum and guar gum (clarified)	R
Iron oxides	R
Isomalt	R
Monomagnesium phosphate	N
Patent Blue V	R
Sunset Yellow FCF	R
Trisodium diphosphate	N

[a] N: New specifications prepared; R: Existing specifications revised; T: tentative specifications; W: Existing specifications withdrawn.

3. Flavouring agents

3.1. Flavourings evaluated by the Procedure for the Safety Evaluation of Flavouring Agents

3.1.1 Aliphatic, linear α,β-unsaturated aldehydes, acids and related alcohols, acetals and esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
(Z)-2-Penten-1-ol	1793	N	No safety concern
(E)-2-Decen-1-ol	1794	N	No safety concern
(Z)-Pent-2-enyl hexanoate	1795	N	No safety concern
(E)-2-Hexenyl octanoate	1796	N	No safety concern
trans-2-Hexenyl 2-methylbutyrate	1797	N	No safety concern
Hept-trans-2-en-1-yl acetate	1798	N	No safety concern
(E,Z)-Hept-2-en-1-yl isovalerate	1799	N	No safety concern
trans-2-Hexenal glyceryl acetal	1800	N	No safety concern
trans-2-Hexenal propylene glycol acetal	1801	N	No safety concern
cis- and trans-1-Methoxy-1-decene	1802	N	No safety concern
(E)-Tetradec-2-enal	1803	N	No safety concern
(E)-2-Pentenoic acid	1804	N	No safety concern
(E)-2-Octenoic acid	1805	N	No safety concern
Ethyl trans-2-butenoate	1806	N	No safety concern
Hexyl 2-butenoate	1807	N	No safety concern
Ethyl trans-2-hexenoate	1808	N	No safety concern
(E,Z)-Methyl 2-hexenoate	1809	N	No safety concern
Hexyl trans-2-hexenoate	1810	N	No safety concern
Methyl trans-2-octenoate	1811	N	No safety concern
Ethyl trans-2-octenoate	1812	N	No safety concern
(E,Z)-Methyl 2-nonenoate	1813	N	No safety concern
Ethyl trans-2-decenoate	1814	N	No safety concern

[a]N: new specifications prepared

3.1.2 Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
Ethyl (E)-2-methyl-2-pentenoate	1815	N	No safety concern
2-Methylbutyl 3-methyl-2-butenoate	1816	N	No safety concern
(+/-)(E,Z)-5-(2,2-Dimethylcyclopropyl)-3-methyl-2-pentenal	1817	N	No safety concern
(E,Z)-4-Methylpent-2-enoic acid	1818	N	No safety concern
(+/-)-4-Ethyloctanal	1819	N	No safety concern
(E)-Geranyl 2-methylbutyrate	1820	N	No safety concern
(E)-Geranyl valerate	1821	N	No safety concern
(E)-Geranyl tiglate	1822	N	No safety concern
(E)-Citronellyl 2-methylbut-2-enoate	1823	N	No safety concern
(E)-Ethyl tiglate	1824	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
(E,Z)-Geranic acid	1825	N	No safety concern
Prenyl formate	1826	N	No safety concern
Prenyl acetate	1827	N	No safety concern
Prenyl isobutyrate	1828	N	No safety concern
Prenyl caproate	1829	N	No safety concern
(+/-)-Dihydrofarnesol	1830	N	No safety concern
(E,Z)-3,7,11-Trimethyldodeca-2,6,10-trienyl acetate	1831	N	No safety concern
(E,Z)-Phytol	1832	N	No safety concern
(E,Z)-Phytyl acetate	1833	N	No safety concern
Structural class II			
Methyl 2-methyl-2-propenoate	1834	N	No safety concern

[a]N: new specifications prepared

3.1.3 Aliphatic secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
Isopropenyl acetate	1835	N	No safety concern
1-Octen-3-yl acetate	1836	N	No safety concern
1-Octen-3-yl butyrate	1837	N	No safety concern
6-Methyl-5-hepten-2-yl acetate	1838	N	No safety concern
3-(Hydroxymethyl)-2-octanone	1839	N	No safety concern
(+/-)-[R-(E)]-5-Isopropyl-8-methylnona-6,8-dien-2-one	1840	N	No safety concern
(+/-)-cis- and trans-4,8-Dimethyl-3,7-nonadien-2-ol	1841	N	No safety concern
2,4-Dimethyl-4-nonanol	1850	N	No safety concern
Structural class II			
(+/-)-1-Hepten-3-ol	1842	N	No safety concern
(E, Z)-4-Octen-3-one	1843	N	No safety concern
(E)-2-Nonen-4-one	1844	N	No safety concern
(E)-5-Nonen-2-one	1845	N	No safety concern
(Z)-3-Hexenyl 2-oxopropionate	1846	N	No safety concern
(+/-)-cis- and trans-4,8-Dimethyl-3,7-nonadien-2-yl acetate	1847	N	No safety concern
(E)-1,5-Octadien-3-one	1848	N	No safety concern
10-Undecen-2-one	1849	N	No safety concern
8-Nonen-2-one	1851	N	No safety concern

[a]N: new specifications prepared.

3.1.4 Substances structurally related to menthol

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
Menthyl valerate	1852	N	No safety concern
2-(l-Menthoxy)ethanol	1853	N	No safety concern
l-Menthyl acetoacetate	1854	N	No safety concern
l-Menthyl (R,S)-3-hydroxybutyrate	1855	N	No safety concern
8-p-Menthene-1,2-diol	1860	N	No safety concern
Structural Class II			

Flavouring agent	No.	Specificationsa	Conclusions based on current estimated intake
l-Piperitone	1856	N	No safety concern
2,6,6-Trimethylcyclohex-2-ene-1,4-dione	1857	N	No safety concern
Menthyl pyrrolidone carboxylate	1858	N	No safety concern
3,9-Dimethyl-6-(1-methylethyl)-1,4-dioxaspiro[4.5]decan-2-one	1859	N	No safety concern
d-2,8-p-Menthadien-1-ol	1861	N	No safety concern

[a]N: new specifications prepared.

3.1.5 Monocyclic and bicyclic secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural Class I			
Dehydronootkatone	1862	N	No safety concern
Isobornyl isobutyrate	1863	N	No safety concern
l-Bornyl acetate	1864	N	No safety concern
Thujyl alcohol	1865	N	No safety concern
Structural class II			
Vetiverol	1866	N	No safety concern
Vetiveryl acetate	1867	N	No safety concern
3-Pinanone	1868	N	No safety concern
Isobornyl 2-methylbutyrate	1869	N	No safety concern
Verbenone	1870	N	No safety concern

[a]N: new specifications prepared.

3.1.6 Aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
Methyl hexanoate	1871	N	No safety concern
Hexyl heptanoate	1872	N	No safety concern
Hexyl nonanoate	1873	N	No safety concern
Hexyl decanoate	1874	N	No safety concern
Heptyl heptanoate	1875	N	No safety concern
Dodecyl propionate	1876	N	No safety concern
Dodecyl butyrate	1877	N	No safety concern

[a]N: new specifications prepared.

3.1.7 Hydroxy- and alkoxy- substituted benzyl derivatives

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
4-Hydroxy-3,5-dimethoxy benzaldehyde	1878	N	No safety concern
Vanillin 3-(l-menthoxy)propane-1,2-diol acetal	1879	N	No safety concern
Sodium 4-methoxybenzoyloxyacetate	1880	N	No safety concern
Vanillin propylene glycol acetal	1882	N	No safety concern
4-Methoxybenzoyloxyacetic acid	1883	N	No safety concern
Structural class III			
Divanillin	1881	N	No safety concern

[a]N: new specifications prepared.

3.1.8 Miscellaneous nitrogen-containing substances

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Structural class II			
Methyl isothiocyanate	1884	N	No safety concern
Ethyl isothiocyanate	1885	N	No safety concern
Isobutyl isothiocyanate	1886	N	No safety concern
Isoamyl isothiocyanate	1887	N	No safety concern
Isopropyl isothiocyanate	1888	N	No safety concern
3-Butenyl isothiocyanate	1889	N	No safety concern
2-Butyl isothiocyanate	1890	N	No safety concern
4-(Methylthio)butyl isothiocyanate	1892	N	No safety concern
4-Pentenyl isothiocyanate	1893	N	No safety concern
5-Hexenyl isothiocyanate	1894	N	No safety concern
5-(Methylthio)pentyl isothiocyanate	1896	N	No safety concern
6-(Methylthio)hexyl isothiocyanate	1897	N	No safety concern
Structural class III			
Amyl isothiocyanate	1891	N	No safety concern
Hexyl isothiocyanate	1895	N	No safety concern

[a]N: new specifications prepared.

3.1.9 Furan-substituted aliphatic hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids and related esters, sulfides, disulfides and ethers

The Committee concluded that the Procedure could not be applied to this group, because of the unresolved toxicological concerns. Studies that would assist in the safety evaluation include investigations of the influence of the nature and position of ring substitution on metabolism and on covalent binding to macromolecules. Depending on the findings, additional studies might include assays related to the mutagenic and carcinogenic potential of representative members of this group.

Flavouring agent	JECFA No.	Specifications[a]
Structural Class II		
2-Methylfuran	1487	S
2,5-Dimethylfuran	1488	S
2-Ethylfuran	1489	S
2-Butylfuran	1490	S
2-Pentylfuran	1491	S
2-Heptylfuran	1492	S
2-Decylfuran	1493	S
3-Methyl-2-(3-methylbut-2-enyl)-furan	1494	S
3-(2-Furyl)acrolein	1497	S
3-(5-Methyl-2-furyl)prop-2-enal	1499	S
2-Furyl methyl ketone	1503	S
2-Acetyl-5-methylfuran	1504	S
2-Acetyl-3,5-dimethylfuran	1505	S
2-Butyrylfuran	1507	S
(2-Furyl)-2-propanone	1508	S
2-Pentanoylfuran	1509	S
1-(2-Furyl)butan-3-one	1510	S

Flavouring agent	JECFA No.	Specifications[a]
4-(2-Furyl)-3-buten-2-one	1511	S
Ethyl 3-(2-furyl)propanoate	1513	S
Isobutyl 3-(2-furan)propionate	1514	S
Isoamyl 3-(2-furan)propionate	1515	S
Isoamyl 4-(2-furan)butyrate	1516	S
Phenethyl 2-furoate	1517	S
Furfuryl methyl ether	1520	S
Ethyl furfuryl ether	1521	S
Difurfuryl ether	1522	S
2,5-Dimethyl-3-furanthiol acetate	1523	S
Furfuryl 2-methyl-3-furyl disulfide	1524	S
3-[(2-Methyl-3-furyl)thio]-2-butanone	1525	S
O-Ethyl S-(2-furylmethyl)thiocarbonate	1526	S
Structural Class III		
2,3-Dimethylbenzofuran	1495	S
2,4-Difurfurylfuran	1496	S
2-Methyl-3(2-furyl)acrolein	1498	S
3-(5-Methyl-2-furyl)-butanal	1500	S
2-Furfurylidene-butyraldehyde	1501	S
2-Phenyl-3-(2-furyl)prop-2-enal	1502	S
3-Acetyl-2,5-dimethylfuran	1506	S
Pentyl 2-furyl ketone	1512	S
Propyl 2-furanacrylate	1518	S
2,5-Dimethyl-3-oxo-(2H)-fur-4-yl butyrate	1519	S

[a]S: Specifications maintained. The specifications monographs will include a statement that the safety evaluation has not been completed.

3.1.10 Alkoxy-substituted allylbenzenes present in foods, essential oils, and used as flavouring agents

The Committee concluded that the data reviewed on the six alkoxy-substituted allylbenzenes provide evidence of toxicity and carcinogenicity to rodents given high doses for several of these substances. A mechanistic understanding of these effects and their implications for human risk have yet to be fully explored, and will have a significant impact on the assessment of health risks from alkoxy-substituted allylbenzenes at the concentrations at which they occur in food.

Flavouring agent	No.	Specifications[a]
Apiole	1787	N
Elemicin	1788	N
Estragole*	1789	N
Methyl eugenol*	1790	N
Myristicin	1791	N
Safrole*	1792	N

[a]N: new specifications prepared. The specifications monographs will include a statement that the safety evaluation has not been completed.

3.2 Re-evaluation of safety of certain flavourings

At the fifty-ninth, sixty-first, sixty-third and sixty-fifth meetings of the Committee, only "anticipated" annual volumes of productions were provided for some flavouring agents and used in the MSDI calculation. These volumes were used for expedience in completing a safety evaluation, but the conclusions of the Committee were made conditional pending the submission of actual poundage data.

Actual production volumes were subsequently submitted for all 143 requested flavouring agents and were evaluated by the Committee. The two flavouring substances requiring a re-evaluation were No. 1414, l-monomenthyl glutarate and No. 1595, 2-isopropyl-N,2,3-trimethylbutyramide.

The Committee concluded that the Procedure could not be applied to 2-isopropyl-*N*,2,3-trimethylbutyramide, because of evidence of clastogenicity in the presence, but not in the absence, of metabolic activation.

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Ethyl cyclohexanecarboxylate	963	S	No safety concern
10-Hydroxymethylene-2-pinene	986	S	No safety concern
2,5-Dimethyl-3-furanthiol	1063	S	No safety concern
Propyl 2-methyl-3-furyl disulfide	1065	S	No safety concern
Bis(2-methyl-3-furyl) disulfide	1066	S	No safety concern
Bis(2,5-dimethyl-3-furyl) disulfide	1067	S	No safety concern
Bis(2-methyl-3-furyl) tetrasulfide	1068	S	No safety concern
2,5-Dimethyl-3-furan thioisovalerate	1070	S	No safety concern
Furfuryl isopropyl sulfide	1077	S	No safety concern
2-Methyl-3,5- or 6-(furfurylthio)pyrazine	1082	S	No safety concern
3-[(2-Methyl-3-furyl)thio]-4-heptanone	1085	S	No safety concern
2,6-Dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone	1086	S	No safety concern
4-[(2-Methyl-3-furyl)thio]-5-nonanone	1087	S	No safety concern
2-Methyl-3-thioacetoxy-4,5-dihydrofuran	1089	S	No safety concern
4-Hydroxy-4-methyl-5-hexenoic acid gamma-lactone	1157	S	No safety concern
(+/-) 3-Methyl-gamma-decalactone	1158	S	No safety concern
4-Hydroxy-4-methyl-7-cis-decenoic acid gamma-lactone	1159	S	No safety concern
Tuberose lactone	1160	S	No safety concern
Dihydromintlactone	1161	S	No safety concern
Mintlactone	1162	S	No safety concern
Dehydromenthofurolactone	1163	S	No safety concern
(+/-)-(2,6,6-Trimethyl-2-hydroxycyclohexylidene) acetic acid gamma-lactone	1164	S	No safety concern
2-(4-Methyl-2-hydroxyphenyl)propionic acid gamma-lactone	1167	S	No safety concern
2,4-Hexadien-1-ol	1174	S	No safety concern
(E,E)-2,4-Hexadienoic acid	1176	S	No safety concern
(E,E)-2,4-Octadien-1-ol	1180	S	No safety concern
2,4-Nonadien-1-ol	1183	S	No safety concern
(E,Z)-2,6-Nonadien-1-ol acetate	1188	S	No safety concern
(E,E)-2,4-Decadien-1-ol	1189	S	No safety concern
Methyl (E)-2-(Z)-4-decadienoate	1191	S	No safety concern
Ethyl 2,4,7-decatrienoate	1193	S	No safety concern
(+/-) 2-Methyl-1-butanol	1199	S	No safety concern
2-Methyl-2-octenal	1217	S	No safety concern
4-Ethyloctanoic acid	1218	S	No safety concern
8-Ocimenyl acetate	1226	S	No safety concern
3,7,11-Trimethyl-2,6,10-dodecatrienal	1228	S	No safety concern
12-Methyltridecanal	1229	S	No safety concern
1-Ethoxy-3-methyl-2-butene	1232	S	No safety concern
2,2,6-Trimethyl-6-vinyltetrahydropyran	1236	S	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Cycloionone	1239	S	No safety concern
2,4-Dimethylanisole	1245	S	No safety concern
1,2-Dimethoxybenzene	1248	S	No safety concern
4-Propenyl-2,6-dimethoxyphenol	1265	S	No safety concern
erythro and threo-Mercapto-2-methylbutan-1-ol	1289	S	No safety concern
(±)2-Mercapto-2-methylpentan-1-ol	1290	S	No safety concern
3-Mercapto-2-methylpentanal	1292	S	No safety concern
4-Mercapto-4-methyl-2-pentanone	1293	S	No safety concern
spiro[2,4-Dithia-1-methyl-8-oxabicyclo(3.3.0)octane-3,3'-(1'-oxa-2'-methyl)-cyclopentane]	1296	S	No safety concern
2,3,5-Trithiahexane	1299	S	No safety concern
Diisopropyl trisulfide	1300	S	No safety concern
2-(2-Methylpropyl)pyridine	1311	S	No safety concern
2-Propionylpyrrole	1319	S	No safety concern
2-Propylpyridine	1322	S	No safety concern
4-Methylbiphenyl	1334	S	No safety concern
delta-3-Carene	1342	S	No safety concern
Farnesene (alpha and beta)	1343	S	No safety concern
1-Methyl-1,3-cyclohexadiene	1344	S	No safety concern
trans-2-Octen-1-yl acetate	1367	S	No safety concern
trans-2-Octen-1-yl butanoate	1368	S	No safety concern
cis-2-Nonen-1-ol	1369	S	No safety concern
(E)-2-Octen-1-ol	1370	S	No safety concern
(E)-2-Butenoic acid	1371	S	No safety concern
(E)-2-Decenoic acid	1372	S	No safety concern
(E)-2-Heptenoic acid	1373	S	No safety concern
(Z)-2-Hexen-1-ol	1374	S	No safety concern
trans-2-Hexenyl butyrate	1375	S	No safety concern
(E)-2-Hexenyl formate	1376	S	No safety concern
trans-2-Hexenyl isovalerate	1377	S	No safety concern
trans-2-Hexenyl propionate	1378	S	No safety concern
trans-2-Hexenyl pentanoate	1379	S	No safety concern
(E)-2-Nonenoic acid	1380	S	No safety concern
(E)-2-Hexenyl hexanoate	1381	S	No safety concern
(Z)-3- & (E)-2-Hexenyl propionate	1382	S	No safety concern
2-Undecen-1-ol	1384	S	No safety concern
Dihydronootkatone	1407	S	No safety concern
beta-Ionyl acetate	1409	S	No safety concern
alpha-Isomethylionyl acetate	1410	S	No safety concern
3-(l-Menthoxy)-2-methylpropane-1,2-diol	1411	S	No safety concern
Bornyl butyrate	1412	S	No safety concern
d,l-Menthol-(±)-propylene glycol carbonate	1413	S	No safety concern
l-Monomenthyl glutarate	1414	S	No safety concern
l-Menthyl methyl ether	1415	S	No safety concern
p-Menthane-3,8-diol	1416	S	No safety concern
Taurine	1435	S	No safety concern
L-Arginine	1438	S	No safety concern
L-Lysine	1439	S	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
Tetrahydrofurfuryl cinnamate	1447	S	No safety concern
(±)-2-(5-Methyl-5-vinyltetrahydrofuran-2-yl)propionaldehyde	1457	S	No safety concern
Ethyl 2-ethyl-3-phenylpropanoate	1475	S	No safety concern
2-Oxo-3-phenylpropionic acid and	1478	S	No safety concern
Sodium 2-Oxo-3-phenylpropionate	1479	S	No safety concern
2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one	1483	S	No safety concern
4-Allylphenol	1527	S	No safety concern
2-Methoxy-6-(2-propenyl)phenol	1528	S	No safety concern
Eugenyl isovalerate	1532	S	No safety concern
cis-3-Hexenyl anthranilate	1538	S	No safety concern
Citronellyl anthranilate	1539	S	No safety concern
Ethyl N-methylanthranilate	1546	S	No safety concern
Ethyl N-ethylanthranilate	1547	S	No safety concern
Isobutyl N-methylanthranilate	1548	S	No safety concern
Methyl N-formylanthranilate	1549	S	No safety concern
Methyl N-acetylanthranilate	1550	S	No safety concern
Methyl N,N-dimethylanthranilate	1551	S	No safety concern
N-Benzoylanthranilic acid	1552	S	No safety concern
Trimethyloxazole	1553	S	No safety concern
2,5-Dimethyl-4-ethyloxazole	1554	S	No safety concern
2-Ethyl-4,5-dimethyloxazole	1555	S	No safety concern
2-Isobutyl-4,5-dimethyloxazole	1556	S	No safety concern
2-Methyl-4,5-benzo-oxazole	1557	S	No safety concern
2,4-Dimethyl-3-oxazoline	1558	S	No safety concern
Butyl isothiocyanate	1561	S	No safety concern
Benzyl isothiocyanate	1562	S	No safety concern
Phenethyl isothiocyanate	1563	S	No safety concern
4,5-Dimethyl-2-propyloxazole	1569	S	No safety concern
4,5-Epoxy-(E)-2-decenal	1570	S	No safety concern
beta-Ionone epoxide	1571	S	No safety concern
Epoxyoxophorone	1573	S	No safety concern
Ethylamine	1579	S	No safety concern
Propylamine	1580	S	No safety concern
Isopropylamine	1581	S	No safety concern
Isobutylamine	1583	S	No safety concern
sec-Butylamine	1584	S	No safety concern
Pentylamine	1585	S	No safety concern
2-Methylbutylamine	1586	S	No safety concern
Hexylamine	1588	S	No safety concern
2-(4-Hydroxyphenyl)ethylamine	1590	S	No safety concern
1-Amino-2-propanol	1591	S	No safety concern
Butyramide	1593	S	No safety concern
1,6-Hexalactam	1594	S	No safety concern
2-Isopropyl-N,2,3-trimethylbutyramidee	1595	S	**Further information is needed**
N-Ethyl (E)-2,(Z)-6-nonadienamide	1596	S	No safety concern
N-Cyclopropyl (E)-2,(Z)-6-nonadienamide	1597	S	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current estimated intake
N-Isobutyl (E,E)-2,4-decadienamide	1598	S	No safety concern
(±)-N,N-Dimethyl menthyl succinamide	1602	S	No safety concern
1-Pyrroline	1603	S	No safety concern
2-Acetyl-1-pyrroline	1604	S	No safety concern
2-Propionylpyrroline	1605	S	No safety concern
Isopentylidene isopentylamine	1606	S	No safety concern
2-Methylpiperidine	1608	S	No safety concern
Triethylamine	1611	S	No safety concern
Tripropylamine	1612	S	No safety concern
N,N-Dimethylphenethylamine	1613	S	No safety concern
Trimethylamine oxide	1614	S	No safety concern
Piperazine	1615	S	No safety concern

Annex 1

Sixty-ninth meeting of the
Joint FAO/WHO Expert Committee on Food Additives (JECFA)
Rome, Italy, 17-26 June 2008

Members

Prof Jack Bend, Department of Pathology, University of Western Ontario, Canada

Prof Maria Cecilia de Figueiredo Toledo, University of Campinas, SP, Brazil

Dr Yoko Kawamura, National Institute of Health Sciences, Tokyo, Japan

Dr Paul M. Kuznesof, Silver Spring, MD, USA

Dr John C. Larsen, National Food Institute, Technical University of Denmark, Denmark (Chairman)

Dr Catherine LeClercq, National Research Institute for Food and Nutrition (INRAN), Rome, Italy

Dr Antonia Mattia, Food and Drug Administration, College Park, MD, USA

Mrs Inge Meyland, National Food Institute, Technical University of Denmark, Denmark (vice-Chairman)

Dr Gérard Pascal, INRA (Institut National de la Recherche Agronomique), L'Etang-La-Ville, France

Dr Josef Schlatter, Food Toxicology Section, Swiss Federal Office of Public Health, Zürich, Switzerland

Ms Elizabeth Vavasour, Food Directorate, Health Canada, Ottawa, Canada

Dr Madduri Veerabhadra Rao, Central Laboratories Unit, United Arab Emirates University, United Arab Emirates

Prof Ronald Walker, School of Biomedical and Molecular Sciences, University of Surrey, Surrey, UK

Mrs Harriet Wallin, National Food Safety Authority (Evira), Helsinki, Finland

Dr Brian Whitehouse, Bowdon, Cheshire, United Kingdom

Secretariat

Dr Peter J. Abbott, Canberra, Australia (WHO Temporary Adviser)

Ms Janis Baines, Food Standards Australia New Zealand, Canberra Australia (FAO Expert)

Dr Diane Benford, Food Standards Agency, London, United Kingdom (WHO Temporary Adviser)

Dr Annamaria Bruno, Secretariat of the Codex Alimentarius Commission, Food and Agriculture Organization, Rome, Italy (FAO Codex Secretariat)

Dr Richard Cantrill, American Oil Chemists' Society, Urbana, IL, USA (FAO Expert)

Dr Ruth Charrondiere, Nutrition and Consumer Protection Division, Food and Agriculture Organization, Rome, Italy (FAO Staff Member)

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Dr Myoengsin Choi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (WHO Staff Member)

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Prof Symon M. Mahungu, Egerton University, Njoro, Kenya (FAO Expert)

Mrs Heidi Mattock, Tignieu Jameyzieu, France (Editor)

Dr Hyo-Min Lee, National Institute of Toxicological Research, Seoul, Republic of Korea (WHO Temporary Adviser)

Dr Ian C. Munro, CanTox Health Sciences International, Mississauga, Ontario, Canada (WHO Temporary Adviser)

Dr Utz Mueller, Food Standards Australia New Zealand, Canberra Australia (WHO Temporary Adviser)

Dr Zofia Olempska-Beer, US Food and Drug Administration, College Park, MD, USA (FAO Expert)

Mrs Marja E.J. Pronk, Center for Substances and Integrated Risk Assessment, National Institute for Public Health and the Environment, Bilthoven, The Netherlands (WHO Temporary Adviser)

Prof Andrew G. Renwick, Clinical Pharmacology Group, University of Southampton, Southampton, United Kingdom (WHO Temporary Adviser)

Prof I. Glenn Sipes, Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, USA (WHO Temporary Adviser)

Dr Klaus Schneider, FoBiG (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH), Freiburg, Germany (WHO Temporary Adviser)

Dr Angelika Tritscher, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (WHO Joint Secretary)

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Dr Annika Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization, Rome, Italy (FAO Joint Secretary)

Prof Gary M Williams, Environmental Pathology and Toxicology, New York Medical College, Valhalla, NY, USA (WHO Temporary Adviser)

Annex 2

Recommendations and further information required

Paprika extract:
Data on the composition and capsaicin content of batches of paprika extract for use as a colour produced by a variety of manufacturers. Information as to whether the material used in the toxicological tests submitted was representative of all the products in commerce. If not, additional toxicological data on representative material would be needed for the evaluation of paprika extract for use as a colour.

The Committee recommended that the specifications for paprika oleoresin be revised at a future meeting in order to allow the differentiation of paprika extract used as a colour from paprika oleoresin used as a flavour.

Polydimethylsiloxane:
Results of studies to elucidate the mechanism and relevance of the ocular toxicity observed in the experimental studies and data on actual use levels in foods should be provided before the end of 2010.

Sulfites – dietary exposure assessment and maximum levels (MLs) in foods:
Countries that have not yet done so could consider collecting data on the current use of sulfites in food and beverages available on their markets and investigating whether dietary exposure in some subpopulations exceeds the ADI. On the basis of this investigation, individual countries and the food industry could consider the possibility of taking one or more of the following measures to reduce dietary exposure to sulfites so that the ADI is not exceeded in the population:

(1) align national legislation with Codex MLs where these are lower;

(2) take action to effectively enforce national MLs;

(3) encourage research on alternative methods of preservation, particularly on applications in which the use of sulfites is responsible for a significant contribution;

(4) take action so that the use of sulfites is reduced in foods where safe alternative solutions are available.

Codex Alimentarius Commission codes of practices for certain groups of food commodities, such as fruit juice, dried fruit and processed meat, could be amended to include suggestions to help countries and the food industry in the implementation of a reduction of the use of sulfites in food.

Furan-substituted aliphatic hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids and related esters, sulfides, disulfides and ethers (JECFA Nos, Structural Class II: 1487, 1488, 1489, 1490, 1491, 1492, 1493, 1494, 1497, 1499, 1503, 1504, 1505, 1507, 1508, 1509, 1510, 1511, 1513, 1514, 1515, 1516, 1517, 1520, 1521, 1522, 1523, 1524, 1525, 1526; Structural Class III: 1495, 1496, 1498, 1500, 1501, 1502, 1506, 1512, 1518, 1519):
The Committee concluded that the Procedure could not be applied to this group of flavouring agents, because of the unresolved toxicological concerns. Studies that would assist in the safety evaluation include investigations of the influence of the nature and position of ring substitution on metabolism and on covalent binding to macromolecules. Depending on the findings, additional studies might include assays related to the mutagenic and carcinogenic potential of representative members of this group of flavours.

Alkoxy-substituted allylbenzenes present in foods, essential oils, and used as flavouring agents (Apiole JECFA No. 1787, Elemicin No. 1788, Estragole No. 1789, Methyl eugenol No. 1790, Myristicin No 1791, Safrole No 1792):
There is evidence of toxicity and carcinogenicity to rodents given high doses for several of these substances. A mechanistic understanding of these effects and their implications for human risk have yet to be fully explored, and will have a significant impact on the assessment of health risks from alkoxy-substituted allylbenzenes at the concentrations at which they occur in food. Further research is needed to assess the

potential risk to human health from low-level dietary exposure to alkoxy-substituted allylbenzenes present in foods and essential oils and used as flavouring agents.

2-isopropyl-N,2,3-trimethylbutyramide (JECFA No. 1595):
The Committee concluded that the Procedure could not be applied to 2-isopropyl-N,2,3-trimethylbutyramide, because of because of evidence of clastogenicity in the presence, but not in the absence, of metabolic activation. Information that would assist in resolving the concerns would include data on the potential of this compound to form reactive metabolites and on whether clastogenicity is also expressed in vivo, as well as additional information on the effects found in the kidney (tubular nephrosis, tubular dilatation with granular casts and hyaline droplet formation) at relatively low doses.

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

Incorporation of the single portion exposure technique (SPET) into the Procedure for the Safety Evaluation of Flavouring Agents

JECFA employs the maximized survey-derived intake (MSDI) method as a measure of the dietary exposure to flavouring agents for use in the Procedure for the Safety Evaluation of Flavouring Agents (the Procedure). The MSDI provides a per-capita estimate of the dietary exposure to a flavouring agent that is compared with the relevant threshold of toxicological concern (TTC) for each structural class in a decision-tree approach according to the Procedure (for Structural Classes, see Cramer et al., 1978[*]). The MSDI is based on the reported amount of the flavouring agent introduced into the food supply per year in specific regions, currently Europe, the USA and Japan, corrected for under-reporting, and assuming that 10% of the relevant population would consume foods containing the flavouring agent.

The Committee considered issues related to dietary exposure to flavouring agents at its forty-fourth, forty-sixth, forty-ninth, fifty-fifth, sixty-third, sixty-fifth, sixty-seventh and sixty-eight meetings. The main concern expressed by the Committee was that the MSDI method may significantly underestimate dietary exposure to some flavouring agents. This could be the case for flavouring agents consumed by less than 10% of the population, especially where they might be used in a few food categories, and for flavouring agents with an uneven distribution of dietary exposure among consumers. The uneven distribution might be due to a combination of factors, including different use levels across and within food categories, restriction to use in a few foods or food categories and different levels of consumption for different foods.

The single portion exposure technique (SPET) was developed by the Committee at its sixty-seventh meeting to account for presumed patterns of consumer behaviour with respect to food consumption and the possible uneven distribution of dietary exposure for consumers of foods containing flavouring agents. The SPET provides an estimate of dietary exposure for an individual who consumes a specific food product containing the flavouring agent every day. The SPET combines an average (or usual) added use level with a standard portion size for a food category. Among all the food categories with a reported use level, the dietary exposure from the single food category leading to the highest dietary exposure from one portion is taken as the SPET estimate. The standard portion does not reflect high levels of food consumption reported in national dietary surveys. It was intended that the higher value of the two dietary exposure estimates (MSDI or SPET) would be used within the Procedure.

At its sixty-eighth and its present meeting, the Committee performed a number of SPET and MSDI calculations with the aim of:

- determining whether a set of criteria could be identified for future selection of flavouring substances for which the MSDI could underestimate dietary exposure. In these cases, extra information on added use levels recommended by the industry would be required to calculate a SPET estimate;
- evaluating the possible impact of using both the MSDI and SPET estimates of dietary exposure in the Procedure for different flavour groups.

[*] Cramer GM, Ford RA, and Hall RA. Estimation of toxic hazard – a decision tree approach. Food and Cosmetics Toxicology, 1978; 16:255-276.

Investigation to develop criteria for the identification of flavouring agents requiring additional consideration

At its sixty-eighth meeting, the Committee calculated SPET estimates for 57 flavouring agents based on use levels provided by IOFI[†], 44 with low production volumes (< 10 kg/year) and 13 with intermediate to high production volumes (production volumes corresponding to an amount that was greater than one third of the relevant TTC). These flavouring agents were selected from all structural classes and eight different groups. For 4 out of the 57 flavouring agents selected, the MSDI was greater than the corresponding SPET estimate. Although for the remaining 53 flavouring agents the SPET estimate was greater than the corresponding MSDI, different steps through the Procedure would only have been required in 2 cases where the SPET estimate exceeded the relevant TTC. The Committee concluded that, using this small group of flavours for the analysis, it was not possible to develop any selection criteria (based on production volume, structural class or flavouring group) to identify cases where the MSDI would have underestimated dietary exposure and different steps through the Procedure would have been required if the SPET estimate were to be used in the Procedure. Consequently, for the present meeting of the Committee, additional data on use levels for another set of flavouring agents with intermediate to high volumes of production were requested from and provided by IOFI to extend the analysis.

Analysis of data for 40 flavouring agents considered at the present meeting

IOFI data were made available to calculate SPET estimates for 40 flavouring agents from 15 different flavouring groups of intermediate to high production volume. Of these, 28 were in structural class I, 6 in class II and 6 in class III. For class I flavouring agents, none of the SPET estimates exceeded the TTC, whereas the MSDI exceeded the TTC in one case. For class II flavouring agents, one SPET estimate exceeded the TTC while no MSDI estimates exceeded the TTC. For class III flavouring agents, all six SPET estimates exceeded the TTC while two of the MSDI estimates exceeded the TTC. Cases where the SPET estimate exceeded the MSDI and exceeded the TTC occurred in this group of flavouring agents across different production volumes, structural classes and flavour groups, a similar finding to that for the 57 flavouring agents considered at the sixty-eighth meeting.

Analysis of a larger data set of flavouring agents

Because the analyses of flavouring agents considered at the sixty-eighth and the present meeting were inconclusive, the Committee collected use-level data from other sources to determine whether suitable criteria for predicting when the MSDI might underestimate dietary exposure could be developed based on a larger group of flavouring agents. Additionally, the likelihood that the SPET estimate would exceed the relevant TTC when the MSDI did not was examined. Overall, SPET estimates for 549 flavouring agents were calculated, based on use levels derived from three main data sets:

- for 225 flavouring agents: recent and refined[‡] use-level data provided by IOFI to the Committee or to the European Commission (DG SANCO) in 2007 and 2008.
- for 198 flavouring agents: refined[2] use-levels data collected in an industry survey (NAS-NRC) conducted in the USA in 1977.
- for 268 flavouring agents: use levels proposed by industry for flavouring agents registered as FEMA GRAS[§], published between 1965 and 2007

Some flavouring agents were assessed using more than one source of use levels, resulting in a total of 691 SPET estimates.

Some of the portion sizes used in the SPET calculations were updated at this meeting based on reported food-consumption levels, including the addition of new portion sizes (Appendix 1).

[†] The International Organization of the Flavor Industry (IOFI) collated data on added use levels from the European Flavour and Fragrance Association (EFFA), the Flavor and Extract Manufacturers Association of the United States (FEMA) and the Japanese Flavour and Fragrance Materials Association (JFFMA) and submitted these data on behalf of the three organizations.

[‡] In this context, "refined" means that the information is derived from use levels in specific foods or food types, rather than broad food categories (e.g., "fruit-flavoured yogurt" as opposed to "dairy products").

[§] GRAS, or Generally Recognized As Safe, is a regulatory concept specific to the United States Federal Food Drug and Cosmetic Act. Any substance added to food requires a food additive regulation for its use, unless its intended use is GRAS. Food ingredients whose use is GRAS are not required by law to receive FDA approval before marketing. FEMA has been publishing lists of flavouring substances, and associated use levels at or below which they have deemed their use to be GRAS, for more than 30 years.

In nearly all cases (92%), the SPET estimate was greater than the MSDI and it was more likely that the SPET estimate was greater than the TTC of the relevant structural class than the corresponding MSDI. The SPET estimate was most frequently greater than the TTC in class III, but this also occurred in classes I and II (see Table 1).

The Committee considered the use of FEMA GRAS use levels to be less desirable than the more specific levels provided by IOFI, as FEMA GRAS values are projected and probably overestimate actual use levels. IOFI provided high quality use-level data from recent surveys and informed the Committee that with very few exceptions there is a strong agreement between recent and older use-level surveys and that comparison of these surveys supports the conclusion that use levels for flavouring agents with similar flavouring effect are generally similar, and they have not changed significantly over time.

For the flavouring agents with IOFI use-level data only, the differences between the two dietary exposure estimates were examined. The Committee considered that it would be inappropriate to use the SPET estimates based on NAS-NRC data from 1977 or FEMA GRAS levels for this purpose.

Overall, for the group of 225 flavouring agents with IOFI use-level data, 50% had a SPET estimate that was less than two orders of magnitude higher than the MSDI (median ratio of SPET to MSDI was 85). Twenty-one flavouring agents had a MSDI that was higher than the SPET estimate by up to two orders of magnitude. For the remaining 204 flavouring agents, the SPET estimate was higher than the MSDI. Of these, 24 had SPET estimates that were four to six orders of magnitude higher than the MSDI estimate.

Table 1. Comparison of SPET and MSDI with TTC for flavouring agents in structural classes I, II, and III

	Source of use-level data		
	IOFI	NAS-NRC	FEMA GRAS
	2007–2008	1977	1965–2007
	(*n* = 225)	(*n* = 198)	(*n* = 268)
Class I, SPET > TTC	1/70 (1%)	38/121 (31%)	25/111 (23%)
Class II, SPET > TTC	1/12 (8%)	13/58 (22%)	32/62 (52%)
Class III, SPET > TTC	86/143 (60%)	12/19 (63%)	77/95 (81%)
Total, SPET > TTC	**88/225 (39%)**	**63/198 (32%)**	**134/268 (50%)**
Class I, MSDI > TTC	2/70 (3%)	5/121 (4%)	1/111 (1%)
Class II , MSDI > TTC	0/12 (0%)	4/58 (7%)	1/62 (2%)
Class III, MSDI > TTC	12/143 (8%)	1/19 (5%)	12/95 (13%)
Total, MSDI > TTC	**14/225 (6%)**	**10/198 (5%)**	**14/268 (5%)**

Note: Some flavouring agents were assessed using more than one source of use levels

From the analysis of the MSDI and SPET estimates for the 549 flavouring agents, the Committee concluded that it was not possible to develop criteria, based on production volume, structural class or flavour group, to predict when the MSDI might underestimate dietary exposure and when the SPET estimate, but not the MSDI, was likely to exceed the TTC.

Consideration of the incorporation of the SPET estimate in the Procedure

The Committee considered the consequences of incorporating the SPET estimate into the Procedure, using two flavour groups as an example. One group was evaluated on the A-side of the Procedure (6 hydroxyl- and alkoxy-substituted benzyl derivatives, section 4.1.7), and one group on the B-side (miscellaneous nitrogen-containing substances, section 4.1.8). In four cases, IOFI use-level data were available. For the other 16 flavouring agents, FEMA GRAS levels were used for the SPET estimate for the purposes of this exercise only, as these were the only use levels available.

For these two groups of flavouring agents, the food categories responsible for the highest dietary exposure in one standard portion were beverages, either alcoholic or non-alcoholic (for nine flavouring agents), processed fruit (two cases), processed vegetables (one case), meat products (two cases), cereals and cereal products such as baked goods (four cases), condiments (one case), milk and dairy-based drinks (one case).

Hydroxyl- and alkoxy-substituted benzyl derivatives

In applying the Procedure for the Safety Evaluation of Flavouring Agents using the MSDI for the six flavouring agents in the hydroxyl- and alkoxy-substituted benzyl derivatives group of flavouring agents, the Committee assigned five flavouring agents (Nos 1878–1880, 1882, 1883) to structural class I and the remaining flavouring agent (No. 1881) to structural class III. The evaluation of all agents in this group proceeded via the A-side of the Procedure. According to the Procedure using the MSDI, the safety of these six flavouring agents raised no concern because the dietary exposure was below the relevant TTC.

Incorporation of the SPET estimate in the Procedure would have resulted in different steps through the Procedure for three of the six flavouring agents. SPET estimates based on IOFI use levels were only available for one of the flavouring agents in this group (No. 1882). The estimated dietary exposure to sodium 4-methoxybenzoyloxyacetate (No. 1880) and 4-methoxybenzoyloxyacetic acid (No. 1883) exceeded the threshold of concern (TTC) for structural class I (1800 μg per day) using the SPET estimate. Similarly, the dietary exposure to divanillin (No. 1881) exceeded the TTC for structural class III (90 μg per day).

Miscellaneous nitrogen-containing substances

In applying the Procedure for the Safety Evaluation of Flavouring Agents using the MSDI for the 14 flavouring agents in the group of miscellaneous nitrogen-containing substances, the Committee assigned 12 (Nos 1884–1890, 1892–1894, 1896, and 1897) to structural class II and the remaining 2 (Nos 1891 and 1895) to structural class III (Cramer et al., 1978). None of the flavouring agents in this group could be predicted to be metabolized to innocuous products. The evaluation of these 14 flavouring agents therefore proceeded via the B-side of the Procedure. According to the Procedure using the MSDI, the safety of these 14 flavouring agents raised no concern.

Incorporation of the SPET estimate in the Procedure would have resulted in different steps through the Procedure for two of the fourteen flavouring agents, (Nos 1894 and 1895) as they would not have progressed to step B4. SPET estimates based on IOFI use levels were only available for three flavouring agents in this group (Nos 1889, 1893, 1894).

The results for these two flavouring groups indicated that the incorporation of the SPET estimate into the Procedure for flavouring agents going though the A-side of the Procedure will more often require appropriate toxicity data on these flavouring agents or on closely-related substances to complete the safety evaluation at Step A5. For flavouring agents going through the B-side of the Procedure, additional toxicological data will more often be required for those flavouring agents that do not progress to step B4. In all these cases, additional data would need to be included in the submission for the flavouring agents. IOFI use-level data would need to be submitted in the data package for all flavouring agents going through either side of the Procedure to enable SPET estimates to be made.

Combined intake

The SPET estimate for a flavouring agent represents the dietary exposure for a daily consumer of a standard portion of food containing the substance. The combination of SPET estimates for related flavouring agents could greatly overestimate dietary exposure. The Committee therefore considered that the estimate of combined dietary exposure in the Procedure should continue to be based on the MSDI estimates, as outlined in the report of the sixty-eighth meeting.

Conclusion

The Committee noted that MSDI and SPET estimates of dietary exposure provide different and complementary information. Use of the SPET estimate addresses previous concerns expressed by the Committee about the dietary exposure methodology used in the Procedure, because the SPET estimates take account of the possible uneven distribution of dietary exposures to a flavouring agent for consumers of foods containing that substance. The higher value of the two dietary exposure estimates (MSDI or SPET) should be used within the Procedure.

As it was not possible to elaborate criteria to identify the flavouring agents for which the MSDI underestimated dietary exposure and SPET estimates should be used, the Committee concluded it was necessary to incorporate SPET estimates into the Procedure for all flavouring agents considered at future meetings of the Committee. The Committee agreed that it would not be necessary to re-evaluate flavouring agents that have already been assessed using the Procedure.

To enable a safety evaluation using the Procedure to be undertaken, the Committee requested that added use-level data be provided for each flavouring agent in a timely fashion before the meeting, in addition to up-to-date data on production volumes, as part of the data package for the safety evaluation. The Committee will not perform a safety evaluation in the absence of such data.