Food and Agriculture Organization of the United Nations

World Health Organization

82nd Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting – Food additives
Summary and conclusions, 2016
Geneva, 7–16 June 2016

Issued 21 June 2016

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 7 to 16 June 2016. The purpose of the meeting was to evaluate certain food additives (including flavouring agents).

Dr A. Mattia, Center for Food Safety and Applied Nutrition, United States Food and Drug Administration, served as Chairperson, and Mrs I. Meyland, Denmark, served as Vice-Chairperson.

Dr M. Lipp, Office for Food Safety, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, Department of Food Safety and Zoonoses, World Health Organization, served as Joint Secretaries.

The present meeting was the eighty-second in a series of similar meetings. The tasks before the Committee were (a) to elaborate principles governing the evaluation of food additives (including flavouring agents); (b) to undertake safety evaluations of certain food additives (including flavouring agents); and (c) to review and prepare specifications for certain food additives (including flavouring agents).

The Committee evaluated the safety of 10 food additives, revised the specifications for 22 other food additives (including 16 modified starches), evaluated 26 flavouring agents according to the Procedure for the Safety Evaluation of Flavouring Agents and revised the specifications for six flavouring agents.

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

The participants in the meeting are listed in Annex 1. Items of a general nature that the Committee would like to disseminate quickly are included in Annex 2. Future work and recommendations are listed in Annex 3.

Toxicological and dietary exposure monographs on most of the substances that were considered will be published in WHO Food Additives Series No. 73. New and revised specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs 19.

More information on the work of JECFA is available at:

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/

and

http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/

Toxicological information and information on specifications

Food additives evaluated toxicologically and assessed for dietary exposure

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological and dietary exposure conclusions
Allura Red AC	R[a]	The Committee concluded that the new data do not give reason to revise the ADI and **confirmed the ADI of 0–7 mg/kg body weight** (bw). The Committee noted that the range of estimated dietary exposures to Allura Red AC for children based on reported or industry use data were below the upper bound of the ADI and concluded that dietary exposure to Allura Red AC for children and all other age groups does not present a health concern.
Carob bean gum	R[b]	**The Committee concluded that the available studies are not sufficient for the evaluation of carob bean gum for use in infant formula at the proposed use level**.[c] The Committee requests toxicological data from studies in neonatal animals, adequate to evaluate the safety for use in infant formula, to complete the evaluation.
Lutein esters from *Tagetes erecta*	R[d]	**The Committee removed the temporary designation[e]** (because the tentative status of the specifications was removed) **and established an ADI "not specified"** for lutein esters from *Tagetes erecta*.
Octenyl succinic acid (OSA)–modified gum arabic	R[f]	**The Committee removed the temporary designation[e] and established an ADI "not specified"** for OSA-modified gum arabic. The Committee confirmed the validity of the dietary exposure estimate for risk assessment purposes set at a previous meeting.
Pectin	R[g]	The no-observed-adverse-effect level (NOAEL) in a previously evaluated neonatal pig study was recalculated to be 1049 mg/kg bw per day using measured concentrations of pectin in milk replacer rather than target concentrations. At the new maximum proposed use level of 0.2%, the estimated exposure of infants 0–12 weeks of age would be up to 360 and 440 mg/kg bw per day at mean and high consumption. The margins of exposure for average and high consumers are 2.9 and 2.4, respectively, when compared with the NOAEL of 1049 mg/kg bw per day. On the basis of a number of considerations, **the Committee concluded that the margins of exposure calculated for the use of pectin at 0.2% in infant formula indicate low risk for the health of infants and are not of concern**.
Quinoline Yellow	R[h]	The Committee concluded that it was reasonable to use toxicology data on D&C Yellow No. 10 to support the database for Quinoline Yellow. **The Committee established an ADI of 0–3 mg/kg bw** (rounded value) for Quinoline Yellow on the basis of a NOAEL of 250 mg/kg bw per day for effects on body weight and organ weights

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological and dietary exposure conclusions
		in two long-term studies in rats on D&C Yellow No. 10. An uncertainty factor of 100 was applied to account for interspecies and intraspecies variability. The Committee concluded that dietary exposure to Quinoline Yellow for children and all other age groups does not present a health concern.
Rosemary extract	T[i]	**The Committee established a temporary ADI of 0–0.3 mg/kg bw for rosemary extract, expressed as carnosic acid and carnosol,** on the basis of a NOAEL of 64 mg carnosic acid + carnosol/kg bw per day, the highest dose tested in a short-term toxicity study in rats, with application of a 200-fold uncertainty factor. This uncertainty factor incorporates a factor of 2 to account for the temporary designation of the ADI. The Committee made the ADI temporary pending the submission of studies to elucidate the potential developmental and reproductive toxicity of the rosemary extract under consideration. An additional uncertainty factor to account for the lack of a chronic toxicity study was not considered necessary based on the absence of adverse effects in the short-term toxicity studies at doses up to and including the highest dose tested. **The temporary ADI applies to rosemary extract that meets the specifications prepared at the present meeting. It will be withdrawn if the required data are not provided by the end of 2018.** The Committee noted that the dietary exposure estimates for rosemary extract for high consumers, 0.09–0.81 mg/kg bw per day (as carnosic acid plus carnosol), may exceed the upper bound of the temporary ADI by up to 2.7-fold (for young children at the top end of the range of estimated dietary exposures). Based on the conservative nature of the dietary exposure assessments, in which it was assumed that all foods contained rosemary extracts at the maximum use level, the Committee concluded that this exceedance of the temporary ADI does not necessarily represent a safety concern.
Steviol glycosides	N[j] N,T[k]	**The Committee confirmed the ADI of 0–4 mg/kg bw, expressed as steviol. The Committee also confirmed that rebaudioside A from multiple gene donors expressed in *Yarrowia lipolytica* is included in the ADI.** The Committee concluded that it was not necessary to make the ADI temporary because the requested information to complete the specifications refers only to an update of the method and has no safety implication. The Committee noted that the predicted maximum dietary exposure to steviol glycosides of 4.0–4.4 mg/kg bw per day for young children who were high consumers exceeded the upper bound of the ADI (up to 110%), but the ADI was not exceeded for other age groups. Considering the conservative nature of the dietary exposure estimate, based on maximum use levels applied to all food consumed from categories with permissions for use in the countries assessed, steviol glycosides are not

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological and dietary exposure conclusions
		likely to present a health concern for any age group.
Tartrazine	R[l]	**The Committee established an ADI of 0–10 mg/kg bw**, on the basis of a NOAEL of 984 mg/kg bw per day for reductions in body weight in a chronic rat study, with application of a 100-fold uncertainty factor to account for interspecies and intraspecies variability. **The Committee withdrew the previous ADI of 0–7.5 mg/kg bw per day.** The Committee noted that the dietary exposure estimate for children aged 1–10 years was below the upper bound of the ADI and concluded that dietary exposure to tartrazine for the general population, including children, does not present a health concern.
Xanthan gum	R[m]	A NOAEL of 750 mg/kg bw per day was established for xanthan gum in neonatal pigs, which are an appropriate animal model for the assessment of the safety of the additive for infants. The margin of exposure based on this NOAEL and the conservative estimate of xanthan gum intake of 220 mg/kg bw per day by infants (high energy requirements for fully formula-fed infants) is 3.4. On the basis of a number of considerations, the Committee concluded that the consumption of xanthan gum in infant formula or formula for special medical purposes intended for infants is of no safety concern at the maximum proposed use level of 1000 mg/L.

N: new specifications; R: existing specifications revised; T: tentative specifications

[a] The method for the determination of lead was changed from atomic absorption to any method appropriate to the specified level. Updated HPLC conditions were added for determining subsidiary colouring matters and organic compounds other than colouring matters. The method of assay was changed to visible spectrophotometry, and spectrophotometric data were provided for the colour dissolved in water.

[b] For carob bean gum and carob bean gum (clarified). A limit for lead of 0.5 mg/kg for use in infant formula was introduced. There were insufficient data to set a limit for arsenic. The method descriptions for the determination of lead and sample preparation for residual solvents were updated.

[c] The Committee noted that the current use level of carob bean gum for infant formula or for formula for special medical purposes intended for infants in CODEX STAN 72-1981 (1000 mg/L) is much lower than the proposed use level (10 000 mg/L).

[d] The tentative status was removed. The assay value was increased from 60% to 75% for total carotenoids, a method for the determination of the proportion of zeaxanthin in total carotenoids (<10%) was included and amendments were made to the method for the determination of waxes.

[e] ADI "not specified" is used to refer to a food substance of very low toxicity that, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary exposure to 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.

[f] The tentative status was removed.

[g] The limit for lead for general use was lowered from 5 to 2 mg/kg, a limit for lead of 0.5 mg/kg for use in infant formula was introduced and the method descriptions for the determination of lead and sample preparation for residual solvents were updated.

[h] The tentative status was removed. Methods for determining lead and zinc were revised, the titanium trichloride assay was replaced with assay by spectrophotometry, the maximum wavelength of absorbance and absorptivity value for the colour dissolved in water were added, and HPLC conditions for determining the subsidiary colouring matters and organic compounds other than colouring matter and for assaying the colouring components were added.

[i] The published gas chromatography–mass spectrometry method for the determination of key volatiles of rosemary extract was included. Additional information is required to finalize the specifications (see Future work and recommendations below).

[j] A new specifications monograph (Rebaudioside A from Multiple Gene Donors Expressed in *Yarrowia lipolytica*) was prepared for the yeast-derived product.

[k] New tentative specifications for steviol glycosides were established, including a new title name (Steviol Glycosides from *Stevia rebaudiana* Bertoni) to reflect the separation of specifications by source material. The Definition and Assay specification was expanded from nine named leaf-derived steviol glycosides to include any mixture of steviol glycoside compounds derived from *Stevia rebaudiana* Bertoni, provided that the total percentage of steviol glycosides is not less than 95%. Additional information is required to finalize the specifications (see Future work and recommendations below).

[l] The method for the determination of lead was changed from atomic absorption to any method appropriate to the specified level. Updated HPLC conditions were added for determining subsidiary colouring matters and organic compounds other than colouring matters. The method of assay was changed to visible spectrophotometry, and spectrophotometric data were provided for the colour dissolved in water.

[m] The limit for lead in xanthan gum was maintained at 2 mg/kg for general use, and a limit for lead of 0.5 mg/kg for use in infant formula was introduced. The test method for the determination of residual solvents that employs a gas chromatographic method using a packed column was replaced with a method using a capillary column.

Food additives considered for specifications only

Food additive	Specifications
Acetylated distarch adipate	R, T[a,b]
Acetylated distarch phosphate	R, T[a,b]
Acetylated oxidized starch	R[b]
Acid treated starch	R, T[a,b]
Alkaline treated starch	R, T[a,b]
Aspartame	R[c]
Bleached starch	R, T[a,b]
Cassia gum	R, T[d]
Citric and fatty acid esters of glycerol	R[e]
Dextrin roasted starch	R, T[a,b]
Distarch phosphate	R, T[a,b]
Enzyme-treated starch	R, T[a,b]
Hydroxypropyl distarch phosphate	R, T[a,b]
Hydroxypropyl starch	R, T[a,b]
Monostarch phosphate	R, T[a,b]
Octanoic acid	R[f]
Oxidized starch	R[b]
Phosphated distarch phosphate	R, T[a,b]
Starch acetate	R[b]
Starch sodium octenyl succinate	R, T[a,b,g]
Total colouring matters	R[h]

R: existing specifications revised; T: tentative specifications

[a] Additional information is required for the removal of the tentative status (see Future work and recommendations below).

[b] The Committee noted that all the modified starches may additionally be subjected to bleaching and therefore included the appropriate purity tests in the revised specifications.

[c] The purity tests for 5-benzyl-3,6-dioxo-2-piperazineacetic acid and other optical isomers were replaced by new published and validated high-performance liquid chromatography (HPLC) tests. The identification characteristic for solubility in ethanol was changed from “slightly soluble” to “practically insoluble or insoluble”.

[d] The Committee decided to remove the current method for anthraquinones from the specifications and make the specifications tentative. The additional information required for the removal of the tentative status is noted under Future work and recommendations below.

[e] A limit for lead of 0.5 mg/kg for use in infant formula was introduced.

[f] The infrared spectrum identity test conditions and the reference spectrum were included.

[g] The limit for lead (2 mg/kg) was maintained, as no data were received in response to the call for data.

[h] Procedure 1 (water-soluble colouring matters) and Procedure 3 (lakes) were revised. Table 1 was revised to give spectrophotometric data for 17 synthetic colours, their aluminium lakes, cochineal extract and carmine dissolved in water and buffers. Reagents, solution preparations and sample preparation information were added. Equations shown in Procedures 1, 2 and 3 were edited. The tentative status of the method was removed. Where available, information on the wavelength of maximum absorbance, absorptivity and/or specific absorbance (including information on the solvent used) for the 17 synthetic colours and cochineal extract used to form a lake was included in Table 1 of the revised method. The Committee noted that chloroform is listed as a reagent in Procedure 2 (organic solvent–soluble colouring matters) and decided that efforts should be made to replace it.

Flavouring agents evaluated by the Procedure for the Safety Evaluation of Flavouring Agents

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

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class III			
2-(2-Hydroxy-4-methyl-3-cyclohexenyl)propionic acid gamma-lactone	2223	N	No safety concern
2-(2-Hydroxyphenyl)-cyclopropanecarboxylic acid delta-lactone	2224	N	No safety concern

N: new specifications

B. Aliphatic and aromatic amines and amides

The Committee concluded that the concerns previously expressed by the Committee at its sixty-ninth meeting as to in vivo genotoxicity and how to address the kidney effects and identify a NOAEL have not been sufficiently addressed and that the Procedure still could not be applied to 2-isopropyl-*N*,2,3-trimethylbutyramide (No. 1595).[1]

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class III			
N1-(2,3-Dimethoxybenzyl)-*N2*-(2-(pyridin-2-yl)ethyl)oxalamide	2225	N	No safety concern
(*R*)-*N*-(1-Methoxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide	2226	N	No safety concern
(*E*)-*N*-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-(3,4-dimethoxyphenyl)prop-2-enamide	2227	N	No safety concern
(*E*)-3-Benzo[1,3]dioxol-5-yl-*N*,*N*-diphenyl-2-propenamide	2228	N	No safety concern
N-Ethyl-5-methyl-2-(methylethenyl)cyclohexanecarboxamide	2229	N[a]	Additional data required to complete evaluation
N-Ethyl-2,2-diisopropylbutanamide	2005	M[b]	Additional data required to complete evaluation
N-(2-Hydroxyethyl)-2,3-dimethyl-2-	2010	M[b]	Additional data required to

[1] The statement currently contained in the specifications indicating that the safety evaluation had not been completed will be maintained.

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
isopropylbutanamide			complete evaluation
N-(1,1-Dimethyl-2-hydroxyethyl)-2,2-diethylbutanamide	2011	M[b]	Additional data required to complete evaluation

M: existing specifications maintained; N: new specifications

[a] The specifications include a statement that the safety evaluation for the flavouring agent had not been completed.

[b] The statement currently contained in the specifications indicating that the safety evaluation had not been completed will be maintained.

C. Aliphatic secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class II			
9-Decen-2-one	2216	N	No safety concern
Yuzunone	2217	N	No safety concern
1,5-Octadien-3-ol	2218	N	No safety concern
3,5-Undecadien-2-one	2219	N	No safety concern
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-ol	2220	N	No safety concern
(±)-1-Cyclohexylethanol	2221	N	No safety concern

N: new specifications

D. Cinnamyl alcohol and related substances

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
Ethyl alpha-acetylcinnamate	2211	N	No safety concern
Ethyl 2-hydroxy-3-phenylpropionate	2213	N	No safety concern
Structural class III			
3-(3,4-Methylenedioxyphenyl)-2-methylpropanal	2212	N[a]	Additional data required to complete evaluation
Cinnamaldehyde propyleneglycol acetal	2214	N	No safety concern
2-Phenylpropanal propyleneglycol acetal	2215	N	No safety concern

N: new specifications

[a] The specifications include a statement that the safety evaluation for the flavouring agent had not been completed.

E. Tetrahydrofuran and furanone derivatives

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class II			
2,5-Dimethyl-3(2*H*)-furanone	2230	N	No safety concern
Structural class III			
2,5-Dimethyl-4-ethoxy-3(2*H*)-furanone	2231	N	No safety concern
5-Methyl-3(2*H*)-furanone	2232	N	No safety concern
Ethyl 2,5-dimethyl-3-oxo-4(2*H*)-furyl carbonate	2233	N	No safety concern
4-Acetyl-2,5-dimethyl-3(2*H*)-furanone	2234	N[a]	Additional data required to complete evaluation

N: new specifications

[a] The specifications include a statement that the safety evaluation for the flavouring agent had not been completed.

Flavouring agents considered for specifications only

Flavouring agent	No.	Specifications
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one	1114	R[a]
6,10-Dimethyl-5,9-undecadien-2-one	1122	R[b]
3-Ammonium isovalerate	1203	R[c]
Theaspirane	1238	R[d]
alpha-Bisabolol	2031	R[e]
Glutamyl-valyl-glycine	2123	R[f]

[a] The Committee changed the assay minimum from greater than 98% as the *cis* isomer to greater than 95% as a sum of isomers, revised the ranges for refractive index and specific gravity, and introduced new information on the isomeric composition of the flavouring agent.

[b] The Committee indicated that the assay minimum was for a sum of isomers, changed the Chemical Abstracts Service (CAS) number, revised the information for solubility in ethanol, revised the ranges for refractive index and specific gravity, and introduced new information on the isomeric composition of the flavouring agent.

[c] The Committee corrected the molecular weight and chemical formula and revised the melting point range for the flavouring agent.

[d] The Committee lowered the assay minimum from greater than 97% (sum of stereoisomers) to greater than 85% (sum of stereoisomers), revised the ranges for refractive index and specific gravity, and introduced new information on the isomeric composition and secondary components of the flavouring agent.

[e] The Committee changed the assay minimum from greater than 93% to greater than 95% as a sum of isomers, added a second CAS number, revised the ranges for refractive index and specific gravity, clarified the range of the secondary component, and introduced new information on the isomeric composition of the flavouring agent.

[f] The Committee lowered the assay minimum from greater than 99% to greater than 95%.

Annex 1

Eight-second meeting of the Joint FAO/WHO Expert Committee on Food Additives

Geneva, 7–16 June 2016

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Annex 2

General considerations

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

Revisions of the Procedure for the Safety Evaluation of Flavouring Agents

The European Food Safety Authority (EFSA) and WHO recently reviewed the general threshold for toxicological concern (TTC) approach in a joint project, building on existing and ongoing work in this area. An expert workshop was convened in December 2014, primarily to provide recommendations as to how the existing TTC framework may be improved and expanded by updating/revising the Cramer classification scheme and extending the TTC approach. An important aspect was also to develop a globally harmonized decision-tree for a tiered approach on the application of the TTC in the risk assessment of chemicals from oral exposures.[1]

Based on the recommendations from this expert workshop, the Committee discussed the consequences for the existing JECFA Procedure for the Safety Evaluation of Flavouring Agents, which is based on the TTC concept, and proposed a revised Procedure. The main change proposed is to remove question 2 of the existing Procedure ("Can the substance be predicted to be metabolized to innocuous products?") and in consequence combine the A-side and B-side of the existing Procedure, because:

1) metabolism is an inherent part of the Cramer, Ford & Hall scheme[2] and the TTC values for the different classes;
2) models for predicting metabolism can have significant limitations, including lack of information on interspecies extrapolation and alterations in metabolite profiles arising from saturation of metabolic pathways;
3) prediction of the major pathways of metabolism may not reflect the hazard associated with a minor pathway; and
4) the B-side of the existing procedure requires toxicity data on the compound or a structurally related substance even if the dietary exposure was below the TTC value, which is inconsistent with the TTC concept.

Another change is to add an initial question regarding genotoxicity and in consequence to delete step B5 ("Do the conditions of use result in an intake greater than 1.5 µg/day?") from the Procedure. The Committee noted that this is the original United States Food and Drug Administration threshold of regulation value of 1.5 µg/person per day, but that this value is of little practical application in the Procedure. Moreover, the Cramer class thresholds as applied would be adequately protective for a non-genotoxic cancer end-point.

The Committee recommends these points for consideration when deciding on the adequacy of a resulting margin of exposure at step 5 of the revised procedure:

- What is the overall strength of the database?
- Is the margin of exposure based on a NOAEL for the flavouring agent or for a structurally related substance?
- What is the effect on which the NOAEL is based?

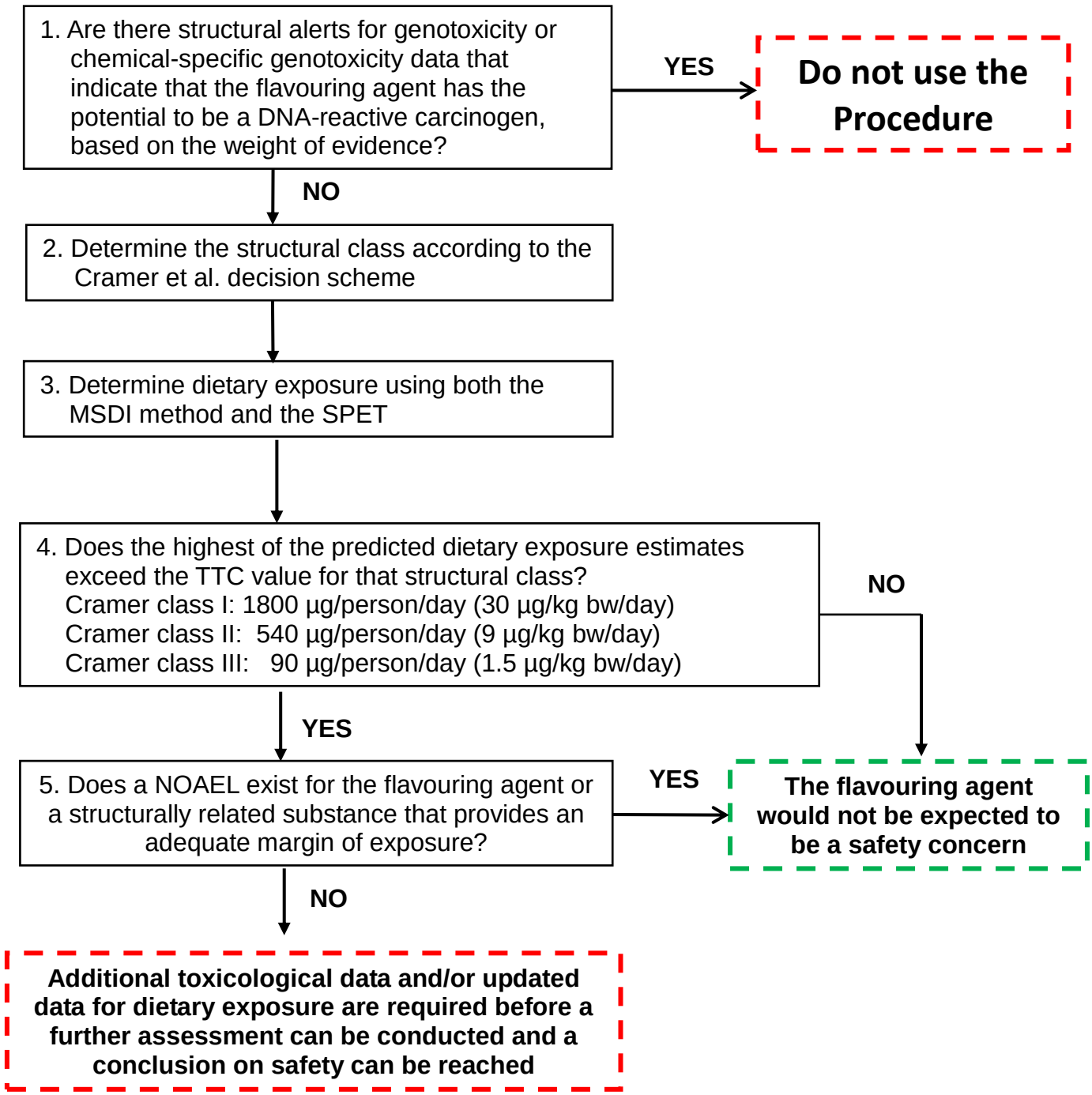
[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/1006e.pdf
[2] Cramer GM, Ford RA, Hall RL. Estimation of toxic hazard – a decision tree approach. Food Cosmet Toxicol. 1978;16:255–76.

- Is the NOAEL the highest dose tested or identified from a single-dose study?
- What is the duration of the study from which the NOAEL is identified?

If the overall database is considered, based on expert judgement, to be sufficiently robust, the Committee considered that a margin of exposure that accommodates at least a default safety factor as used in the assessment of food additives may be sufficient to conclude that the flavouring agent would not be expected to be a safety concern at current estimated levels of dietary exposure.

The Committee further concluded that the revised Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) should be applied in its future evaluations.

Fig. 1
Revised Procedure for the Safety Evaluation of Flavouring Agents



The Committee noted that application of the new Procedure would not have an impact on previous evaluations, because genotoxicity is considered in the current Procedure, metabolism is considered in the Cramer decision-tree and, overall, this new procedure is equally robust.

Approach for prioritizing flavouring agents for re-evaluation

The Committee at its seventy-ninth meeting held a preliminary discussion concerning the fact that the submission of additional toxicology data, including genotoxicity data, and/or exposure data for previously evaluated flavouring agents may trigger the need for re-evaluation of previously evaluated flavouring agents. The present Committee reiterated the need for the development of an approach, including a prioritization process, for the re-evaluation of flavouring agents based on all available toxicological data and updated exposure estimates. When developing such an approach, compounds that are used as comparators for structurally related compounds will require specific attention when new data on these become available. The Committee also noted that there is a need to compile data on all flavouring agents that were reported in the monographs of previous meetings and from other sources but not re-evaluated, to assist the prioritization for the re-evaluation.

Moreover, for any flavouring agents for which new toxicological studies are submitted, the sponsor needs to provide updated exposure data.

Limits for lead in specifications of food additives for use in infant formula

The Committee at its seventy-ninth meeting considered four additives for use in infant formula and formula for special medical purposes – namely, carrageenan, pectin, citric and fatty acid esters of glycerol (CITREM) and starch sodium octenyl succinate. At its Eighth Session, the Codex Committee on Contaminants in Foods (CCCF) set a maximum limit (ML) of 0.01 mg/kg for lead in infant formula (as consumed). The Committee at the seventy-ninth meeting noted that three of the four food additives considered for risk assessment at that meeting (pectin, CITREM and starch sodium octenyl succinate) could result in exceedance of the ML for lead in infant formula at proposed use levels if lead were present at the specification limits listed in the individual monographs (i.e. at 5 mg/kg in pectin and at 2 mg/kg in both CITREM and starch sodium octenyl succinate). The seventy-ninth JECFA also noted that the introduction of lower lead limits in the specifications (e.g. 1 mg/kg for pectin, 0.5 mg/kg for CITREM and 0.1 mg/kg for starch sodium octenyl succinate) would result in none of these additives exceeding the ML for lead in the final infant formula (i.e. 0.01 mg/kg) if these additives were included in infant formula at the maximum use level reviewed by JECFA.

For the current meeting, data were requested on the levels of lead present in CITREM, pectin and starch sodium octenyl succinate for use in infant formula, and the Committee received data on levels of lead in CITREM and pectin, but not for starch sodium octenyl succinate.

The Committee evaluated the data presented for levels of lead in 12 non-consecutive lots of CITREM. The levels of lead were below 0.1 mg/kg, the limit of quantification of the method (inductively coupled plasma optical emission spectrometry), demonstrating that the lead level of 0.5 mg/kg proposed by the seventy-ninth JECFA was achievable for CITREM used in infant formula. The current limit of 2 mg/kg for lead in the CITREM specifications monograph was maintained for general use, and a limit of 0.5 mg/kg was included for use in infant formula. The Committee also evaluated data presented for levels of lead in pectin for use in infant formula analysed by two different analytical methods. Levels reported for lead in 12 non-consecutive lots of pectin analysed by inductively coupled plasma atomic emission spectrometry were below the limit of detection of the method (0.4 mg/kg). The mean level of lead reported for five non-consecutive lots of pectin analysed by inductively coupled plasma

mass spectrometry was 0.017 mg/kg. Based on the data provided, the Committee noted that the levels of lead in pectin intended for use in infant formula were below the level of 1 mg/kg considered by the Committee at the seventy-ninth meeting. The current limit of 5 mg/kg for pectin in the specifications monograph was reduced to 2 mg/kg for general use, and a limit of 0.5 mg/kg was included for use in infant formula.

The Committee also considered the levels of lead in the specifications monographs of two other additives on the agenda for consideration for use in infant formula – namely, carob bean gum and xanthan gum – in light of this discussion. Based on the data provided, the Committee maintained the lead limits in the specifications monographs for these two additives for general use (2 mg/kg) and reduced them to 0.5 mg/kg for use in infant formula.

Based on the data submitted for CITREM, pectin, carob bean gum and xanthan gum, the Committee was reassured that the overall criterion for lead levels in the ingredients for use in infant formula is achievable. However, the Committee further reaffirmed that it is the responsibility of the infant formula manufacturers to ensure that the lead levels in the final infant formula (as consumed) comply with the ML for lead as set by the Eighth Session of CCCF.

The Committee recommended that all additives (including starch sodium octenyl succinate) for use in infant formula be reviewed for lead levels in the specifications.

Annex 3

Future work and recommendations

General considerations

Revisions of the Procedure for the Safety Evaluation of Flavouring Agents

The Committee recommended that the revised Procedure for the Safety Evaluation of Flavouring Agents should be applied in its future evaluations.

Approach for prioritizing flavouring agents for re-evaluation

The Committee reiterated the need for the development of an approach, including a prioritization process, for the re-evaluation of flavouring agents based on all available toxicological data and updated exposure estimates.

Replacement of packed column gas chromatographic methods in the specifications monographs

The Committee recommended that the FAO JECFA Secretariat establish a process to identify the food additive specifications monographs containing packed column gas chromatographic methods and request suitable methods (through a call for data), in order for the Committee to replace these methods in the specifications monographs.

Revision of the FAO JECFA Monographs 1, Combined Compendium of Food Additive Specifications, Volume 4

The Committee recommended that the FAO JECFA Secretariat establish a process for the revision of FAO JECFA Monographs 1, Combined Compendium of Food Additive Specifications, Volume 4.

Limits for lead in specifications of food additives for use in infant formula

The Committee recommended that all additives for use in infant formula be reviewed for lead levels in the specifications.

Limits for arsenic in specifications of food additives for use in infant formula

The Committee recommended that all additives for use in infant formula be reviewed for arsenic levels in the specifications.

Use of chloroform as solvent in the test methods associated with specifications monographs for synthetic colours

The Committee recommended the development of analytical methods with suitable replacement solvent(s), in order to replace chloroform, in the future.

General inclusion of infrared spectra

The Committee recommended that all future specifications for new flavouring agents contain a high-quality readable infrared spectrum in the data submission.

Inclusion of chemical structures in the JECFA flavourings database

The Committee recommended that chemical structures be included in the JECFA flavourings database.

Specific food additives (other than flavouring agents)

Carob bean gum

The Committee concluded that the available information is not sufficient for the evaluation of carob bean gum for use in infant formula at the proposed use level and requests toxicological data on neonatal animals, adequate to evaluate the safety for use in infant formula, to complete the evaluation.

The Committee noted that the sponsor also identified a cold-soluble carob bean gum for use in infant formula. However, no information was provided on the manufacturing and composition of the product, and the Committee was unclear which product is used in infant formula and formula for special medical purposes intended for infants.

Cassia gum

The Committee noted that cassia gum can be obtained from a number of companies and requested information on validated methods of analysis currently in use by providers of cassia gum. The methods submitted should contain details of the use of standard (reference) materials, the extraction efficiency of the initial steps, the recovery of the analytes in question, performance data and the results of the analysis of several batches of the material in commerce.

The tentative specifications will be withdrawn unless the requested information is submitted **before 31 December 2017**.

Citric and fatty acid esters of glycerol (CITREM)

The Committee recommended that data be submitted for the replacement of the packed column gas chromatography test method for the determination of total citric acid with a suitable method using a capillary/wide-bore column for consideration at a future meeting.

Lutein esters from **Tagetes erecta**

The Committee at its seventy-ninth meeting considered establishing a group ADI “not specified” for lutein esters from *Tagetes erecta* that would include lutein from *Tagetes erecta* and synthetic zeaxanthin and related xanthophylls. The current Committee was not able to consider this aspect in detail and recommended that this be taken up at a future meeting.

Modified starches

The Committee prepared tentative specifications for the following 13 modified starches and requires the following information for the removal of the tentative status:

Modified starch	Information required on
Dextrin roasted starch (INS No. 1400)	• A suitable method for the Dispersion or Reducing Sugars Distinguishing Test
Acid treated starch (INS No. 1401)	• A suitable method for the Dispersion or Reducing Sugars Distinguishing Test

Modified starch	Information required on
Alkaline treated starch (INS No. 1402)	• A suitable method for the Dispersion or Reducing Sugars Distinguishing Test
Bleached starch (INS No. 1403)	• Typical levels of residual reagents or by-products
Enzyme-treated starch (INS No. 1405)	• A suitable method for the Dispersion or Reducing Sugars Distinguishing Test
Monostarch phosphate (INS No. 1410)	• A suitable test for identification of the phosphate groups
Distarch phosphate (INS No. 1412)	• A suitable test for identification of the phosphate groups and of crosslinking
Phosphated distarch phosphate (INS No. 1413)	• A suitable test for identification of the phosphate groups and of crosslinking
Acetylated distarch phosphate (INS No. 1414)	• A suitable test for identification of the phosphate groups and of crosslinking
Acetylated distarch adipate (INS No. 1422)	• A suitable test for identification of the adipate groups • Levels of free adipic acid
Hydroxypropyl starch (INS No. 1440)	• A suitable method for the determination of propylene chlorohydrin
Hydroxypropyl distarch phosphate (INS No. 1442)	• A suitable method for the determination of propylene chlorohydrin • A suitable test for identification of the phosphate groups
Starch sodium octenyl succinate (INS No. 1450)	• A suitable test for identification of octenylsuccinate groups

The Committee recommended that the call for data also include method of manufacture for each of the 16 modified starches. The missing data are required **by 31 December 2017**.

Rosemary extract

The Committee made the ADI temporary pending the submission of studies to elucidate the potential developmental and reproductive toxicity of the rosemary extract under consideration. The temporary ADI will be withdrawn if the required data are not provided **by the end of 2018**.

The Committee prepared tentative specifications and requested validation information on the method for determination of residual solvents **by the end of 2018**.

The Committee requested that data on typical use levels in foods be provided **by the end of 2018** in order to refine the dietary exposure estimates.

Steviol glycosides

The specifications were made tentative pending submission of following information **by 31 December 2017**:

- method of assay to replace the existing method and including as many steviol glycosides as possible (at least those listed in Appendix 1 of the specifications) in steviol glycoside mixtures, along with supporting validation information and chromatograms;
- analysis results from a minimum of five batches for commercial samples, including supporting chromatograms.

Flavouring agents

Aliphatic and aromatic amines and amides

The Committee concluded that the concerns previously expressed by the Committee at its sixty-ninth meeting as to in vivo genotoxicity and how to address the kidney effects and identify a NOAEL had not been sufficiently addressed and that the Procedure for the Safety Evaluation of Flavouring Agents still could not be applied to 2-isopropyl-*N*,2,3-trimethylbutyramide (No. 1595). Information that would assist in resolving the concerns would include data informing on the difference in response observed in the kidney of male and female rats in the comet assay and on the potential of this compound to form reactive metabolites, as well as additional information on the kidney effects found at relatively low doses.

For *N*-ethyl-2,2-diisopropylbutanamide (No. 2005), *N*-(2-hydroxyethyl)-2,3-dimethyl-2-isopropylbutanamide (No. 2010) and *N*-(1,1-dimethyl-2-hydroxyethyl)-2,2-diethylbutanamide (No. 2011), NOAELs for these flavouring agents or structurally related substances were not available. Although No. 1595 is structurally related, the Committee concluded that No. 1595 could not be evaluated using the Procedure, and therefore this flavouring agent was not suitable to support the evaluation of these three flavouring agents. Therefore, for these three flavouring agents, the Committee concluded that additional data would be necessary to complete the evaluation.

For some previously evaluated flavouring agents in this group, additional toxicity data were available for this meeting. For *N*-isobutyl (*E*,*E*)-2,4-decadienamide (No. 1598) and (2*E*,6*E*/*Z*,8*E*)-*N*-(2-methylpropyl)-2,6,8-decatrienamide (No. 2077), the new studies resulted in lower NOAELs. In light of general considerations on the Procedure for the Safety Evaluation of Flavouring Agents and the need for an approach for re-evaluation in light of new data (see above), the Committee recommends re-evaluation of these two flavouring agents at a future meeting.

Additional data required to complete the evaluation according to the Procedure for the Safety Evaluation of Flavouring Agents

Additional toxicological and/or dietary exposure information is required to complete the toxicological evaluation of six flavouring agents (Nos 2005, 2010, 2011, 2212, 2229 and 2234).