Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-first meeting
Rome, 10-19 June 2003

SUMMARY AND CONCLUSIONS

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 10 to 19 June 2003. The purpose of the meeting was to evaluate certain food additives and contaminants.

Mrs Inge Meyland, Senior Scientific Adviser, Institute of Food Research and Nutrition, Danish Veterinary and Food Administration, Søborg, Denmark, served as Chairman and Professor Ron Walker, Emeritus Professor of Food Science, School of Biomedical and Life Sciences, University of Surrey, Guildford, England served as Vice-Chairman.

Dr Manfred Luetzow, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, and Dr Sam Page, International Programme on Chemical Safety, World Health Organization, served as joint secretaries.

The present meeting was the sixty-first in a series of similar meetings. The tasks before the Committee were (a) to elaborate further principles for evaluating the safety of food additives and contaminants; (b) to evaluate certain food additives and flavouring agents; (c) to review and prepare specifications for selected food additives and flavouring agents; (d) to evaluate a water-treatment agent; (e) to evaluate a nutritional source for iron; and (f) to evaluate certain contaminants.

The report of the meeting will appear 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 recommendations. Information on specifications for the identity and purity of certain food additives 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. Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 3 and 4.

Toxicological monographs or monograph addenda on most of the substances that were considered will be published in WHO Food Additives Series No. 52.

New and revised specifications for the identity and purity of the compounds will be published in FAO Food and Nutrition Paper Series 52, Addendum 11.

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

www.fao.org/es/esn/jecfa/index_en.stm

www.who.int/pcs/jecfa/jecfa.htm

Toxicological recommendations and information on specifications

1. Food additives evaluated toxicologically

Food additive	Specifi-cations [a]	Acceptable daily intake (ADI) and other toxicological recommendations
Annatto extract (solvent-extracted bixin) - "Annatto B" [b]	R, T	0 – 7 mg/kg bw (temporary); for preparations containing not less than 85 % pigment (as bixin, of which not more than 2.5% is norbixin) [c]
Annatto extract (solvent-extracted norbixin) - "Annatto C"	R, T	0 – 0.4 mg/kg bw (temporary); for preparations containing not less than 85% pigments (as norbixin) [c]
Annatto extract (oil-processed bixin suspension) - "Annatto D"	R, T	No ADI established, since no data on toxicity were available
Annatto extract (aqueous-processed bixin) - "Annatto E"	R, T	0 – 4 mg/kg bw (temporary); for a preparations containing not less than 25% pigments (as bixin, of which not more than 7% is norbixin) [c]
Annatto extract (alkali-processed norbixin) - "Annatto F"	R, T	0 – 0.4 mg/kg bw (temporary); for a preparation containing not less than 35% pigments (as norbixin) [c]
Annatto extract (alkali-processed norbixin, not acid-precipitated) - "Annatto G"	R, T	No ADI established, since no data on toxicity were available
Curcumin	R	0-3 mg/kg bw
Diacetyltartaric and fatty acid esters of glycerol (DATEM)	-	0-50 mg/kg bw
Enzyme preparations		
Alpha-amylase from *Bacillus licheniformis* containing a genetically engineered alpha-amylase gene from *B. licheniformis*	N	Not specified [d]
Laccase from *Myceliophthora thermophila* expressed in *Aspergillus oryzae*	N	Not specified [d]
Mixed xylanase, β-glucanase enzyme preparation, produced by a strain of *Humicola insolens*	N	Not specified [d]
Xylanase from *Thermomyces lanuginosus* expressed in *Fusarium venenatum*	N	Not specified [d]
Neotame	N	0 – 2 mg/kg bw
Polyvinyl alcohol	N	0–50 mg/kg bw
Quillaia extract (Type 1) [e]	R	0 – 5 mg/kg bw
Quillaia extract (Type 2) [e]	N	No ADI established due to limited information on the qualitative and quantitative composition
D-Tagatose	R	0 – 125 mg/kg bw (temporary)

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

[b] To ensure clarity of the text, the Committee adopted for the report the designations B, C, D, E, F, G, as employed in the submitted information to refer to the different extracts under evaluation.

[c] The ADI is established for the extract as tested biologically and specified. It is not expressed in relation to content of bixin and/or nor-bixin.

[d] 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.

[e] Quillaia extract (Type 1) : saponin content of 20 - 26%; quillaia extract (Type 2): saponin content of 75 - 90%.

2. Food additive considered for specifications only

Food Additive	Specifications [a]
beta-Carotene from *Blakeslea trispora*	R
Magnesium silicate	R
Monomagnesium phosphate	S, T
Natamycin	R
Sucrose esters	R
Talc	R
Trisodium diphosphate	R, T

[a] R, existing specifications revised; S, existing specifications were not considered; T, tentative specifications.

3. Revision of heavy metals limits for food additives

At its fifty-fifth meeting, the Committee began its implementation of a systematic five-year programme to replace the outdated test for heavy metals (as lead) in all existing food additive specifications with appropriate limits for individual metals of concern. At the present meeting, the heavy metals and arsenic limits of 39 additives were reviewed. The functional uses of these included absorbent, antioxidant, antifoaming, carrier solvent, clouding agent, colour retention, emulsifier and sequestrant applications.

Comments on the Committee's new proposed limits are invited. If alternative values and supporting data are not received by the deadline for submission of data for the sixty-third meeting (30 November 2003), the proposed metal limits will be adopted and supersede the existing limits, replacing those published in FAO Food and Nutrition Paper 52 and its addenda 1 to 10.

Additive name	INS	As	Pb	Cd	Hg
Activated carbon		3	5	-	-
Aluminium potassium sulfate	0522	-	5	-	-
Aluminium sulfate (anhydrous)	0520	-	5	-	-
Ascorbic acid	0300	-	2	-	-
Ascorbyl palmitate	0304 (i)	-	2	-	-
Ascorbyl stearate	0304 (ii)	-	2	-	-
Bone phosphate	0542	3	2	-	-
Butylated hydroxyanisole (BHA)	0320	-	2	-	-
Butylated hydroxytoluene (BHT)	0321	-	2	-	-
Calcium ascorbate	0302	-	2	-	-
Calcium disodium ethylenediaminetetraacetate	0385	-	2	-	-
Cupric sulfate	0519	-	10	-	-
Dilauryl thiodipropionate	0389		2	-	-
Disodium ethylenediaminetetraacetate	0386	-	2	-	-
Dodecyl gallate	0312	-	2	-	-
Erythorbic acid	0315		2	-	-
Ethyl protocatechuate	-		2	-	-
Ferrous lactate	0585	-	1	-	-
Isopropyl citrate mixture	0384	-	2	-	-
Lecithin	0322	-	2	-	-

Additive name	INS	As	Pb	Cd	Hg
Octyl gallate	0311	-	2	-	-
Polydimethyl siloxane	0900	-	1	-	-
Polyethylene glycols	1521	-	1	-	-
Potassium lactate solution	0326	-	2	-	-
Potassium polyphosphates	0452 (ii)	3	4	-	-
Propyl gallate	0310	-	2	-	-
Sodium aluminium phosphate, acidic	0541 (i)	3	2	-	-
Sodium ascorbate	0301	-	2	-	-
Sodium caseinate	-	-	2	-	-
Sodium erythorbate	0316	-	2	-	-
Sodium lactate (solution)	0325	-	2	-	-
Stannous chloride	0512	-	2	-	-
Sucrose acetate isobutyrate	0444	-	2	-	-
Tertiary butylhydroquinone	0319	-	2	-	-
Thiodipropionic acid	0388	-	2	-	-
Tocopherol concentrate mixed	0307 b	-	2	-	-
Tocopherol concentrate, d-alpha	0307 a	-	2	-	-
Tocopherol, dl-alpha	0307 c	-	2	-	-
Triethyl citrate	1505	-	2	-	-

4. Flavouring agents evaluated using the Procedure for the Safety Evaluation of Flavouring Agents Check for specs and conclusions

A. Alicyclic, alicyclic-fused and aromatic-fused ring lactones

Flavouring agent	No.	Specifi-cations [a]	Conclusions based on current intake
4-Hydroxy-4-methyl-5-hexenoic acid gamma lactone	1157	N	No safety concern
(+/-) 3-Methyl-gamma-decalactone	1158	N	No safety concern
4-Hydroxy-4-methyl-7-cis-decenoic acid gamma lactone	1159	N	No safety concern
Tuberose lactone	1160	N	No safety concern
Dihydromintlactone	1161	N	No safety concern
Mintlactone	1162	N	No safety concern
Dehydromenthofurolactone	1163	N	No safety concern
(+/-)-(2,6,6-Trimethyl-2-hydroxycyclohexylidene)acetic acid gamma-lactone	1164	N	No safety concern
Sclareolide	1165	N	No safety concern
Octahydrocoumarin	1166	N	No safety concern
2-(4-Methyl-2-hydroxyphenyl)propionic acid-gamma-lactone	1167	N	No safety concern
3-Propylidenephthalide	1168	N	No safety concern
3-n-Butylphthalide	1169	N	No safety concern
3-Butylidenephthalide	1170	N	No safety concern
Dihydrocoumarin	1171	R	No safety concern
6-Methylcoumarin	1172	N	No safety concern

[a]N: new specifications prepared; R: revised specifications.

B. Aliphatic di- and trienals and related alcohols, acids, and esters

Flavouring agent	No.	Specifi-cations[a]	Conclusions based on current intake
2,4-Pentadienal	1173	N	No safety concern
(E,E)-2,4-Hexadien-1-ol	1174	N	No safety concern
trans,trans-2,4-Hexadienal	1175	N	No safety concern
(E,E)-2,4-Hexadienoic acid	1176	N	See footnote [b]
Methyl sorbate	1177	N	No safety concern
Ethyl sorbate	1178	N	No safety concern
2,4-Heptadienal	1179	N	No safety concern
(E,E)-2,4-Octadien-1-ol	1180	N	No safety concern
trans,trans-2,4-Octadienal	1181	N	No safety concern
2-trans,6-trans-Octadienal	1182	N	No safety concern
2,4-Nonadien-1-ol	1183	N	No safety concern
2,6-Nonadien-1-ol	1184	N	No safety concern
2,4-Nonadienal	1185	N	No safety concern
Nona-2-trans-6-cis-dienal	1186	N	No safety concern
2-trans-6-trans-Nonadienal	1187	N	No safety concern
(E,Z)-2,6-Nonadien-1-ol acetate	1188	N	No safety concern
(E,E)-2,4-Decadien-1-ol	1189	N	No safety concern
2-trans,4-trans-Decadienal	1190	N	No safety concern
Methyl (E)-2-(Z)-4-decadienoate	1191	N	No safety concern
Ethyl trans-2-cis-4-decadienoate	1192	N	No safety concern
Ethyl 2,4,7-decatrienoate	1193	N	No safety concern
Propyl 2,4-decadienoate	1194	N	No safety concern
2,4-Undecadienal	1195	N	No safety concern
trans,trans-2,4-Dodecadienal	1196	N	No safety concern
2-trans-6-cis-Dodecadienal	1197	N	No safety concern
2-trans-4-cis-7-cis-Tridecatrienal	1198	N	No safety concern

[a]N: New specifications prepared. [b] An ADI of 0 to 25 mg/kg bw was established at the 17th meeting. The ADI was maintained and the use of the chemical as a flavouring agent subsumed in the ADI.

C. Aliphatic branched-chain unsaturated alcohols, aldehydes, acids, and related esters

Flavouring agent	No.	Specifi-cations[a]	Conclusions based on current intake
(+/-) 2-Methyl-1-butanol	1199	N	No safety concern
3-Methyl-2-buten-1-ol	1200	N	No safety concern
2-Methyl-2-butenal	1201	N	No safety concern
3-Methyl-2-butenal	1202	N	No safety concern
Ammonium isovalerate	1203	N	No safety concern
3-Methylcrotonic acid	1204	N	No safety concern
trans-2-Methyl-2-butenoic acid	1205	N	No safety concern
Isobutyl 2-butenoate	1206	N	No safety concern
2-Methylallyl butyrate	1207	N	No safety concern
4-Methyl-2-pentenal	1208	N	No safety concern
2-Methyl-2-pentenal	1209	N	No safety concern
2-Methyl-2-pentenoic acid	1210	N	No safety concern
2,4-Dimethyl-2-pentenoic acid	1211	N	No safety concern
2-Methylheptanoic acid	1212	N	No safety concern
Isobutyl angelate	1213	N	No safety concern
2-Butyl-2-butenal	1214	N	No safety concern
2-Isopropyl-5-methyl-2-hexenal	1215	N	No safety concern
2-Ethyl-2-heptenal	1216	N	No safety concern
2-Methyl-2-octenal	1217	N	No safety concern
4-Ethyloctanoic acid	1218	N, T	No safety concern
dl-Citronellol	1219	R	See footnote [b]
Citronellal	1220	N	No safety concern
3,7-Dimethyl-6-octenoic acid	1221	N	No safety concern
Rhodinol	1222	N	No safety concern
Geraniol	1223	N	No safety concern
Nerol	1224	N	No safety concern
Citral	1225	R	See footnote [b]
8-Ocimenyl acetate	1226	N	No safety concern
2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal	1227	N	No safety concern
3,7,11-Trimethyl-2,6,10-dodecatrienal	1228	N	No safety concern
12-Methyltridecanal	1229	N	No safety concern
Farnesol	1230	N	No safety concern

[a] N: new specifications prepared; R: revised specifications; T: tentative specifications. [b] A group ADI of 0 to 0.5 mg/kg bw expressed as citral, was established for citral, citronellol, geranyl acetate, linalool and linalyl acetate at the 23rd meeting. The ADI was maintained and the use of the chemical as a flavouring agent subsumed in the ADI.

D. Aliphatic and aromatic ethers

Flavouring agent	No.	Specifi-cations[a]	Conclusions based on current intake
sec-Butyl ethyl ether	1231	N	No safety concern
1-Ethoxy-3-methyl-2-butene	1232	N	No safety concern
1,4-Cineole	1233	N	No safety concern
Eucalyptol	1234	N	No safety concern
Nerol oxide	1235	N	No safety concern
2,2,6-Trimethyl-6-vinyltetrahydropyran	1236	N	No safety concern
Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran	1237	N	No safety concern
Theaspirane	1238	N	No safety concern
Cycloionone	1239	N	No safety concern
1,5,5,9-Tetramethyl-13-oxatricyclo(8.3.0.0(4,9))tridecane	1240	N	No safety concern
Anisole	1241	N	No safety concern
o-Methylanisole	1242	N	No safety concern
p-Methylanisole	1243	N	No safety concern
p-Propylanisole	1244	N	No safety concern
2,4-Dimethylanisole	1245	N	No safety concern

Flavouring agent	No.	Specifi-cations[a]	Conclusions based on current intake
1-Methyl-3-methoxy-4-isopropylbenzene	1246	N	No safety concern
Carvacryl ethyl ether	1247	N	No safety concern
1,2-Dimethoxybenzene	1248	N	No safety concern
m-Dimethoxybenzene	1249	N	No safety concern
p-Dimethoxybenzene	1250	N	No safety concern
3,4-Dimethoxy-1-vinylbenzene	1251	N	No safety concern
Benzyl ethyl ether	1252	N	No safety concern
Benzyl butyl ether	1253	R	No safety concern
Methyl phenethyl ether	1254	N	No safety concern
Diphenyl ether	1255	N	No safety concern
Dibenzyl ether	1256	R	No safety concern
beta-Naphthyl methyl ether	1257	N	No safety concern
beta -Naphthyl ethyl ether	1258	N	No safety concern
beta -Naphthyl isobutyl ether	1259	N	No safety concern

[a]N: new specifications prepared; R: revised specifications.

E. Hydroxypropenylbenzenes

Flavouring agent	No.	Specifi-cations[a]	Conclusions based on current intake
Isoeugenol	1260	N	No safety concern
Isoeugenyl formate	1261	N	No safety concern
Isoeugenyl acetate	1262	N	No safety concern
Isoeugenyl phenylacetate	1263	N, T	No safety concern
Propenylguaethol	1264	N	No safety concern
4-Propenyl-2,6-dimethoxyphenol	1265	N	No safety concern
Isoeugenyl methyl ether	1266	N	No safety concern
Isoeugenyl ethyl ether	1267	N	No safety concern
Isoeugenyl benzyl ether	1268	N	No safety concern

[a]N: new specifications prepared; T: tentative specifications.

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

Flavouring agent	No.	Specifica-tions[a]	Conclusions based on current intake
Isoprenyl acetate	1269	N	No safety concern
4-Pentenyl acetate	1270	N	No safety concern
3-Hexenal	1271	N	No safety concern
3-Hexenyl formate	1272	N	No safety concern
Ethyl 5-hexenoate	1273	N,T	No safety concern
cis-3-Hexenyl propionate	1274	N	No safety concern
cis-3-Hexenyl isobutyrate	1275	N	No safety concern
(Z)-3-Hexenyl (E)-2-butenoate	1276	N	No safety concern
cis-3-Hexenyl tiglate	1277	N	No safety concern
cis-3-Hexenyl valerate	1278	N	No safety concern
3-Hexenyl 2-hexenoate	1279	N	No safety concern
(Z)-4-Hepten-1-ol	1280	N	No safety concern
Ethyl cis-4-heptenoate	1281	N	No safety concern
(Z)-5-Octenyl propionate	1282	N	No safety concern
(Z,Z)-3,6-Nonadien-1-ol	1283	N	No safety concern
(E)-3,(Z)-6-Nonadien-1-ol	1284	N	No safety concern
(E,Z)-3,6-Nonadien-1-ol acetate	1285	N	No safety concern
9-Decenal	1286	N	No safety concern
4-Decenoic acid	1287	N	No safety concern
cis-4-Decenyl acetate	1288	N	No safety concern

[a] N: new specifications prepared; T: tentative specifications.

G. Simple aliphatic and aromatic sulfides and thiols

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
erythro and threo-3-Mercapto-2-methylbutan-1-ol	1289	N	No safety concern
(+/-)2-Mercapto-2-methylpentan-1-ol	1290	N	No safety concern
3-Mercapto-2-methylpentan-1-ol (racemic)	1291	N, T	No safety concern
3-Mercapto-2-methylpentanal	1292	N	No safety concern
4-Mercapto-4-methyl-2-pentanone	1293	N	No safety concern
(+/-) Ethyl 3-mercaptobutyrate	1294	N	No safety concern
Ethyl 4-(acetylthio)butyrate	1295	N	No safety concern
spiro(2,4-Dithia-1-methyl-8-oxabicyclo(3.3.0)octane-3,3'-(1'-oxa-2'-methyl)-cyclopentane)	1296	N, T	No safety concern
2-(Methylthio)ethanol	1297	N	No safety concern
Ethyl 5-(methylthio)valerate	1298	N	No safety concern
2,3,5-Trithiahexane	1299	N	No safety concern
Diisopropyl trisulfide	1300	N	No safety concern

[a] N: new specifications prepared; T: tentative specifications.

5. Flavouring agents considered for specifications only

No.	Flavouring agent	Specifications[a]
42	Isoamyl formate	61st/R
53	Citronellyl formate	61st/R,T
54	Geranyl formate	61st/R
55	Neryl formate	61st/R,T
56	Rhodinyl formate	61st/R
57	Citronellyl acetate	61st/R
60	Rhodinyl acetate	61st/R
61	Citronellyl propionate	61st/R
62	Geranyl propionate	61st/R
65	Citronellyl butyrate	61st/R
66	Geranyl butyrate	61st/R
68	Rhodinyl butyrate	61st/R,T
71	Citronellyl isobutyrate	61st/R
73	Neryl isobutyrate	61st/R
95	Heptanal	61st/R
98	Octanal	61st/R
101	Nonanal	61st/R
104	Decanal	61st/R
107	Undecanal	61st/R
110	Lauric aldehyde	61st/R
112	Myristaldehyde	61st/R
117	Propyl formate	61st/R
119	n- Amyl formate	61st/R
124	Isobutyl formate	61st/R
170	n- Amyl heptanoate	61st/R
180	Methyl laurate	61st/R
205	Methyl 2-methylbutyrate	61st/R
212	2- Methylbutyl 2-methylbutyrate	61st/R
237	6- Hydroxy-3,7-dimethyloctanoic acid lactone	61st/R
244	3- Heptyldihydro-5-methyl-2(3H)-furanone	61st/R
272	3,7- Dimethyl-1-octanol	61st/R
302	2,6- Dimethyl-4-heptanone	61st/R
303	2,6- Dimethyl-4-heptanol	61st/R
322	cis-5- Octen-1-ol	61st/R
323	cis-5- Octenal	61st/R
325	cis-6- Nonenal	61st/R
329	9- Undecenal	61st/R
332	Linoleic and linolenic acid (mixture)	61st/R
337	Methyl cis-4-octenoate	61st/R
338	Ethyl cis-4-octenoate	61st/R
346	Methyl linoleate & Methyl linolenate (mixture)	61st/R
348	2,6- Dimethyl-6-hepten-1-ol	61st/R
349	2,6- Dimethyl-5-heptenal	61st/R
358	Linalyl formate	61st/R
360	Linalyl propionate	61st/R
384	beta- Damascone	61st/R
385	alpha- Damascone	61st/R
396	Dehydrodihydroionone	61st/R
397	Dehydrodihydroionol	61st/R
399	Methyl-beta-ionone	61st/R,T
409	3- Hydroxy-2-pentanone	61st/R
410	2,3- Pentadione	61st/R
417	2,3- Undecadione	61st/R
419	Ethylcyclo-pentenolone	61st/R
422	3- Ethyl-2-hydroxy-4-methylcyclopent-2-en-1-one	61st/R
423	5- Ethyl-2-hydroxy-3-methylcyclopent-2-en-1-one	61st/R
435	Piperitone	61st/R
443	l- Menthol ethylene glycol carbonate	61st/R
465	2- Methylthioacetaldehyde	61st/R
468	4-(Methylthio)butanal	61st/R
470	2-(Methylthio)methyl-2-butenal	61st/R

No.	Flavouring agent	Specifications[a]
471	2,8- Dithianon-4-ene-4-carboxaldehyde	61st/R,T
473	Methylthiomethyl butyrate	61st/R
479	Methylthiomethyl hexanoate	61st/R
480	Ethyl 3-(methylthio)butyrate	61st/R
488	S- Methyl 4-methylpentanethioate	61st/R
489	S- Methyl hexanethioate	61st/R
495	1- Methylthio-2-propanone	61st/R
502	Di(butan-3-one-1-yl) sulfide	61st/R
504	S- Methyl benzothioate	61st/R,T
519	2- Ethylhexanethiol	61st/R
548	4- Methoxy-2-methyl-2-butanethiol	61st/R
556	3- Mercaptohexyl hexanoate	61st/R
557	1- Mercapto-2-propanone	61st/R,T
559	2- Keto-4-butanethiol	61st/R
568	Allyl methyl disulfide	61st/R
569	Methyl 1-propenyl disulfide	61st/R
570	Propenyl propyl disulfide	61st/R,T
571	Methyl 3-methyl-1-butenyl disulfide	61st/R
583	Methyl ethyl trisulfide	61st/R
586	Allyl methyl trisulfide	61st/R
590	Methyl 2-hydroxy-4-methylpentanoate	61st/R
592	Citronelloxyacetaldehyde	61st/R
603	Ethyl 2,4-dioxohexanoate	61st/R
604	3-(Hydroxymethyl)-2-heptanone	61st/R
605	1,3- Nonanediol acetate (mixed esters)	61st/R,T
615	Butyl ethyl malonate	61st/R,T
625	Dibutyl sebacate	61st/R
628	Ethyl aconitate (mixed esters)	61st/R,T
631.2	3-Methyl-2-oxobutanoic acid, sodium salt	61st/R,T
632.2	3-Methyl-2-oxopentanoic acid, sodium salt	61st/R,T
633.2	4-Methyl-2-oxopentanoic acid, sodium salt	61st/R,T
668	Linalyl cinnamate	61st/R
669	Terpinyl cinnamate	61st/R
704	p- Tolyl laurate	61st/R
735	2- Phenylphenol	61st/R
737	2,3,6- Trimethylphenol	61st/R
918	Glyceryl monostearate	61st/R
923	Glycerol 5-hydroxydecanoate	61st/R
924	Glycerol 5-hydroxydodecanoate	61st/R
937	Pyruvaldehyde	61st/R

[a]R, existing specifications revised; S, existing specifications were maintained; T, the existing, new, or revised specifications are tentative and new information is required.

6. Evaluation of a water-treatment agent

Agent	Specifications [a]	Tolerable daily intake (TDI) and other toxicological recommendations
Sodium dichloroisocyanurate (NaDCC)	N	0-2.0 mg /kg of body weight for anhydrous NaDCC; applicable for intake from drinking-water treated with NaDCC for the purpose of disinfection

7. Evaluation of a nutritional source for iron

Source	Specifications [a]	Toxicological recommendation
Ferrous glycinate (processed with citric acid)	N	Suitable for use as a source of iron for supplementation and fortification, providing that the total intake of iron did not exceed the provisional maximum tolerable daily intake of 0.8mg/kg body weight/day

8. Contaminants

Contaminant	Tolerable intake and other toxicological recommendations
Cadmium	Provisional tolerable weekly intake (PTWI) of 7 µg/kg bw (maintained)
Methyl mercury	Provisional tolerable weekly intake (PTWI) of 1.6 µg/kg bw

Annex 1

Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Rome, 10-19 June 2003

Members

Dr Christopher E. Fisher, Hatfield, Herts, UK

Dr David G. Hattan, Food and Drug Administration, College Park, MD, USA

Dr Yoko Kawamura, National Institute of Health Sciences, Tokyo

Dr Paul M. Kuznesof, Food and Drug Administration, College Park, MD, USA

Dr Inge Meyland, The Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark *(Chairman)*

Dr Gérard Pascal, Institut National de la Recherche Agronomique (INRA), Paris, France

Dr Madduri Veerabhadra Rao, Central Laboratories Unit, U.A.E. University, Al Ain, United Arab Emirates

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

Dr Gerrit J.A. Speijers, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, The Netherlands

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

Dr Philippe Verger, National Institute for Agricultural Research, SAFE Consortium on food safety, Brussels, Belgium

Prof Ronald Walker, School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey, United Kingdom *(Vice-Chairman)*

Dr Harriet Wallin, National Food Agency, Helsinki, Finland

Dr Donald Brian Whitehouse, Bowdon, Cheshire, UK

Secretariat

Dr Peter J. Abbott, Food Standards Australia New Zealand (FSANZ), Canberra, Australia *(WHO Temporary Adviser)*

Dr David C. Bellinger, Harvard Medical School, Children's Hospital, Boston, MA, USA *(WHO Temporary Adviser)*

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

Dr Simon Brooke-Taylor, Woonona, NSW, Australia *(WHO Temporary Adviser)*

Dr Richard C. Cantrill, AOCS, Champaign IL, USA *(FAO Consultant)*

Dr Michael DiNovi, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD, USA *(WHO Temporary Adviser)*

Ms S. Kathleen Egan Center for Food Safety & Applied Nutrition, Food and Drug Administration (FDA), College Park, MD, USA *(WHO Temporary Adviser)*

Mr Teru Ehara, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland *(WHO Staff Member)*

Mr John Fawell, Bucks, United Kingdom *(WHO Temporary Adviser)*

Mr Mark Feeley, Bureau of Chemical Safety, Food Directorate, Health Canada, Ottawa, ON, Canada(WHO Temporary Adviser)

Prof Fujio Kayama, Division of Environmental Immunology & Toxicology, Department of Health Science, Jichi Medical School, Tochigi, Japan *(WHO Temporary Adviser)*

Prof Robert Kroes, Institute for Risk Assessment Sciences, Utrecht University, Soest, The Netherlands *(WHO Temporary Adviser)*

Dr Charles A. Lawrie, Novel Foods Division, UK Food Standards Agency, London *(FAO Consultant)*

Dr Catherine Leclercq, National Research Institute for Food and Nutrition (INRAN), Rome, Italy *(FAO Consultant)*

Dr Enedina Lucas Vinuela, National Public Health Institute, Santiago, Chile *(FAO Consultant)*

Dr Manfred Luetzow, Food and Nutrition Division, Food and Agriculture Organization of the United Nations (FAO), Rome, Italy (*FAO Joint Secretary)*

Dr Antonia Mattia, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, College Park, MD, USA *(WHO Temporary Adviser)*

Dr Heidi Mattock, St Jean d'Ardières, France *(Editor)*

Dr Gerald Moy, Food Safety Department, World Health Organization, Geneva, Switzerland *(WHO Staff Member)*

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

Dr Akiyoshi Nishikawa, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan *(WHO Temporary Adviser)*

Dr Zofia Olempska-Beer, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD, U.S.A. *(FAO Consultant)*

Dr Sam Page, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland *(Acting WHO Joint Secretary)*

Mrs Ir 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)*

Dr Silvia Liliana Resnik, Comision de Investigaciones Cientificas, La Plata, Pcia de Buenos Aires, Argentina *(FAO Consultant)*

Dr Sushil Kumar Saxena, SGS India Pvt. Ltd., Gurgaon (Haryana), India *(FAO Consultant)*

Mrs Nathalie Scheidegger, Ministry of Agriculture, Nature Management and Food Quality, The Hague, Netherlands (WHO Temporary Adviser)

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

Dr James Smith, Prince Edward Island Food Technology Centre, Charlottetown, PE, Canada *(FAO Consultant)*

Dr Ivan Stankovic, Institute of Bromatology, Faculty of Pharmacy, Belgrade, Serbia and Montenegro *(FAO Consultant)*

Dr Chiharu Tohyama, Environmental Health Sciences Division, National Institute for Environmental Studies, Tsukuba, Japan *(WHO Temporary Adviser)*

Dr Angelika Tritscher, Department Quality and Safety Assurance, Nestlé S.A., Lausanne, Switzerland, *(WHO Temporary Adviser)*[*]

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

[*] Appointed WHO Joint Secretary

Annex 2

Further information required or desired

Annatto extracts

The Committee requested additional information to clarify the role that the non-pigment components of the extract play in the expression of the qualitative and quantitative differences in toxicity of the various extracts. In addition the Committee requested data on reproductive toxicity of an extract, such as Annatto F, that contains norbixin.

Monomagnesium phosphate, trisodium diphosphate

Information on the method for loss on drying for the hydrates is necessary in order to express the assay on the dry basis for the above additives. Requested by end of 2004.

D-Tagatose

The Committee requested information on the histological examination of the adrenals, kidneys and testes of the rats from the two-year study by 2006.

Annex 3

An edited version of this section will appear in the report of the sixty-first 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 extensive editing.

General considerations

1. Working definition of "flavouring agent"

At its 59th session, the Committee recognised the need for a working definition of the term "flavouring agent" and recommended that such a definition be agreed at a future meeting. At the present meeting, the Committee noted that a range of regulatory definitions of "flavouring" and similar terms exist in different countries and concluded that any definition would need to be elaborated in an international forum such as Codex.

The Committee re-iterated the criteria that generally need to be met for an individual flavouring agent to be evaluated according to the existing procedure for the safety evaluation of flavouring agents:

- The substance should be chemically defined, so that at least 95% of the commercially used material consists either of the named chemical, or of the named chemical and identified secondary constituents
- The substance is added to food for flavouring purposes, including the generation of active flavouring substances during storage or processing of the food
- There is a valid estimate of current exposure to the named substance and, if appropriate, its breakdown or reaction products.

Some substances that have a use as flavouring agents may have previously been evaluated by JECFA in relation to other food additive functions. The use of such a flavouring agent, or its products, is included in the relevant ADI.

2. Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food

The Committee was informed about the progress of this Project and recognized its importance. The Committee noted that several issues being considered by this Project were of particular relevance to some of their present evaluations:

- dose–response modelling of endpoints which cannot be assigned a threshold, both carcinogenic and non-carcinogenic
- probabilistic modelling for estimation of intake
- biomarkers of effect and their relationships to disease outcome
- relevance of reversible, non-progressive treatment-related effects
- longer tolerable intake periods, e.g. PTMI, for contaminants with longer biological half-lives
- revision of the approach to the safety evaluation of flavouring agents, in order to accommodate natural flavours
- approaches for the development of specifications for complex mixtures, particularly those of natural origin.

3. Compendium of food additive specfications and Guide to specifications

At 46th and the 55th meeting the Committee had recommended the revision of the *Compendium of food additive specfications* and *Guide to specifications*. At the present meeting the Secretariat presented a project that had been proposed recently to FAO with the following objectives:

To update the current edition of the *Guide to specifications* and to publish it together with a consolidated edition of the Compendium of Food Additive Specifications as one document in two volumes. The new edition shall reflect current state of the art of analytical methodologies and practice by regulators and industry. These methods need also to respect the fact that they are applied by laboratories in developing and developed countries with different levels of equipment and expertise.

The update shall consider the general guidelines laid out by JECFA and the Joint FAO/WHO Conference on Food Additives (summarized in EHC 70) and the work of other relevant standard setting bodies. The update shall be available in print and electronically. Depending on the availability of funds the project will start during 2003 and will terminate in 2005.

4. Consideration of Flavouring Agents with High Intakes Evaluated Using the "B" Side of the Safety Evaluation Procedure

At the present meeting, two flavouring agents, dihydrocoumarin (No. 1171) and 6-methylcoumarin (No. 1172) evaluated using the Procedure for the Safety Evaluation of Flavouring Agents could not be predicted to be metabolised to innocuous end products (step B2) and their intake exceeded the human intake threshold for their structural class at step B3. In accordance with the Procedure, these substances required more extensive toxicity data to complete their evaluation. In considering substances requiring more extensive data, the Committee noted that such data would include metabolism and toxicity studies on the substance. In addition refined estimates of intake may be needed. Data on structurally-related substances may also be used to support the evaluation. These studies would need to be of sufficient quality and duration to evaluate the flavouring agent at its specified intake.

The Committee noted that flavouring agents requiring more extensive data be clearly identified in the report of the meeting and that a complete description of the evaluation of such flavouring agents be provided in the report item and monograph. The Committee recommended that the guidelines for the preparation of monographs for flavouring agents be revised to ensure that a consistent approach is applied to the evaluation of such substances.

5. Safety Evaluation of Natural Flavouring Complexes

At the present meeting, the Committee considered a working paper outlining a revision to the safety evaluation of flavouring agents to accommodate the safety evaluation of natural flavourings that are complex mixtures (natural flavouring complexes). These flavourings are obtained from a single source material by physical processes such as distillation, or extraction with water or organic solvents. Many natural flavouring complexes consist of mixtures of individual flavouring agents, several of which have been previously evaluated by the Committee. The revised Procedure builds on the Procedure for the Safety Evaluation of Flavouring Agents (Annex 1, Reference 131). The revised Procedure organizes the components of a natural flavouring complex into congeneric groups, which become the focus of the safety evaluation. The steps in the existing Procedure have been modified to accommodate the evaluation of congeneric groups and provide for an overall evaluation of the natural flavouring complex.

In considering the revised Procedure, the Committee noted that several hundred natural flavouring complexes were currently in commercial use. These include essential oils, which are relatively well characterized in terms of their chemical composition, as well as extracts and oleoresins, some of which are currently less well characterized. Since compositional data are required to complete a safety evaluation using the revised Procedure, the Committee noted that further modification of the Procedure may be required for natural flavouring complexes that cannot be well characterized in terms of their composition.

The Committee concluded that the revised Procedure provides a potentially efficient way of evaluating natural flavouring complexes that are well characterized, such as essential oils. To determine the applicability of the revised Procedure, the Committee recommended that a small number of natural flavouring complexes be evaluated at a future meeting.

The Committee noted that numerous products from different geographical regions are used as flavouring complexes, and the importance of ensuring that an inventory of commercial products be compiled was stressed. The Committee considered it necessary to take account of the range of composition of natural flavouring complexes across all regions.

The Committee is aware that different organizations have different approaches to the establishment of specifications for natural flavouring complexes. The Committee also noted that criteria would need to be developed to elaborate specifications for natural flavouring complexes.

6. Provision of scientific advice by FAO and WHO

The Committee was informed about a consultative process initiated by FAO and WHO, which will consider the provision of scientific advice by both organizations to the Codex Alimentarius Commission and to Member countries.

Such advice may be elaborated by committees, such as JECFA, ad hoc consultations or consultants. This process is designed to improve the scientific advice provided with regard to quality, independence, integrity, transparency, timeliness, efficiency and sustainability. The outcome of the process will be a set of recommendations, addressed to the Directors-General of FAO and WHO, for the development of a consistent, harmonized and flexible over-arching framework ("umbrella"), which is realistic, feasible and acceptable to all stakeholders.

The Committee noted that this exercise would take into consideration and build upon the experience of, and the improvements already being implemented by the Secretariat of this Committee.

Maria Lourdes Costarrica (FAO) and Wim van Eck (WHO) are responsible for the coordination of this consultative process.

7. Use of maximum levels for food additives in intake assessment

The Committee assesses the dietary exposure to food additives using a tiered approach according to the JECFA guidelines (www.fao.org/es/ESN/jecfa/index_en.stm / www.who.int/pcs/jecfa/jecfa.htm). One of these tiers consists of combining estimated food intakes from various geographical regions with the draft proposed Maximum Levels (draft MLs) of additives for the Codex General Standard on Food Additives (GSFA).

The Committee observes that, in most cases, the MLs in Codex standards are higher than the typical use levels reported by governments and industry. For example, at the present meeting the Committee evaluated annatto extracts and noted that they are used at a level of 35 mg/kg in Mimolette cheese. However, a ML of 600 mg/kg is proposed in the GSFA for all cheese. This example also illustrates that some food additives are listed in the GSFA for use in very broad food categories when they are in reality, used in a very limited number of applications.

When draft MLs are the only available information on additive use levels in food, the estimation of the intake using high proposed GSFA levels have resulted in unrealistic intake estimates. In some cases these intake estimates were many times the corresponding ADI. Consequently, the Committee suggests that the CCFAC may wish to review MLs with the intent to lower them or restrict their use to food subcategories, as appropriate. Alternatively, CCFAC may consider providing the Committee with typical use levels to allow for more realistic exposure assessments.

8. Chemical and Technical Assessments

At previous meetings the Committee had access to documents prepared for new or existing food additives (*Technical Data Sheets*) that were used internally because detailed information on manufacturing processes described therein could contain commercially sensitive data. These documents, however, also contain valuable information on chemical and technological aspects of compounds under discussion which was not made public. At its 59th meeting the Committee recommended that comprehensive information on technological use levels for foods should be included in this document which should also form the basis for intake assessment. Furthermore, the importance of specifications as an integral part of the risk assessment of food additives was stressed.

Considering these recommendations the Secretariat has adapted the format and structure of the *Technical Data Sheet* and renamed it the *Chemical and Technical Assessment (CTA)* with the intention of making this document publicly available. The *CTA* reflects and emphasises the role chemical characterization plays in the risk assessment of food additives. The document is prepared by an expert assigned before the meeting. The document is intended to provide to the Committee the basic information related to identity, purity and use of the food additive, as related to its risk assessment.

The drafting expert responsible for preparing a *CTA* is asked to identify those sections of a confidential nature and the Secretariat will ensure their removal before publication. The *CTA*s will be available via the FAO JECFA website; it is not anticipated to publish them in print.

At the present meeting the Committee reviewed the first set of CTA for certain food additives and provided feedback to the Secretariat on the *FAO guidelines on the structure and content of the document called "Chemical and Technical Assessment (CTA)"*.

Annex 4

The Committee reviewed new data for cadmium and methyl mercury and took note of additional submissions related to these contaminants. This section of the report will be edited extensively before its formal publication. This draft is being made available so that the information is disseminated quickly, particularly for use by the Codex Committee on Food Additives and Contaminants and for consideration by interested third parties.

Cadmium

Cadmium was evaluated at the sixteenth, thirty-third, forty-first and fifty-fifth meetings of the Committee. At the sixteenth meeting, the Committee allocated a Provisional Tolerable Weekly Intake (PTWI) of 400-500 µg of cadmium per person. At the subsequent three meetings, the Committee retained this PTWI, but expressed it in terms of the intake of cadmium per kg of body weight (7 µg per kg of body weight). At the fifty-fifth meeting, the Committee concluded that the prevalences of renal tubular dysfunction that correspond to various intakes of dietary cadmium could serve as a reasonable basis for risk assessment. The Committee concluded that the risk of excess renal tubular dysfunction in the population would be negligible below a urinary cadmium excretion of 2.5 µg/g of creatinine. The Committee noted, however, that these estimates are based on a model that is dependent on the values assumed for key parameters (e.g. dietary bioavailability, age dependency of the intake/excretion ratio). Although new information indicated that a proportion of the general population may be at increased risk of tubular dysfunction at the current PTWI of 7 µg/kg bw, the Committee maintained the PTWI at this value because of lack of precision in the risk estimates. The Committee made several recommendations regarding the types of data that would be needed in order to reduce the uncertainty in the prevalence estimates. A considerable number of new studies addressed certain aspects of the issues identified in these recommendations and served as the basis for the Committee's deliberations at the present meeting.

Animal studies

In test species, the oral bioavailability of cadmium ranges on average from 0.5 to 3.0%. Experimental studies have also identified various factors that can significantly influence the extent of cadmium absorption and retention from the diet. These factors include sex, developmental stage, and nutritional status. Low dietary concentrations of protein and of essential minerals such as zinc, calcium, copper, and iron have been shown to promote cadmium absorption while, in contrast, high or adequate dietary concentrations reduce cadmium absorption and retention. Following absorption, cadmium is distributed mainly to the liver, with subsequent redistribution to the kidney in conjugated forms such as cadmium–metallothionein and cadmium–albumin.

Chronic oral exposure to cadmium can result in a variety of progressive histopathological changes in the kidney, including proximal tubule epithelial cell damage, interstitial fibrosis, and glomerular basal cell damage with limited tubular cell regeneration. Biochemical indications of renal damage are seen in the form of low molecular weight proteinuria, glucosuria and aminoaciduria. Tubular dysfunction also results in increased urinary cadmium excretion. Decreases in bone calcium levels and increased urinary excretion of calcium have also been associated with exposure to cadmium. Cadmium can induce malignant transformation of animal and human cells *in vitro*.

Investigations into the ability of cadmium compounds to induce developmental effects in experimental animals have shown that decreased fetal weight, skeletal malformations and increased fetal mortality are common findings, usually in combination with indices of maternal toxicity. However, developmental neurobehavioural effects, including decreased locomotor and exploratory activity and certain electrophysiological changes, have been seen in the absence of any overt symptoms of maternal toxicity and appear to be a more sensitive indicator of toxicity.

Variable immune system effects have been observed in cadmium-exposed experimental animals, including increased virus-induced mortality in mice co-exposed to non-lethal doses of cadmium and RNA viruses.

Human studies

A number of new epidemiologic studies have been published since the fifty-fifth Report. These studies have evaluated the relationships of cadmium exposure to various health effects, particularly renal dysfunction, mortality, and calcium/bone metabolism.

Cadmium accumulates in the kidney, and because of its long half-life in humans, steady-state concentrations in the renal cortex are reached only after about 40 years.

Recent studies conducted in Japan, Europe, China, and the United States have attempted to refine estimates of the dose–effect/dose–response relationship between environmental exposure to cadmium and renal dysfunction. In a Swedish study (OSCAR) of more than 1,000 individuals aged 16-80 years, the group with a urinary cadmium level of 0.5-1 μg/g creatinine, compared to the group with cadmium levels of <0.3 μg/g creatinine, had a nearly three-fold increase in the prevalence of tubular proteinuria. Above a urinary cadmium level of 5 μg/g creatinine, the prevalence of tubular proteinuria was increased five-fold. Two studies of populations with low levels of urinary cadmium (means of 0.23 μg/g creatinine and 0.26 μg/g creatinine) found associations between markers of early kidney damage and urinary cadmium levels. However, the findings were inconsistent between these two studies, although urinary β_2-microglobulin and N-acetyl-β-D-glucosaminidase (NAG) were measured in both studies as indices of tubular dysfunction. In one study, only β_2-microglobulin was associated with urinary cadmium level while in the other study, only NAG was associated with urinary cadmium level. In an ecologic study, the prevalence of end-stage renal disease was significantly, although modestly, related to the extent of environmental cadmium exposure, as determined by area of residence. However, individual biomarkers of exposure were not measured in this study. In aggregate, the new data are consistent with the hypothesis that low-level environmental exposure to cadmium is associated with an increased prevalence of proximal renal tubular dysfunction, as assessed by biomarkers.

The epidemiological studies conducted in regions of Japan with varying levels of environmental cadmium identified several issues that make the interpretation of studies of low environmental cadmium exposure and renal function difficult. In some studies, a crude association between urinary cadmium and a biomarker of effect disappeared after adjusting for age. Simple adjustment for creatinine might be misleading if comparisons involve people differing in physique, physical activity, sex, age, and race. The appropriate levels of urinary biomarkers to use as cut-off values for identifying tubular proteinuria might also vary depending upon physiological or disease conditions. Finally, the long-term health implications of the changes in renal function observed at low urinary cadmium levels are uncertain.

It is well-established that cadmium-induced low molecular weight proteinuria can progress to an acquired Fanconi syndrome (the continuous loss of calcium and phosphorus into urine) and/or the disturbance of vitamin D metabolism in the damaged kidneys. The latter may eventually progress to Itai-itai disease, characterized by osteomalacia.

Some recent reports suggest that environmental exposure to cadmium, even at low levels, may alter calcium metabolism in bone tissue independently of the renal effects, and may increase the risk of osteoporosis and bone demineralization. Bone mineral density studies conducted on participants in the OSCAR study indicated that the age- and sex-adjusted risk of having reduced bone density was increased two-fold among individuals with blood-cadmium levels of 0.6 to 1.1 μg/L and three-fold for individuals with blood-cadmium levels above 1.1 μg/L. Two studies, one in Belgium and one in Japan, corroborated this association, but bone mineral density was correlated with age and body weight, and only weakly with urinary cadmium concentration. Two studies in Japan, one in which environmental cadmium exposure was moderate and one in which it was high, showed no correlation between cadmium exposure and bone mineral density or calcium excretion, after adjustment for age, body mass index, and menstrual status. Calcium excretion was not correlated with cadmium exposure, but with deterioration of renal tubular function, which was due mainly to ageing.

Bone metabolism is influenced by many factors, such as age, oestrogen status, physique, physical activity, nutritional status, ethnic group, and environmental factors such as sunlight. None of the studies adjusted for possible confounding by all of these factors. These studies were therefore considered by the Committee to be preliminary.

The Committee reviewed additional studies investigating the associations between cadmium exposure and other non-renal health effects, including diabetes, hypertension, carcinogenicity, reproductive outcomes, and neurotoxicity. The Committee found the results of these studies to be too preliminary to serve as the basis for its evaluation. The Committee took note, however, of a study that indicated that, among individuals without evidence of renal disease, the prevalence of type 2 diabetes was significantly increased at urinary cadmium levels exceeding 1 μg/g creatinine. Further work is needed to clarify the contribution of cadmium exposure to this disease.

Dietary intake

At the 55th meeting of JECFA in 2000, the Committee evaluated dietary intake of cadmium based on data from a number of countries. For the current meeting, the Committee updated its review by including new information from Australia, Croatia, France, Greece, Japan, Lithuania, Nigeria, Slovakia, Spain, and the European Union. The combined data show that cadmium concentrations in most foods range from about 0.01 to 0.05 mg/kg, although higher levels were found in nuts and oil seeds, molluscs, and offal (especially liver and kidney). Estimates of mean intake of cadmium based on national studies ranged from 0.7 to 6.3 μg/kg of body weight per week. Mean dietary intakes derived from WHO GEMS/Food Regional Diets (based on food balance sheets) and average cadmium concentrations in those regions range from 2.8 to 4.2 μg/kg of body weight per week. These estimates constitute

approximately 40 to 60% of the current PTWI of 7μg/kg of body weight. Because total food consumption for high consumers is estimated to be about twice the mean, total cadmium intake may exceed the PTWI for some individuals. Regarding the major dietary sources of cadmium, the following foods contributed 10% or more to the PTWI in at least one of the GEMS/Food regions: rice, wheat, starchy roots/tubers, and molluscs. Vegetables (excluding leafy vegetables) contribute >5% to the PTWI in two regions.

Evaluation

The Committee considered an extensive amount of new information, particularly from a series of Japanese environmental epidemiological studies, that addressed issues identified as research needs in the Committee's report from the fifty-fifth meeting. The Committee reaffirmed its conclusion that renal tubular dysfunction is the critical health outcome with regard to cadmium toxicity. Although some recent Japanese, European, and USA studies using sensitive biomarkers indicated that changes in renal function and bone/calcium metabolism are observed at urinary cadmium levels below 2.5 μg/g creatinine, the Committee noted that appreciable uncertainty remains regarding the long-term health significance of these changes. In addition, the Committee noted inconsistencies among studies in the specific biomarkers of renal function most commonly associated with urinary cadmium levels. Although recent studies suggest that increased cadmium biomarker levels are associated with health effects such as diabetes, hypertension, pancreatic cancer, fetal growth, and neurotoxicity, the Committee concluded that these data are not, at this time, sufficiently robust to serve as a basis for the evaluation. The Committee reaffirmed its conclusion that an excess prevalence of renal tubular dysfunction will not be expected to occur if urinary cadmium level remains below 2.5 μg/g creatinine, even under a range of plausible assumptions about the relationship between the amount of cadmium bioavailable from the diet and the urinary excretion of cadmium. Uncertainty remains about how these assumptions affect the predicted excess prevalence of renal tubular dysfunction at urinary cadmium levels above 2.5 μg/g creatinine. The Committee concluded that the new data available since the fifty-fifth meeting do not provide a sufficient basis for revising the PTWI and therefore maintained the current PTWI of 7 μg/kg body weight. No excess prevalence of tubular dysfunction would be predicted to occur at the current PTWI under the most appropriate assumptions about the fractional bioavailability of cadmium and the percentage of absorbed cadmium that is excreted in urine. The Committee noted that two issues being considered by the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food are of particular relevance to the present evaluation: the dose-response assessment of biomarkers of effect and their relation to disease outcome, and the possible specification of longer tolerable intake periods (e.g., PTMI) for contaminants with longer biological half-lives. The Committee recommended that the evaluation of cadmium be revisited when this project is completed.

Methylmercury

Methylmercury was previously evaluated at the sixteenth, twenty-second, thirty-third and fifty-third meetings of JECFA (Annex 1, reference *144*). At the latter meeting, the Committee reaffirmed the previously established Provisional Tolerable Weekly Intake (PTWI) for methylmercury of 200 μg (3.3 μg per kg of body weight) for the general population, but noted that the fetus and infants may be at a greater risk of toxic effects. The Committee concluded that data from studies undertaken in the Seychelles and Faroe Islands, which were evaluated at the fifty-third meeting, did not provide consistent evidence concerning the neurodevelopmental effects on children of mothers whose methylmercury intakes resulted in hair-mercury burdens of 20 mg/kg and below. Adverse effects on neurodevelopment were reported in the Faroes Island studies, but not in the Seychelles Islands study. However, different neurobehavioural assessment methods had been used for the different cohorts. The Committee recommended that methylmercury be re-evaluated in a subsequent meeting in order to consider the analysis of the eight-year neurodevelopmental evaluations of the Seychelles cohort and other relevant data that might become available. The Committee noted that fish make an important nutritional contribution to the diet, especially in certain regional and ethnic diets, and recommended that when considering setting limits for methylmercury concentration in fish or on fish consumption, nutritional benefits should be weighed against the possibility of adverse effects. Studies published since the fifty-third meeting were considered at the present meeting.

Observations in animals

In its previous assessment, the Committee reviewed an extensive collection of experimental data which indicated that the developing nervous system, particularly in non-human primates, is a sensitive target for methylmercury.

In all experimental animal species evaluated, methylmercury is readily absorbed (up to 95%) following oral exposure. Methylmercury effectively crosses both the blood–brain barrier and the placenta, resulting in higher levels of mercury in the fetal than the maternal brain. The major route of methylmercury elimination is in the bile and faeces, with neonatal animals having a lower excretory capacity than adults. Experimental evidence indicates a possible protective effect of selenium against some aspects of methylmercury toxicity, but results are conflicting.

Ataxia, paralysis, loss of coordination, and hind limb crossing are common neurological signs of methylmercury exposure in rodents. Changes in behaviour, decreased activity, and deficiencies in learning and memory are also observed. In rodents, methylmercury neurotoxicity usually becomes evident at doses that also affect other organ systems. Neurotoxic effects observed in non-human primates are consistent with the symptoms of Minamata disease, the syndrome observed in humans poisoned with methylmercury via the consumption of contaminated seafood. The nature and severity of symptoms are dependent on dose and duration of exposure, as well as developmental stage. From a mechanistic perspective, methylmercury exposure *in vitro* disrupts intracellular calcium homeostasis, induces reactive oxygen species and oxidative DNA damage, and inhibits axonal morphogenesis and cell cycle progression in neuroepithelial cells.

In rodents, treatment of pregnant females with methylmercury induces abortions, increases fetal resorption and malformations, and reduces offspring viability. Methylmercury also affects the rodent immune system, inducing reduced mast cell function and, at high oral doses, decreased spleen and thymus cell viability.

Observations in humans

At its fifty-third meeting, the JECFA noted that methylmercury can induce toxic effects in several organ systems (nervous system, kidney, liver, reproductive organs), and the present Committee confirmed that neurotoxicity is considered the most sensitive endpoint. In humans, indices of neurotoxicity include neuronal loss, ataxia, visual disturbances, impaired hearing, paralysis and death. Both the central and peripheral nervous systems exhibit signs of methylmercury-induced damage.

Information about the neurotoxicity of chronic fetal exposure to low doses of methylmercury has come primarily from epidemiological studies of populations in which fish consumption is relatively high. The results of neurodevelopmental assessments of the Seychelles Child Development Study cohort at 8 years of age are consistent with results obtained at younger ages, and provide no evidence for inverse associations between maternal methylmercury exposure and neurodevelopment in children. Many of the neuropsychological test instruments included in the battery were the same as those used in the Faroe Islands cohort study and which had been observed to be associated, in 7-year-old children, with biomarkers of prenatal methylmercury exposure. In addition, further analyses of data from the assessments of the Seychellois children that were conducted at 5.5 years of age have been published, which include the application of alternative statistical approaches, the adjustment for additional potential confounding factors, and more detailed evaluation of specific test scores. The results of these analyses did not alter the conclusion that in this population of frequent fish-consumers, no adverse effects of prenatal methylmercury exposure have been detected.

No new data from the main Faroe Islands study were available. Additional analyses of the assessments conducted at seven years of age were carried out to explore the issue of age- and test-dependent variation on susceptibility to methylmercury. Analyses were also conducted to evaluate the extent to which the methylmercury-associated neuropsychological deficits in this cohort are attributable to episodes of higher methylmercury exposure during pregnancy (associated with whale-meat meals), residual confounding due to concomitant exposure to PCBs, and methylmercury-associated effects on children's visual function. The analyses did not support a role for any of these factors in accounting for the positive associations in this study.

In a second smaller cohort assembled in the Faroe Islands (182 infants), prenatal methylmercury exposure was found to be inversely related to newborn neurological status and to postnatal growth at 18 months of age. The association was still present after adjusting for exposure to 28 PCB congeners and 18 organochlorine pesticides or their metabolites.

A small number of new epidemiological studies of neurodevelopment were reported, although these were cross-sectional rather than prospective in design, involved much smaller sample sizes than either the Seychelles or Faroe Islands studies, and, in most cases, higher methylmercury exposures. A cross-sectional study of adult neurotoxicity reported significant mercury-associated neurobehavioural deficits in a sample in which the current hair-mercury level of all participants was below 15 mg/kg. Because of the cross-sectional design of this study and because an adult's hair-mercury level does not accurately reflect past levels during the critical exposure period for neurodevelopment, the Committee considered that these results could not form the basis of a dose–response assessment.

Additional epidemiological studies have addressed issues such as reproductive toxicity, immunotoxicity, cardiotoxicity, and general medical status. With regard to reproductive toxicity, a methylmercury-associated decrease in the ratio of male:female births in the area of Minamata City during the period of peak pollution was reported, but the ratio subsequently returned to control levels. In a case–control study, higher blood mercury levels were found among infertile than fertile couples. With respect to cardiotoxicity, in a cohort study, hair-mercury levels of 2 mg/kg or greater were associated with a doubling of the risk of suffering an acute myocardial infarction and, over a 4-year follow-up interval, with increased atherosclerotic disease. The results of two large case–control studies investigating

mercury exposure and coronary heart disease were in conflict with one another, however, one study reporting significantly higher toenail-mercury levels in cases than in controls whereas the other reported similar toenail-mercury levels in both groups. In the latter study, half the participants were dentists and had levels of toenail-mercury that were twice as high as those of non-dentists, suggesting that much of their exposure was to metallic mercury rather than to methylmercury. In another study, high fish consumption, the primary route of methylmercury exposure, was associated with an increased risk of stroke, but no biomarkers of mercury exposure were measured. The Committee determined that the available evidence on the potential cardiotoxicity of methylmercury is not conclusive, but noted that further studies are needed. With regard to general health status, the rates of liver disease, renal disease, and diabetes mellitus were not significantly increased as a function of proximity to Minamata Bay, although the frequencies of many neurological and neuromuscular symptoms were higher.

Dose–response assessments

The Committee concluded that neurotoxicity resulting from *in utero* exposure should be considered to be the most sensitive health outcome for methylmercury toxicity. A number of dose–response assessments have been conducted using the data from the three major epidemiological studies of fetal neurotoxicity, conducted in the Faroes Islands, Seychelles Islands, and New Zealand. These assessments were based on evaluations made of children at 7 years of age in the Faroes Islands study, 5.5 years of age in the Seychelles Islands study, and 6 years of age in the New Zealand study. A comprehensive dose–response assessment using the data from the evaluations of the children in the Seychelles Islands study at 8 years of age has not yet been reported, but the study results were similar to those obtained at 5.5 years of age. Mercury in maternal hair and/or cord blood served as the primary biomarkers of *in utero* exposure to methylmercury in the Faroe Islands and Seychelles Islands studies. Based on a consideration of numerous publications, the Committee confirmed the validity of these biomarkers for both short-term (blood) and longer-term (hair) intake of methylmercury.

The maternal hair-mercury concentration corresponding to a no observed effect level (NOEL) for neurobehavioural effects was identified for the Seychelles Islands study, and a mathematical analysis of the concentration–response relationship was used to determine a benchmark dose lower confidence limit (BMDL) for the Faroes Islands and New Zealand studies. The Committee noted that one child (of the 237) in the New Zealand study sample had a large impact on the BMDLs. The maternal hair-mercury level for this child was 86 mg/kg, more than four times the next highest maternal-hair mercury level in the study sample. Including this observation produced BMDLs of 17 to 24 mg/kg, while omitting it produced BMDLs of 7.4 to 10 mg/kg. Because of uncertainty about which set of BMDLs is most valid, the Committee decided to base the evaluation only on the Faroe Islands and Seychelles Islands studies. The Committee noted, however, that including the New Zealand study did not materially alter the conclusions of the evaluation.

Table: Estimates of maternal hair concentrations associated with the NOEL/BMDL for neurotoxicity associated with in utero exposure

Study	N	NOEL/ BMDL
Faroes	917	12 mg/kg maternal hair[1]
Seychelles	711	15.3 mg/kg maternal hair[2]
Composite		14 mg/kg maternal hair

[1] Budtz-Jorgensen et al., 1999, 2000, 2001; U.S. National Research Council, 2000; Rice et al., 2003

[2] U.S. ATSDR, 1999

The Committee used the average from the two studies, 14 mg/kg maternal hair-mercury, as an estimate of the level in maternal hair reflecting exposures that would be without appreciable adverse effects in the offspring in these two study populations.

Calculation of the steady-state ingestion (μg/kg bw/day) of methylmercury from a maternal hair-mercury concentration requires two steps to be taken into account; conversion of the concentration in maternal hair to that in maternal blood, and conversion of the maternal blood concentration into maternal intake.

The ratio of the concentration of methylmercury in hair to that in blood has been determined in a number of studies, using samples from different study groups and with a variety of analytical methods. The mean hair:blood ratios reported in different studies were mostly in the range 140-370. The Committee used a value of 250 to represent the overall average ratio. The concentration of methylmercury in maternal blood that would be without appreciable adverse effects in the offspring was calculated to be 0.056 mg/L, determined by dividing a maternal hair concentration of 14 mg/kg by the hair:blood ratio of 250.

In humans, the steady state mercury concentration in blood can be related to the average daily intake using a one-compartment model that incorporates refinements (U.S. NRC, 2000) to the original WHO (1990) formula as follows:

$$d = \frac{C \times b \times V}{A \times f \times bw}$$

where C = mercury concentration in blood (μg/L)
b = elimination rate constant (0.014 $days^{-1}$)
V = blood volume (9% of bw – pregnant female)
A = fraction of the dose absorbed (0.95)
f = the absorbed fraction distributed to the blood (0.05)
bw = body weight (65 kg for pregnant female)
d = dose (μg/kg bw/day)

The Committee used values appropriate to conversion during pregnancy, because this is considered to be the vulnerable life stage. Despite an elimination half-life for methylmercury of approximately two months, the maternal body burden at term would be determined largely by intakes in the second and third trimesters of pregnancy.

Using this equation, the Committee determined that a steady-state daily ingestion of methylmercury of 1.5 μg/kg bw/day would result in the concentration in maternal blood estimated to be without appreciable adverse effects in the offspring in these two study populations.

Dietary intake

The fifty-third meeting of the JECFA in 1999 re-evaluated the safety of methylmercury-contaminated foods, and fish in particular. The re-evaluation included consideration of information on potential intake submitted by numerous national bodies. For most populations, fish is the only significant source of methylmercury in food. Generally, concentrations are below 0.4 mg/kg, but fish at the highest trophic levels may contain methylmercury above 5 mg/kg. Older and larger predatory fish species and certain marine mammals contain the highest levels of methylmercury.

At the current meeting, the committee updated its evaluations of national intakes and the use of biomarkers of exposure for methylmercury, including intake information submitted by Australia, France, Japan, New Zealand, and Slovakia. The Committee also evaluated information published in the literature between 1997 and 2003 concerning levels of mercury and methylmercury in various fish species as well as analyses of methylmercury intake in populations consuming large amounts of fish (>100g/p/d). The committee noted that overall methylmercury levels in fish species were similar to those analysed at the fifty-third meeting and therefore concluded that the analyses of exposure conducted at the fifty-third meeting remain current. These estimates range from 0.3-1.5 μg/kg bw/week for the 5 regional GEMS/Food diets and from 0.1 to 2.0 μg/kg bw/week for numerous nationally-reported diets.

Evaluation

The Committee evaluated new information that became available since methylmercury was considered at the fifty-third JECFA meeting. This information included results of studies performed in laboratory animals and humans, and epidemiological studies investigating possible effects of prenatal methylmercury exposure on child neurodevelopment. Neurodevelopment was considered to be the most sensitive health outcome, and *in utero* exposure the most sensitive period of exposure.

The calculations referred to in the dose response assessment used average values for each parameter, and did not allow for inter-individual variability in either the hair:blood ratio or in the elimination rate constant in the above equation. Potential human variability was taken into account by the application of adjustment or uncertainty factors. In choosing the factors to apply to this intake estimate, the Committee considered the following:

1. Neurodevelopment is a sensitive health outcome, and *in utero* exposure is the critical period for methylmercury neurodevelopmental toxicity. Furthermore, the two study samples represent diverse populations. Therefore, no uncertainty factor is needed to account for variation in vulnerability among subgroups.
2. The available data on the hair:blood ratio show both inter-study and inter-subject variability. No population-specific data on hair:blood ratios are available for the Faroe Islands or Seychelles Islands populations. The majority of published study means are within a range of 140 to 370. Few data were available to the Committee on the range of individual hair:blood ratios. The ratios reported for human individuals in a limited number of studies were in the range 137–585. These individual ratios would include any analytical errors. The ratio from the overall average of 250 to the highest study mean was 1.5 (370/250), while the ratio to the highest individual value was 2.3 (585/250). The Committee concluded that the available data on the distribution of individual ratios were not adequate for derivation of a chemical-specific adjustment factor, and decided to apply a factor of 2 to the overall

average of 250 to allow for the likely inter-individual variability, which is indicated by the differences in study means and by the limited available individual data.

3. Inter-individual pharmacokinetic variability should be taken into account when converting the steady-state concentration of mercury in maternal blood to an estimate of daily intake. As limited pharmacokinetic data specific to the study populations used in this assessment were available, the Committee recommended the use of a combined uncertainty factor of 3.2 (100.5) (WHO, 1999) to account for the total human inter-individual variability for dose reconstruction (converting maternal blood concentration to a steady-state dietary intake).

A steady-state intake of 1.5 µg methylmercury/kg bw/day was estimated to represent the exposure that would be expected to be without appreciable adverse effects in children. A total factor of 6.4 (2 x 3.2) was applied to this figure to derive a PTWI of 1.6 µg/kg bw. This PTWI is considered sufficient to protect the developing fetus, the most sensitive subgroup of the population.

Pending reduction in uncertainty associated with various aspects of the derivation of the steady-state intake from maternal hair, the Committee concluded that the uncertainty factor could be refined and possibly reduced. The Committee also reaffirmed its position that fish are an important part of a balanced nutritious diet and that this has to be appropriately considered in public health decisions when setting limits for methylmercury concentrations in fish. The Committee considered whether a PTMI rather than a PTWI for methylmercury should be developed but deferred this decision pending the outcome of the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food.