Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Fifty-third meeting
Rome, 1-10 June 1999

SUMMARY AND CONCLUSIONS

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 1 to 10 June 1999. The purpose of the meeting was to evaluate certain food additives and contaminants.

Dr P.M. Kuznesof, Acting Deputy Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA, served as Chairman. Professor R. Walker, Emeritus Professor of Food Science, School of Biological Sciences, University of Surrey, Guildford, Surrey, United Kingdom, and Dr Junshi Chen, Deputy Director, Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, China, served as Vice-Chairmen.

Dr J. Weatherwax, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, and Dr J.L. Herrman, International Programme on Chemical Safety, World Health Organization, served as joint secretaries.

The present meeting was the fifty-third in a series of similar meetings. The tasks before the Committee were to (a) elaborate further principles for evaluating the safety of food additives and contaminants; (b) undertake toxicological evaluations of certain food additives and contaminants; (c) review and prepare specifications for selected food additives; and (d) assess the intake of selected food additives and 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.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 1.

Toxicological monographs or monograph addenda on most of the substances that were considered will be published in WHO Food Additives Series No. 44.

Specifications for the identity and purity of the compounds listed in Table 1 marked as N; N,T; R; or R,T will be published in FAO Food and Nutrition Paper Series 52, Addendum 7. Specifications for substances marked as S and S,T have been published previously in that series. However, if these specifications have not been adopted as Codex Advisory Specifications, they will be re-published in FAO Food and Nutrition Paper Series No. 52, Addendum 7.

NOTE

This document has been distributed prior to publication of the full report of the fifty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to ensure the fast dissemination of information, in particular to the Codex Alimentarius Commission, to which JECFA is the scientific advisory body on matters relating to food additives and contaminants.

The FAO and WHO Joint Secretaries of JECFA request that further inquiries regarding the compounds evaluated at the meeting be made only ***after*** *the official report has been published and distributed by WHO in the name of both sponsoring Organizations, FAO and WHO. Your cooperation is very much appreciated*

Table 1

Acceptable Daily Intakes (ADIs), other toxicological information, and information on specifications

1. Food additives

Substance	Specifi-cations[1]	Acceptable Daily Intake (ADI) and other toxicological recommendations
Glazing agent		
Hydrogenated poly 1-decene	R	No ADI allocated[2]
Sweetening agent		
Erythritol	N	ADI "not specified"[3]
Thickener		
Curdlan	N	ADI "not specified" (temporary) [3,4,5]
Miscellaneous substances		
γ-Cyclodextrin	R	ADI "not specified"[3]
Sodium iron EDTA	R	Considered to be safe in food fortification programmes[6]
Sodium sulfate	N,T	ADI "not specified"[3,7]

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; T, the existing, new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

[2] Data were insufficient for establishing an ADI.

[3] ADI "not specified" is applied to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in the individual evaluation, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary.

[4] Applies to food additive uses.

[5] See Table 2.

[6] The Committee concluded that sodium iron EDTA (ethylenediamine tetraacetate) could be considered to be safe when used in supervised food fortification programmes in response to a need for iron supplementation of the diet of a population as determined by public health officials. Such programmes would provide daily iron intakes of approximately 0.2 mg/kg bw.

[7] Temporary ADI pending consideration of the "tentative" qualification of the specifications (see Table 2).

2. Substances evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

A. Aliphatic and aromatic sulfides and thiols

Flavouring agent	No.	Specifi-cations[1]	Conclusions based on current intake
Subgroup A - Simple sulfides (i.e., thioethers)			
Methyl sulfide	452	N	No safety concern
Methyl ethyl sulfide	453	N	
Diethyl sulfide	454	N	
Butyl sulfide	455	N	
(1-Butenyl-1) methyl sulfide	457	N,T	
bis(Methylthio)methane	533	N,T	No safety concern
Allyl sulfide	458	N,T	
Methyl phenyl sulfide	459	N	
Benzyl methyl sulfide	460	N	
Subgroup B - Acyclic sulfides with oxidized side chains			
3-(Methylthio)propanol	461	N,T	No safety concern
4-(Methylthio)butanol	462	N,T	
3-(Methylthio)-1-hexanol	463	N	
2-Methylthioacetaldehyde	465	N,T	
3-(Methylthio)propionaldehyde	466	N,T	
3-(Methylthio)butanal	467	N,T	No safety concern
4-(Methylthio)butanal	468	N,T	
3-Methylthiohexanal	469	N	
2-(Methylthio)methyl-2-butenal	470	N,T	
2,8-Dithianon-4-ene-4-carboxaldehyde	471	N,T	
Methyl 3-methylthiopropionate	472	N	No safety concern
Methylthiomethyl butyrate	473	N,T	
Methyl 4-(methylthio)butyrate	474	N	
Ethyl 2-(methylthio)acetate	475	N,T	
Ethyl 3-methylthiopropionate	476	N	
Ethyl 4-(methylthio)butyrate	477	N	No safety concern
3-(Methylthio)propyl acetate	478	N,T	
Methylthiomethyl hexanoate	479	N,T	
Ethyl 3-(methylthio)butyrate	480	N,T	
3-(Methylthio)hexyl acetate	481	N,T	
1-Methylthio-2-propanone	495	N,T	No safety concern
1-(Methylthio)-2-butanone	496	N	
4-(Methylthio)-2-butanone	497	N,T	
4-(Methylthio)-4-methyl-2- pentanone	500	N,T	
Di(butan-3-one-1-yl) sulfide	502	N,T	
o-(Methylthio)-phenol	503	N,T	No safety concern
4-(Methylthio)-2-oxobutanoic acid	501	N	
2-(Methylthiomethyl)-3-phenyl propenal	505	N	
Subgroup C- Cyclic sulfides			
2,5-Dimethyl-2,5-dihydroxy-1,4-dithiane	562	N,T	No safety concern
2,5-Dihydroxy-1,4-dithiane	550	N	
2-Methyl-4-propyl-1,3-oxathiane	464	N,T	
4,5-Dihydro-3(2H)thiophenone	498	N,T	
2-Methyltetrahydrothiophen-3-one	499	N,T	
1,4-Dithiane	456	N,T	No safety concern
2-Methyl-1,3-dithiolane	534	N	
Trithioacetone	543	N,T	
Subgroup D - Thiols			
Methyl mercaptan	508	N,T	No safety concern
Propanethiol	509	N,T	
2-Propanethiol	510	N,T	
1-Butanethiol	511	N	
2-Methyl-1-propanethiol	512	N,T	

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

Flavouring agent	No.	Specifi-cations[1]	Conclusions based on current intake
3-Methylbutanethiol	513	N,T	No safety concern
2-Pentanethiol	514	N,T	
2-Methyl-1-butanethiol	515	N	
3-Methyl-2-butanethiol	517	N	
1-Hexanethiol	518	N,T	
2-Ethylhexanethiol	519	N,T	No safety concern
Prenythiol	522	N	
Thiogeraniol	524	N,T	
Cyclopentanethiol	516	N,T	
2,3, and 10-Mercaptopinane	520	N,T	
Allyl mercaptan	521	N,T	No safety concern
1-p-Menthene-8-thiol	523	N,T	
Benzenethiol	525	N	
Benzyl mercaptan	526	N	
Phenylethyl mercaptan	527	N	
o-Toluenethiol	528	N,T	No safety concern
2,6-Dimethylthiophenol	530	N	
2-Naphthalenethiol	531	N,T	
2-Ethylthiophenol	529	N,T	
Subgroup E - Thiols with oxidized side chains			
2-Mercaptopropionic acid	551	N	No safety concern
Ethyl 2-mercaptopropionate	552	N,T	
Ethyl 3-mercaptopropionate	553	N	
3-Mercaptohexyl acetate	554	N	
3-Mercaptohexyl butyrate	555	N	
3-Mercaptohexyl hexanoate	556	N,T	No safety concern
1-Mercapto-2-propanone	557	N,T	
3-Mercapto-2-butanone	558	N,T	
2-Keto-4-butanethiol	559	N,T	
3-Mercapto-2-pentanone	560	N,T	
3-Mercapto-3-methyl-1-butanol	544	N,T	No safety concern
3-Mercaptohexanol	545	N	
2-Mercapto-3-butanol	546	N,T	
alpha-Methyl-beta-hydroxypropyl alpha-methyl-beta-mercaptopropyl sulfide	547	N	
4-Methyoxy-2-methyl-2-butanethiol	548	N,T	No safety concern
3-Methyl-3-mercaptobutyl formate	549	N	
p-Mentha-8-thiol-3-one	561	N,T	
Sodium 3-mercapto-oxopropionate	563	N	
Subgroup F - Dithiols			
1,2-Ethanedithiol	532	N	No safety concern
1,3-Propanedithiol	535	N	
1,2-Propanedithiol	536	N,T	
1,2-Butanedithiol	537	N	
1,3-Butanedithiol	538	N	
2,3-Butanedithiol	539	N	No safety concern
1,6-Hexanedithiol	540	N	
1,8-Octanedithiol	541	N	
1,9-Nonanedithiol	542	N	
Subgroup G - Simple Disulfides			
Dimethyl disulfide	564	N	No safety concern
Methyl propyl disulfide	565	N,T	
Propyl disulfide	566	N	
Diisopropyl disulfide	567	N	
Methyl 1-propenyl disulfide	569	N,T	
Propenyl propyl disulfide	570	N,T	No safety concern
Methyl 3-methyl-1-butenyl disulfide	571	N,T	
Allyl methyl disulfide	568	N,T	
Allyl disulfide	572	N,T	
Dicyclohexyl disulfide	575	N,T	

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

Flavouring agent	No.	Specifi-cations[1]	Conclusions based on current intake
Methyl phenyl disulfide	576	N	} No safety concern
Methyl benzyl disulfide	577	N	
Benzyl disulfide	579	N,T	
Phenyl disulfide	578	N	
Subgroup H - Disulfides with oxidized side chains			
2-Methyl-2-(methyldithio) propanal	580	N,T	} No safety concern
Ethyl 2-(methyldithio) propionate	581	N,T	
Subgroup I - Trisulfides			
Dimethyl trisulfide	582	N,T	} No safety concern
Methyl ethyl trisulfide	583	N,T	
Methyl propyl trisulfide	584	N,T	
Dipropyl trisulfide	585	N,T	
Allyl methyl trisulfide	586	N,T	} No safety concern
Diallyl trisulfide	587	N,T	
Diallyl polysulfide	588	N,T	
Subgroup J - Heterocyclic disulfides			
3,5-Dimethyl-1,2,4-trithiolane	573	N,T	} No safety concern
3-Methyl-1,2,4-trithiane	574	N,T	
Subgroup K - Thioesters			
S-Methyl thioacetate	482	N,T	} No safety concern
Ethyl thioacetate	483	N	
Methyl thiobutyrate	484	N,T	
Propyl thioacetate	485	N	
Methyl 2-methylthiobutyrate	486	N,T	
S-Methyl 3-methylbutanethioate	487	N,T	} No safety concern
S-Methyl 4-methylpentanethioate	488	N,T	
S-Methyl hexanethioate	489	N,T	
Allyl thiopropionate	490	N,T	
Prenyl thioacetate	491	N	
Methyl 2-(acetyloxy) propionate	492	N	} No safety concern
Methylthio 2-(propionyloxy) propionate	493	N	
3-Acetyl-3-mercaptohexyl acetate	494	N	
S-Methyl benzothioate	504	N,T	
cis & trans-Menthone-8-thioacetate	506a & 506b	N	
Subgroup L - Sulfoxides			
Methylsulfinylmethane	507	N,T	No safety concern

B. Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups.

Flavouring agent	No.	Specifi-cations[1]	Conclusions based on current levels of intake
2-Oxobutyric acid	589	N,T	} No safety concern
Methyl 2-hydroxy-4-methylpentanoate	590	N,T	
Methyl 2-oxo-3-methylpentanoate	591	N,T	
Citronelloxyacetaldehyde	592	N,T	
3-Oxobutanal dimethyl acetal	593	N	
Ethyl 3-hydroxybutyrate	594	N,T	} No safety concern
Ethyl acetoacetate	595	N	
Butyl acetoacetate	596	N,T	
Isobutyl acetoacetate	597	N,T	
Isoamyl acetoacetate	598	N,T	

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

Flavouring agent	No.	Specifi-cations[1]	Conclusions based on current levels of intake
Geranyl acetoacetate	599	N,T	No safety concern
Methyl 3-hydroxyhexanoate	600	N,T	
Ethyl 3-hydroxyhexanoate	601	N	
Ethyl 3-oxohexanoate	602	N	
Ethyl 2,4-dioxohexanoate	603	N,T	
3-(Hydroxymethyl)-2-heptanone	604	N,T	No safety concern
1,3-Nonanediol acetate (mixed esters)	605	N,T	
Levulinic acid	606	N	
Ethyl levulinate	607	N	
Butyl levulinate	608	N	
1,4-Nonanediol diacetate	609	N,T	No safety concern
Hydroxycitronellol	610	N,T	
Hydroxycitronellal	611	N	
Hydroxycitronellal dimethyl acetal	612	N	
Hydroxycitronellal diethyl acetal	613	N,T	
Diethyl malonate	614	N	No safety concern
Butyl ethyl malonate	615	N,T	
Dimethyl succinate	616	N	
Diethyl succinate	617	N	
Fumaric acid	618	R,T	
l-Malic acid	619	R,T	No safety concern
Diethyl malate	620	N,T	
Tartaric acid (d-, l-, dl-, meso-)	621	R	
Diethyl tartrate	622	N	
Adipic acid	623	R	
Diethyl sebacate	624	N	No safety concern
Dibutyl sebacate	625	N	
Ethylene brassylate	626	N	
Aconitic acid	627	N,T	
Ethyl aconitate (mixed esters)	628	N,T	
Triethyl citrate	629	R,T	No safety concern
Tributyl acetylcitrate	630	N,T	
3-Methyl-2-oxobutanoic acid and sodium salt	631	N,T	
3-Methyl-2-oxopentanoic acid and sodium salt	632	N,T	
4-Methyl-2-oxopentanoic acid and sodium salt	633	N,T	
2-Oxopentandioic acid	634	N	No safety concern
3-Hydroxy-2-oxopropionic acid	635	N	

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

3. Allergenicity of peanut and soya bean oils

The Committee reviewed available information on the potential allergenicity of peanut and soya bean oils (see Annex 1) and, on the basis of the following, concluded that distinct processes that would consistently yield safe products have not been defined:

(a) the refining processes of the peanut and soya bean oils clinically tested in humans were not clearly described;
(b) data on the protein content of those oils that had been clinically tested were not available; and
(c) the quality of the analytical procedures, including method validation, for the determination of the concentration of residual protein in the oils was not clear.

See Table 2 for information that would be required for a full re-evaluation.

4. Contaminants

A. Lead

The provisional tolerable weekly intake (PTWI) of 25 µg/kg bw was maintained. Based on a quantitative risk assessment, the Committee concluded that current levels of lead in food would have negligible effects on neurobehavioral development in infants and children. However, examples of foods with high levels of lead remain in commerce. The simulation model that is presented in the report can be used to evaluate the effects of potential intervention procedures. A complete risk assessment of lead should also take other environmental exposures into account.

B. *Methylmercury*

The provisional tolerable weekly intake (PTWI) of 3.3 µg/kg bw was maintained. The Committee considered data on intake, the quantitative relationships between daily intake of methylmercury and concentrations in blood and hair, and ongoing epidemiology studies. The information available was insufficient for evaluating the neurodevelopmental effects on offspring of mothers with low intakes of methylmercury. A clear indication of consistent risk was not detected in the ongoing epidemiology studies. The Committee noted that fish (the major source of methylmercury in the diet) contribute importantly to nutrition, especially in certain regional and ethnic diets, and recommended that, when limits on the methylmercury concentration in fish or on fish consumption are under consideration, the nutritional benefits are weighed against the possibility of harm. See Table 2 for information required for re-evaluation.

C. *Zearalenone*

A provisional tolerable maximum daily intake (PMTDI) of 0.5 µg/kg bw was established.

5. Food additives considered for specifications only

Food Additive	Specifications[1]	Food Additive	Specifications[1]
α-Acetolactate decarboxylase from *Bacillus brevis* expressed in *Bacillus subtilis*	R	Ferrous gluconate	R
		Ferrous sulfate	R
		Ferrous sulfate, dried	N
Adipic acid	R	Fumaric acid	R
α-Amylase from *Bacillus megaterium* expressed in *Bacillus subtilis*	R	Guar gum	R
		Helium	N
		Magnesium gluconate	R
α-Amylase from *Bacillus stearothermophilus* expressed in *Bacillus subtilis*	R	DL-Malic acid	R
		Maltogenic amylase from *Bacillus Stearothermophilus* expressed In *Bacillus subtilis*	R
Argon	N		
Calcium hydrogen sulfite	W	Nitrogen	R
Carob bean gum	R	Oxygen	N
Carotenes, algae	S	Potassium metabisulfite	R
Carotenes, vegetable	S	Potassium sulfite	R
Chymosin A from *Escherichia coli* K-12 containing the prochymosin A gene	R	Riboflavin from *Bacillus subtilis*	R
		Sodium hydrogen sulfite	R
		Sodium metabisulfite	R
Chymosin B from *Aspergillus niger* var. *awarmori* containing the prochymosin B gene	R	Sodium sulfite	R
		Sodium thiosulfate	R
		Sucrose esters of fatty acids	R
Chymosin B from *Kluyveromyces lactis* containing the prochymosin B gene	R	DL-Tartaric acid	R
		L(+)-Tartaric acid	R
		Thaumatin	R
Citric acid	R	Xanthan gum	R

[1] N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing new or revised specifications are tentative and information is needed; W, existing specifications withdrawn.

6. Food additives considered for evaluation of national intake assessments

Substance	Conclusions
Annatto extracts (bixin)	Intake estimates based on proposed GSFA[1] levels and the range of foods in which use is allowed integrated with national food consumption data exceeded the ADI of 0-0.065 mg/kg bw (expressed as bixin). Intake assessments based on national standards did not exceed the ADI for most populations. Data from Brazil, however, provided evidence that a particular group of the population consuming annatto as a condiment have chronic intakes on the order of 150% of the ADI. Considering the overestimation of intake that results from the use of the general assumption that all foods in a category are coloured by the same additive at the maximum level, the Committee concluded that the ADI for bixin is unlikely to be exceeded from the use of annatto extracts. The Committee recommended that annatto extracts be re-evaluated in 2001 (see Table 2).
Canthaxanthin	Intake estimates based on proposed GSFA[1] levels and the range of foods in which use is allowed integrated with national food consumption data exceeded the ADI of 0-0.03 mg/kg bw. Intake assessments based on national standards did not exceed the ADI. Indirect exposure through the use of canthaxanthin as a feed additive for food animals is the major contributor to canthaxanthin intake.
Erythrosine	The potential exists for the intake of erythrosine to exceed the ADI of 0-0.1 mg/kg bw if the proposed GSFA[1] levels are widely adopted at the national level. All national assessments of erythrosine intake were below the ADI. Non-food sources of erythrosine, such as pharmaceutical products, should be included in intake assessments.
Iron oxides	Iron oxides are permitted in the GSFA under conditions of Good Manufacturing Practice. Intake assessments or iron oxides based on national standards did not exceed the ADI of 0-0.5 mg/kg bw.

[1]Intake estimates based on food additive levels in the draft General Standard for Food Additives (GSFA) being developed by the Codex Committee on Food Additives and Contaminants integrated with national food consumption data will grossly overestimate actual intakes in any one country because the GSFA levels are generally compiled by adopting the highest level of use for any one food category submitted by Member States or non-governmental organizations. The range of food uses specified in the GSFA is also usually much wider than in national standards.

Table 2

FURTHER INFORMATION REQUIRED OR DESIRED

Thickener

Curdlan

Information on the use, including the maximum and typical expected levels in the food categories in which curdlan is proposed, and consumption of foodstuffs that might contain curdlan in different regions of the world so that its intake can be assessed, is required for evaluation in 2001.

Miscellaneous substance

Sodium sulfate

Information on the functional effect and actual uses of sodium sulfate in food is required for evaluation in 2001.

Substances evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

Information on those flavouring agents designated as tentative is required for evaluation in 2000.

Peanut and soya bean oils

The results of studies of representative refined peanut and soya bean oils would be required for a full evaluation. These studies should include extensive information on a wide range of oils representing refining procedures used worldwide. Full descriptions of the refining processes used and evidence for the lack of allergenicity of the oils as determined by appropriately designed clinical studies should be provided. Information on the nature and quantity of protein in the oils is essential for defining the level of refinement of the oils tested, with a view toward identifying representative oils that will have been clinically tested to assure safety.

Contaminant

Methylmercury

The 96-month evaluation of the Seychelles cohort and other relevant data that have become available are required for evaluation in 2002.

Food additives considered for evaluation of national intake assessments

Annatto extracts

All relevant toxicological and intake data on annatto extracts are required for evaluation in 2001. The Committee also recommended that the intake of annatto continue to be monitored in those populations in which its consumption is high.

Annex 1

General consideration items

An edited version of these sections will appear in the report of the fifty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). They are reproduced here so that the information is disseminated quickly. This draft is subject to extensive editing.

Table of contents

1. The role of the Committee in risk analysis

Background

Risk analysis in the context of the Codex system has been considered at three FAO/WHO consultations over the last few years. Those consultations outlined the responsibilities of advisory committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and of Codex general subject committees such as the Codex Committee on Food Additives and Contaminants (CCFAC) and clarified the place of their work in the three components of risk analysis: risk assessment, risk management, and risk communication.

The CCFAC at its Thirty-first Session considered a paper on its role in relation to that of JECFA in the risk analysis process. The paper included a discussion on priorities for work, principles for risk assessment policy, and principles for risk assessment output. It included a number of recommendations to both the Codex Committee and the Expert Committee. The Expert Committee was invited by CCFAC to consider and comment on the paper. The Expert Committee's comments are summarized here.

Risk assessment as outlined in the FAO/WHO consultations consists of four steps: (1) hazard identification; (2) hazard characterization (dose–response assessment), (3) exposure assessment, and (4) risk characterization on the basis of the hazard characterization and exposure assessment. It is generally agreed that scientific committees, which are composed of experts serving in their individual capacities as scientists, are responsible for assessing risks and that Codex general subject committees, which consist of government delegates, are responsible for providing recommendations for managing risks. All participants in the process and other interested parties are involved in risk communication.

Although the FAO/WHO consultations have indicated that risk management should be functionally separate from risk assessment, risk assessors and risk managers must be able to communicate iteratively to ensure that the questions asked by the risk managers are understood and addressed, that the risk assessments are clearly described, and that the process operates efficiently.

The FAO/WHO Consultation on Risk Management and Food Safety concluded that "In the process of assessing substances scientific committees continually need to select and utilize various scientific assumptions", including the following:

- "reliance on animal models to establish potential human effects;
- using body weight scaling for interspecies comparison;
- using a 100-fold uncertainty or safety factor to account for likely inter- and intraspecies differences in susceptibility, with guidelines for deviations that are permitted in specified situations;
- permitting contaminants at levels 'as low as reasonably achievable' (ALARA); and
- establishing temporary ADIs for additives and residues of veterinary drugs pending submission of requested data."

That Consultation recommended that the Codex Alimentarius Commission define the role of Codex committees in providing clear, unequivocal guidance for risk assessment policy to the scientific committees. Such guidance should acknowledge the right of scientific committees to make choices in risk assessment but should provide guidelines for the value judgements and policy choices that may be required in risk assessment, including, for instance, the choice of uncertainty (safety) factors at specific points in the risk assessment process. The Codex Alimentarius Commission has recommended that the Codex Committee on Food Additives and Contaminants, in consultation with the Joint FAO/WHO Expert Committee on Food Additives, propose a policy statement on risk assessment that provides such guidelines.

Comments by the present Committee

Any request to the Expert Committee for scientific advice must clearly state the reason for the request and outline the probable options for risk management. Clear communication between risk assessors and risk managers at the initial stage is particularly important because of the long delay that currently exists between meetings of Codex and scientific committees. The present Committee agreed that the outcome of its own assessments and the basis for its recommendations should be clearly documented and should include a description of any uncertainties. Clearer communication between the Codex Committee and the Expert Committee would obviate the need for several rounds of communication and increase the value of the advice provided. Procedures should be developed to enhance communication between meetings of the committees.

Characterizing risk

The Expert Committee characterizes risk in one of two ways: (i) by quantifying the dose (or range of doses, usually from zero upwards) at or below which there is judged to be no appreciable risk or (ii) by describing the relationship between intake and the probability of an adverse response in humans. The former process, sometimes called a 'safety assessment', is used by the Expert Committee when allocating ADIs to food additives and tolerable intakes (expressed on either a weekly or a daily basis) to contaminants. The Expert Committee considered this process to constitute risk assessment; although the ADI or tolerable intake does not represent a quantitative estimate of risk, they represent an intake level at which there is *no appreciable risk* and are used as measures of the safety of a substance at that intake level. Hazard is identified and characterized in the process of establishing ADIs and tolerable intakes, and risk is characterized as being not appreciable when intake does not exceed those values. Uncertainty is incorporated into the value by the magnitude of the safety factor.

The information available to the Expert Committee on toxicological and related aspects (such as pharmacokinetics and pharmacodynamics in animals and humans and information on the dose–response relationship) is generally as complete as that available to national governments. In consequence, hazard, dose–response relationships, NOELs, and derived ADIs and tolerable intakes can be characterized and are applicable internationally. If detailed information on the intake of a substance by various population groups is available, the Committee can characterize the risks for those groups. Such risk characterizations serve as examples for detailed risk assessments by governments.

Potential intake is an integral component of the assessment of flavouring agents using the *Procedure for the Safety Assessment of Flavouring Agents.* When the Committee establishes an ADI "not specified" for food additives, potential intake is also explicitly considered to ensure that it is unlikely for consumers to exceed a level associated with no appreciable risk when the additive is used according to good manufacturing practice for its technological function(s). Of necessity, potential intake relates to probable use of the food additive at the time of assessment, and the use pattern may change over time. As stated in section 2.2.4 of the report of the thirty-ninth meeting of the Committee, a food additive should be referred to the Committee for re-evaluation when new uses that would significantly increase intake are envisaged. It is critical that the use pattern on which the ADI "not specified" is based be well documented by the scientific committee.

Specifications of identity and purity are integral to assessing the risk associated with the use of food additives. Such specifications make it possible to define the product that was tested toxicologically and include identity and purity requirements for the additive. They are considered by the Codex Committee for adoption as 'Codex Advisory Specifications', which are used in risk management to ensure the appropriate purity of the product in commerce.

The assessments of food additives and contaminants differ fundamentally (In this context, naturally occurring toxicants are considered in the same light as contaminants.), primarily because food additives, which are generally of low toxicity, are deliberately added to food to confer specific benefits, whereas contaminants (except for micronutrients) are of no benefit. Food additives can be controlled easily, while the elimination of contaminants from foods often incurs costs, such as a reduction in the availability and/or affordability of foods. Thus, different terms are used for the two, with 'tolerable' being considered more appropriate for the intake of contaminants that are unavoidably associated with the consumption of otherwise wholesome, nutritious foods.

Conservative assumptions are made in establishing ADIs in order to provide confidence that intake up to the maximum value of the ADI represents no appreciable risk. This process is described in *Environmental Health Criteria 70*[1]. In those rare instances in which long-term intake exceeds the ADI, the risk may not be negligible, but it is difficult to quantify since data on adverse effects in humans sufficient to define a dose–response relationship are usually not available.

Assessment of contaminants

With respect to contaminants, the Expert Committee agreed that the relationship between their intake and the probability of an adverse response in humans should ideally be identified in the risk assessment process. If the risk assessment is adequately documented and explained, risk managers can use it to decide on the appropriate level of protection that can reasonably be achieved within the population of concern on the basis of intake levels and considerations of risk–risk and risk–benefit. The Expert Committee used this approach with regard to aflatoxins at its forty-ninth meeting, in which the carcinogenic potencies were estimated for individuals infected with hepatitis B virus and for uninfected persons. The risk for the population was calculated on the basis of the available information on the intake of aflatoxins and hypothetical standards. The population risks were presented as examples. Risk managers should base national standards on consumption and contamination patterns and the incidence of hepatitis B virus infection in their countries, in conjunction with the Expert Committee's estimates of potency and keep in mind that the population risks calculated in the report are only indicative of the range of potential risks.

Although the relationship between intake and the probability of an adverse response should be determined for contaminants, this is usually difficult in practice because of the paucity of quantitative data on the relationship between intake and the incidence of effects in humans, which are necessary to provide confidence in the association between intake and response. For this reason, the Expert Committee will probably continue to establish tolerable intakes for some contaminants in the foreseeable future, as was done for zearalenone at the present meeting. Adherence to a defined tolerable intake may not always be feasible, for instance because it

[1] *Principles for the safety assessment of food additives and contaminants in food.* Environmental Health Criteria 70. World Health Organization, 1987

results in removing a major, nutritious food item. Risk managers must therefore closely consult the evaluation in order to appreciate the risks associated with high levels of intake.

The Expert Committee sometimes recommends an 'irreducible level' for a food contaminant, which it has defined as "that concentration of a substance which cannot be eliminated from a food without involving the discarding of that food altogether, severely compromising the ultimate availability of food supplies". The Consultation on Application of Risk Analysis to Food Standards Issues referred to this concentration as that 'as low as reasonably achievable' (ALARA). Although the risk is not quantified, the general nature and, when possible, the magnitude of the potential risks for toxicity in relation to intake are described in the report. Possible control measures are often given, which are among those that risk managers should consider in establishing standards. When providing such qualitative information on toxicity and possible control options, the Expert Committee performs a risk assessment function.

The acceptable or tolerable intake is an indication of both the *magnitude* and the *duration* of acceptable intake. Unless otherwise indicated, the ADI represents an acceptable daily intake for the lifespan of an individual. Tolerable intakes are expressed on a weekly basis (provisional tolerable weekly intake or PTWI) for contaminants that accumulate in the body when toxicity is associated with long-term intake, whereas they are expressed on a daily basis (provisional maximum tolerable daily intake or PMTDI) for those contaminants that are not known to accumulate in the body and which are of concern when consumed in high quantities over a short period. These end-points should be compared with intake surveys of appropriate duration in the assessment of risk.

Risk assessment policy

The Expert Committee agreed with the Codex Committee that risk assessment policy is an important component of risk analysis. Such policies should be reviewed to ensure that they serve the needs of the Codex. All parties should be aware that this is particularly difficult at the international level because the Expert Committee responds to requests for evaluation not only from the Codex but also directly from FAO and WHO and from Member States.

The Expert Committee considered that most of the risk assessment policies identified at the Consultation on Risk Management and Food Safety (see above) are scientific issues, which should be established by risk assessors. For example, the Expert Committee considers that the magnitude of safety factors is a matter of scientific judgement. The safety factors most appropriate for meeting the Committee's goal of establishing levels of intake that represent no appreciable risk vary from substance to substance, depending on the quality and quantity of the available toxicological, chemical, and intake data. Use during the risk assessment process of an additional, non-scientific factor to protect infants and children, for example, would override the use of scientific judgement based on the available data. An implicit risk assessment policy that has been in effect with regard to food additives for many years is that ADIs should be established that represent no appreciable risk. The Expert Committee is responsible for deciding on the appropriate safety factor in order to accomplish that goal.

2. Food allergies

The primary role of the Expert Committee is to evaluate the safety of and assess the risks associated with food additives and contaminants, and it has elaborated principles and guidelines to assist in this process. In general, it has not previously evaluated specific foods or commodities, as such, and has not developed general principles to do so. The Expert Committee was, however, asked by the Codex Committee on Food Labelling to consider draft recommendations for the labelling of foods that can cause hypersensitivity. The Codex Committee specifically asked the Expert Committee's advice on:

- identifying criteria for adding foodstuffs to the Codex list of common allergenic foods, if found to be necessary;
- developing criteria for identifying products of foodstuffs on the Codex list for which labelling of the food source is not necessary; and
- considering ways in which FAO and WHO could provide guidance in this area to JECFA on a continuing basis.

WHO convened an *ad hoc* Food Allergies Labelling Panel in February 1999 that considered these points and prepared recommendations. The report will be included as an annex to the report of the Expert Committee.

The Expert Committee considered the Panel report and recommendations and concluded that the scientific criteria for adding foodstuffs to the list and for identifying products of foodstuffs to be excluded from the list given in the report of the Panel (see below) form a suitable basis for addressing the allergenicity of food and food products. The Expert Committee agreed that advice from specialists would be essential in addressing future requests of this nature.

Criteria for the addition of foodstuffs to the Codex list

In determining whether a foodstuff should be added to the Codex list of common allergenic foods the Panel recommended that all the following criteria be applied:

i) The existence of a credible cause-and-effect relationship based on a positive double-blind placebo-controlled food challenge or unequivocal reports of a reaction with the typical features of a severe allergic or intolerance reaction;

ii) There should be reports of systemic reactions following exposure to the foodstuff. These reactions include atopic dermatitis, urticaria, angioedema, laryngeal oedema, asthma, rhinitis, abdominal pain, diarrhoea, vomiting, anaphylactic shock, and chronic severe malabsorption syndrome.

iii) Whereas the Panel recognized that the ideal criterion would be prevalence data in children and adults, supported by appropriate clinical studies, i.e. double-blind placebo-controlled food challenges, from the general population of several countries, it noted that currently such information is only available a) for infants, b) from some countries and c) for some foodstuffs. Such information is rarely available for adults. As an alternative, the Panel agreed that available data be used, such as comparative prevalence of the specific food allergy in groups of allergy patients from several countries. This should be supported, ideally, by a double-blind placebo-controlled food challenge.

Criteria for excluding products of foodstuffs on the Codex list from the need for labeling

i) Evidence that a clinical study using double-blind placebo-controlled food challenge has confirmed that the specific product does not elicit allergic reactions in a group of patients with clinical allergy to the parent foodstuff, and

ii) Specifications for the product and its manufacturing process that demonstrate the ability of the process to yield a consistently safe product are available,

iii) Special considerations for coeliac disease:
   a) products of rye, barley and oats would not be required to meet the criteria established in i) and ii) above because IgE-mediated allergic reactions to these cereal grains are not common;
   b) products of wheat, spelt or their hybridized strains would be required to meet the criteria established in i) and ii) above;
   c) products of wheat, rye, barley, oats and spelt or their hybridized strains would be required to adhere to existing Codex specifications for gluten-free products, because such grains can be implicated in coeliac disease.

The Expert Committee noted that the Panel report addresses issues of both risk assessment and risk management. It considered, however, that only the former was in its purview. Therefore, once the Expert Committee has evaluated allergenic risk, it is for the Codex Committee to determine the appropriate risk management steps.

3. Principles governing intake assessments of contaminants

Assessments of the dietary intake of contaminants may be part of an estimate of total exposure that would include contributions from water and non-dietary sources as well as the dietary intake from food. Because an intake assessment is required in order to characterize the risk associated with consumption of contaminants in foods, the Expert Committee established the following principles for assessing intake as part of risk assessment. These principles complement the general principles governing intake assessment specified by previous Committees. The report of the FAO/WHO Expert Consultation on Food Consumption and Exposure Assessment of Chemicals, held in February 1997, contains additional information on estimation of intakes.

The Committee may assess intake over different time frames, depending on the toxicological profile of the contaminant being evaluated. An assessment of acute intake is one that describes intake on a single eating occasion or a single day. An assessment of chronic intake describes intake over a longer time frame.

Acute intake

- An assessment of the intake of a contaminant that has an adverse effect after a single exposure would ideally provide a realistic estimate of the intake of a consumer of large amounts of the contaminant. Statistically, the combination of data on high-percentile consumption and high concentration would yield a point estimate of intake that would be higher than that for the whole population. A more realistic assessment can be obtained by making a detailed simulation that incorporates the entire distribution of short-term food consumption and of the levels of the contaminant in the foods consumed. In practice, the available data are often inadequate for such an analysis, particularly at the international level, and the objective of the assessment may not require such a resource-intensive evaluation. When a detailed analysis is not appropriate, food consumption by a high-percentile consumer should be combined with a high-percentile contaminant concentration. (Use of the 97.5th percentile for both food consumption and residue concentrations have been recommended for assessments of acute exposure to pesticides, for example). The Committee will determine the most appropriate approach on a case-by-case basis, taking into consideration the objective of the assessment and the available data.

Chronic intake

- An assessment of the intake of a contaminant that must be ingested chronically in order to induce an adverse effect should combine the distribution of consumption of the food in the population under consideration with the mean (average) concentration of the contaminant. The mean intake from the resulting distribution represents probable lifetime exposure to the contaminant. This principle reflects the likelihood that no consumer of a contaminant would be exposed continually to a higher-than-average concentration of the contaminant throughout the food supply over a lifetime.

- Typically, a measure of national intake of a contaminant is derived from national data on food consumption and contaminant concentrations.

- National total diet studies, in which foods that represent the diet of the whole population or of sub-populations at risk are analysed for a contaminant, allow estimates of intake of contaminants.

- Mean food consumption in regional diets (such as those described in WHO's GEMS/Food programme) can be used with representative concentrations of contaminants to derive estimates of exposure for broad groups of countries.

- Estimates of intake can be adjusted to reflect the proportion of the food supply that is affected and the effects of processing or cooking on residue levels.

The Committee receives intake assessments and further relevant data from national governments and other interested parties for making risk assessments. The Committee recommended that such submissions include the following:

- a description of the specific chemical form of the contaminant;
- complete descriptions of the foods that contain the contaminant;
- the concentrations of the contaminant in foods as consumed, i.e. prepared for consumption; and
- an explicit description of the values incorporated into an assessment when the concentrations of the contaminant are below the limit of quantification.

4. Residual ethanol

Ethanol is one of several extraction solvents used in the production of various food additives. The specifications for those additives usually include limits for the residues of such solvents. The Committee was requested to consider whether a residue requirement was necessary for ethanol in such cases. It concluded that from the point of view of good manufacturing practices ethanol should be considered no differently from other extraction solvents, and it reaffirmed the specification requirement for residue limits for all such solvents, including ethanol. The Committee noted, for instance, that the existing specifications for two substances, cochineal extract and xanthan gum, indicate that ethanol is used as a solvent in their production, but that the specifications do not contain criteria for residual ethanol. The specification for xanthan gum was revised at the present meeting. The Committee decided to reconsider the specification for cochineal extract at its fifty-fifth meeting in 2000.

5. Heavy metals limit test

The Committee agreed to implement the decisions taken at its forty-ninth and fifty-first meetings to review and replace the heavy metals limit test, with, as appropriate, limits for individual metals of concern in all existing specifications. In order to accomplish this, the Committee decided to review the existing specifications on the basis of functional use (e.g. antioxidant, preservative) and set a target of five years for completion of the task.

The Committee decided to begin by reviewing the limits for heavy metals in emulsifiers at its fifty-fifth meeting in 2000. The call for data for that meeting will include requests for suggestions on individual limits for heavy metals and supporting data. Once the Committee has considered the submissions, proposals will be submitted for consideration by the Codex Committee on Food Additives and Contaminants for eventual adoption by the Codex Alimentarius Commission.

The Committee reaffirmed its earlier conclusions that it would usually set a maximum level of 2 mg/kg for lead and 1 mg/kg for cadmium and for mercury, except when there were good reasons for setting a lower or higher maximum level. The Committee also reaffirmed its earlier decision to include limits for arsenic only when the source from which the additive is prepared, or the nature of the manufacturing method, indicated that such a limit was necessary.

The Committee reaffirmed the point made at earlier meetings that, when the heavy metals limit test is replaced by specific limits, the intention is not to weaken the specifications but to ensure that limits are placed on the levels of those elements that are likely to be of potential concern.

6. Citation of microbial strains

At its fifty-first meeting, the Committee revised an addendum to the general specifications for enzyme preparations used in food processing which addressed preparations from genetically modified organisms. The addendum was originally published in *FAO Food and Nutrition Paper*

52 as Appendix B to Annex 1. At the present meeting, the Committee further reviewed the specifications for numbering of microbial strains in the light of comments received by the Codex Committee on Food Additives and Contaminants at its thirty-first meeting.

The Committee reaffirmed that the requirement for identification of a strain number in the source section of monographs on enzymes prepared from genetically modified organisms might impose unnecessary constraints on the development of production organisms for food-grade enzymes. The Committee concluded that the source section of the monograph on an enzyme derived from a non-pathogenic, non-toxicogenic strain that belongs to a species that includes pathogenic and toxicogenic strains should include the statement that 'the strain is non-pathogenic and non-toxicogenic', and citation of a suitable strain number could be included by way of example.

The Committee therefore amended the requirement for microbial strain numbers in the specifications section of Appendix B to Annex 1 as follows, and decided that this amendment should be published as an annex to *FAO Food and Nutrition Paper 52* Addendum 7:

> "Microbial strain numbers - Any microbial strain that meets the considerations described above should be a safe and suitable host for the introduced DNA. Citation in the monograph of the genus and species of the host organism is usually adequate for those that have been determined to be safe and suitable. Identification at the strain level may impose unnecessary constraints on the development of production microorganisms used to produce food-grade enzymes. In the case of a non-pathogenic, non-toxicogenic strain that belongs to a species that includes pathogenic and toxicogenic strains (e.g. *Escherichia coli*), there should be a requirement in the monograph that the strain be non-pathogenic and non-toxicogenic. Citation of a suitable strain number may be included by way of example."

The Committee further decided that lack of pathogenicity and toxicogenicity was a general requirement that should apply to all microorganisms used to produce food-grade enzymes. It therefore also agreed to the addition of the following text to the end of the section on source materials of the *General specifications for enzyme preparations used in food processing* published as Annex 1 to *FAO Food and Nutrition Paper 52*:

> " When a non-pathogenic, non-toxicogenic strain belongs to a species that includes pathogenic and toxicogenic strains, the source section of the monograph for the enzyme should include a requirement that the strain be non-pathogenic and non-toxicogenic. Citation of a suitable strain number may be included by way of example."

The Committee further agreed that the source section of any monograph for a food additive that has been prepared from a microorganism that belongs to a species that includes pathogenic and toxicogenic strains should include a requirement that the strain be non-pathogenic and non-toxicogenic. Citation of a suitable strain number may be included by way of example.

7. Tentative specifications for food additives

The Committee noted that many of the specifications for food additives (other than flavouring agents) published in the *FAO Compendium of Food Additives* and its addenda are designated as 'tentative', indicating that some information or data were missing or incomplete at the time the specifications were prepared. Some of these specifications have been designated 'tentative' for more than 30 years and often do not indicate why the designation was given. Newer specifications include the reasons.

The Committee prepared two lists that encompass all of the existing tentative specifications except those for flavouring agents. List 1 comprises older tentative specifications that do not include reasons for the tentative designation. List 2 contains the remaining tentative specifications, for which reasons are given for the designation.

List 1 will be attached to the call for data for the fifty-fifth meeting of the Committee in 2000, with a request for information on their present uses in foods and technical data. If no data are received or if the substance is no longer used in foods, the tentative specifications will be withdrawn. The substances in List 2 will also be attached to the call for data for the fifty-fifth meeting with a request for information to resolve the reasons for their designations as 'tentative'.

The Committee will review the available information and data submitted during its fifty-fifth meeting and will decide if the tentative specifications should be withdrawn.

8. Specifications for flavouring agents designated as 'tentative'

Between 1996 and 1998, the Committee developed specifications for the purity of 449 flavouring agents, of which 111 were designated as 'tentative' because certain necessary information was lacking. In making these designations, the Committee relied on its judgement rather than on a carefully defined system. The present Committee agreed that it was important to be consistent in applying tentative designations and agreed that specifications submitted for consideration at the present meeting should be designated as tentative if information had not been provided on:

- chemical formula and relative molecular mass,
- identity test, and
- minimum assay value

and on the additional purity-related criteria:

- boiling-point (for liquids),
- melting-point (for solids),
- refractive index (for liquids), and
- specific gravity (for liquids).

The Committee will, however, consider full specifications when the absence of one or more of the last four purity-related criteria can be justified.

Using this approach, the Committee designated 110 of the 187 specifications submitted for consideration at the present meeting, as tentative. In order to ensure consistency, the Committee agreed that the specifications for the 449 flavouring agents evaluated at the forty-sixth, forty-ninth, and fifty-first meetings should be re-examined by the same approach. As a result, the tentative designation for one of the specifications (No. 8, allyl sorbate) was removed, and 54 other specifications were given a tentative designation. Although some of the flavouring agents are well-characterized substances, e.g. acetaldehyde and acetic acid, they are included because not all of the information required to satisfy the criteria set out above regarding their use as flavouring agents was included in the material submitted.

Overall,174 out of the 449 specifications set at the previous three meetings are now designated as tentative, making a total of 284 designated as tentative out of the 636 specifications for substances considered between 1996 and the present meeting. The Committee agreed that flavouring agents submitted for evaluation at future meetings would *not* be considered for specifications unless the minimum information set out above was provided.

The Committee concluded that its first priority is to seek further information on these tentative specifications; however, it also intends to re-examine the specifications that may not be designated as tentative but for which the minimum assay values are less than 95%, and these will be included in future calls for data. The Committee further agreed that the relevant data should be sought in time for review at its fifty-fifth meeting in 2000, and the flavouring agents on which data are sought will be included in the call for data for that meeting. If these data are not supplied, the specifications will be withdrawn.

9. Evaluation of substances as food additives which are also food ingredients or natural constituents of food

The Committee noted that some substances can be used both as ingredients of food and as food additives (e.g. polyols and turmeric), and some substances used as food additives occur naturally in foods (e.g. carotenes and some flavouring agents). The Committee reaffirmed that in its risk assessments it clearly identifies whether a substance is being evaluated only as a food additive or for additional uses, such as an ingredient, and that the relative contribution of use as a food additive to total intake is identified when possible. When other food uses of the substance are known but all routes of intake have not been evaluated, this will be clearly identified in the assessment. The Committee noted that numerical ADIs refer to exposure from all sources.