Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Seventy-ninth meeting
Geneva, 17–26 June 2014

SUMMARY AND CONCLUSIONS

Issued 2 July 2014

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 17 to 26 June 2014. 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 V. Fattori, Agriculture and Consumer Protection Department, 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 seventy-ninth 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 nine food additives, revised the specifications for five other food additives and evaluated 28 flavouring agents according to the Procedure for Safety Evaluation of 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 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. 70. New and revised

specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs 16.

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/chem/jecfa/en/index.html

Toxicological information and information on specifications

Food additives considered for specifications only

Food additive	Specifications
Citric acid	R[a]
Gellan gum	R[b]
Polyoxyethylene (20) sorbitan monostearate	R[c]
Potassium aluminium silicate	R[d]
Quillaia extract (Type 2)	R[e]

R: existing specifications revised

[a] The method for the oxalate limit test was amended.

[b] The method of assay in the specifications refers to the alginates assay method. This method was replaced by a method without the use of mercury.

[c] Criteria for saponification and hydroxyl values were revised.

[d] The Committee reviewed the existing data as well as new information received from the sponsor and noted that potassium aluminium silicate (PAS) stabilizes the formed layers of titanium dioxide and/or iron oxide in the PAS-based pearlescent pigments. Therefore, the Committee concluded that PAS exerts a technological effect in the PAS-based pearlescent pigments; as a result, PAS could not be considered to function as a carrier according to the Codex definition for carrier. Hence, the Committee decided to delete the functional use as carrier in the specifications.

[e] The upper limit in the loss on drying specification was increased from 80% to 90%.

Food additives evaluated toxicologically and assessed for dietary exposure

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations
Benzoe tonkinensis	R[a]	Given the no-observed-adverse-effect level (NOAEL) of 500 mg/kg body weight (bw) per day for Benzoe tonkinensis identified in a 90-day oral toxicity study in rats and the previously established ADIs for the major components of Benzoe tonkinensis (benzoic acid, benzyl benzoate and vanillin), **the Committee confirmed the conclusion from the seventy-fourth meeting that Benzoe tonkinensis would not be of safety concern at current estimated dietary exposures**, provided that it complies with the specifications prepared at the current meeting, when used as a flavouring agent and in accordance with good manufacturing practice.

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations
Carrageenan (for use in infant formula and formula for special medical purposes intended for infants)	R	The margins of exposure (MOEs) between the NOAEL of 430 mg/kg bw per day (2250 mg/kg formula), the highest dose tested, from a neonatal pig study and human infant exposures at 2–4 weeks of age range from 2 to 12 on a body weight basis and from 2 to 8 on a concentration basis. The Committee noted that although the MOEs are small in magnitude, they are derived from a neonatal pig study in which the highest dose tested was without adverse effects on the gut or on immune parameters, supported by a neonatal minipig study. These new studies allay the earlier concerns that carrageenan, which is unlikely to be absorbed, may have a direct effect on the immature gut. The Committee also took account of the previous toxicological database on carrageenan, which did not indicate other toxicological concerns. It also noted that at carrageenan concentrations higher than 2500 mg/kg, formula becomes highly viscous, which adversely affects palatability and growth. **The Committee concluded that the use of carrageenan in infant formula or formula for special medical purposes at concentrations up to 1000 mg/L is not of concern.** The Committee recognized that there is variability in medical conditions among infants requiring formulas for special medical purposes that contain the higher levels of carrageenan, and the Committee noted that these infants would normally be under medical supervision.
Citric and fatty acid esters of glycerol (CITREM) (for use in infant formula and formula for special medical purposes intended for infants)	R	The Committee considered it unlikely that consumption of formulas containing typical levels of CITREM used in powdered formulas (up to 2.7 g/L as reconstituted), which is equivalent to an exposure to citrate of 440 mg/kg bw per day for the very young infant at the 95th percentile energy intake, would cause diarrhoea. At the high end of the requested range for use (up to 9 g/L), which is equivalent to an exposure to citrate of 1140 mg/kg bw per day for the very young infant at the 95th percentile energy intake, diarrhoea might occur in some infants. **The Committee concluded that there are no toxicological concerns about the use of CITREM in infant formula and formula for special medical purposes at concentrations up to 9 g/L.** At the higher use levels, there is a possibility of diarrhoea from free citric acid released from formula containing CITREM. Given the paucity of clinical data and the fact that exposure assumptions for citric acid have been maximized, it is difficult to estimate the risk of diarrhoea, but it is considered to be low.

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations
Gardenia yellow	No[b]	Given the deficiencies in the toxicological and specifications databases, including incomplete data on the manufacturing process and composition of the material, missing toxicological studies (e.g. long-term toxicity, carcinogenicity, reproductive toxicity and developmental toxicity), the inadequate characterization of the test material in the available toxicological studies and limited reporting of the available studies, **the Committee was unable to evaluate gardenia yellow proposed for use as a food colour.**
Lutein esters from *Tagetes erecta*	N, T[c]	The Committee concluded that there was no need to establish a numerical ADI. This decision was based on a number of factors, including the absence of any observed toxicity of lutein or lutein esters in any of the available toxicological studies in animals; the absence of any adverse effects in humans consuming lutein or lutein esters; the large MOE (>1500) between the NOAEL for lutein in a new 13-week study in rats and the estimated dietary exposure of 0.32 mg/kg bw per day (from additive and natural sources); a 2-fold increase in the NOAEL for lutein as a result of the new 13-week study; and the fact that lutein esters from *Tagetes erecta* are considered to be substitutional for other lutein extracts. **The Committee established a temporary ADI "not specified"[e] for lutein esters from *Tagetes erecta*.** The ADI was made temporary because the specifications for lutein esters from *Tagetes erecta* were tentative. The Committee 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, but this would be possible only when the specifications for lutein esters from *Tagetes erecta* are finalized.
Octenyl succinic acid (OSA)–modified gum arabic	R, T[c]	The tentative status of the specifications was maintained pending the submission of additional data. The Committee noted that additional safety data may also be needed to complete the evaluation of OSA-modified gum arabic. **The Committee decided that the temporary ADI "not specified" will be withdrawn unless adequate data to complete the safety evaluation are submitted by the end of 2015.**
Octenyl succinic acid (OSA)–modified starch (starch sodium octenyl succinate) (for use in infant formula and formula for special medical purposes intended for infants)	R[d]	Taking into account the overall low toxicity of OSA-modified starch, the conservatism in the NOAEL, which was the highest dose tested in a study in neonatal animals, and in the exposure assessments, as well as the supporting evidence from clinical trials and post-marketing surveillance, **the Committee concluded that the consumption of OSA-modified starch in infant formula or formula for special medical purposes intended for infants is not of concern at use levels up to 20 g/L.** New data available since the twenty-sixth meeting confirm the very low toxicity of OSA-modified starch, and **the Committee confirmed the ADI "not specified" established at that meeting for its use as a food additive for the general population.**

Food additive	Specifications	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations
Paprika extract	M	**The Committee established an ADI for paprika extract used as a food colour of 0–1.5[1] mg/kg bw, expressed as total carotenoids**, with the application of an uncertainty factor of 100 to the NOAEL of 153 mg/kg bw per day from a 2-year toxicity and carcinogenicity study in rats. The Committee concluded that dietary exposure to paprika extract used as a food colour does not present a health concern.
Pectin (for use in infant formula and formula for special medical purposes intended for infants)	M	In a 3-week study in neonatal pigs fed pectin-containing milk replacer, the NOAEL was 847 mg/kg bw per day, with decreased feed intake and body weight gain observed at 3013 mg/kg bw per day. Using the NOAEL from this study, the MOEs were estimated to be 0.9 for infants with median energy intake and 0.8 for infants with high (95th percentile) energy intake. The Committee concluded that estimated exposure to pectin from its use in infant formula is in the region of the NOAEL derived from the neonatal pig study and close to the LOAEL based on decreased feed intake and body weight gain. While no overt toxicological effects were observed in the neonatal pigs, decreased food intake and body weight gain would be considered an undesirable effect in human infants. The available clinical studies were mainly conducted with pectin or pectin-derived oligosaccharides at concentrations of 0.2% or less and therefore do not provide support for tolerance and normal growth at the proposed use level. Therefore, **the Committee concluded that the use of pectin in infant formulas at the maximum proposed use level (0.5%) is of concern.**

M: existing specifications maintained; N: new specifications; No: no specifications prepared; R: existing specifications revised; T: tentative specifications

[a] The tentative qualification of the specifications was removed.

[b] No specifications were prepared. Information is required to prepare specifications (see Annex 3).

[c] Additional information is required to finalize the specifications (see Annex 3).

[d] The analytical method for the determination of the octenyl succinyl group in starch sodium octenyl succinate was amended.

[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.

[1] The Committee noted that although derived values, such as health-based guidance values, should be rounded to a single significant figure, it decided to use two significant figures in the present case, as the impact of rounding to one significant figure would be more than 30%.

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

A. Aliphatic and alicyclic hydrocarbons

The Committee determined that the flavouring agent α-ionene (No. 2193), which was submitted for evaluation as part of this flavouring agent group, did not fit into this group on the basis of its chemical structure and did not evaluate α-ionene.

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
1-Octene	2191	N	No safety concern
2,4-Nonadiene	2192	N	No safety concern
4-Methyl-*cis*-2-pentene	2194	N	No safety concern
1-Nonene	2195	N	No safety concern
1,3,5,7-Undecatetraene	2196	N	No safety concern
Mixture of methyl cyclohexadiene and methylene cyclohexene	2197	N	No safety concern

N: new specifications

B. Aliphatic and aromatic ethers

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class III			
Cassyrane	2189	N	No safety concern
1-Cyclopropanemethyl-4-methoxybenzene	2190	N	No safety concern
Nerolidol oxide	2137	M	No safety concern

M: existing specifications maintained; N: new specifications

C. Ionones and structurally related substances

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
β-Isomethylionone	2186	N	No safety concern
Pseudoionone	2187	N	No safety concern
trans-α-Damascone	2188	N	Additional data required to complete evaluation

N: new specifications

D. Miscellaneous nitrogen-containing substances

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class III			
3-[3-(2-Isopropyl-5-methylcyclohexyl)-ureido]-butyric acid ethyl ester	2203	N	No safety concern
4-Amino-5-(3-(isopropylamino)-2,2-dimethyl-3-oxopropoxy)-2-methylquinoline-3-carboxylic acid (and its hemisulfate monohydrate salt)	2204	N	No safety concern
	2204.1	N	No safety concern

N: new specifications

E. Monocyclic and bicyclic secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class II			
2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-ol	2198	N	No safety concern
dl-Camphor	2199	N	No safety concern
l-Fenchone	2200	N	No safety concern
2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one	2201	N	No safety concern

N: new specifications

F. Phenol and phenol derivatives

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class II			
Myricitrin	2207	N	No safety concern
Structural class III			
Naringin dihydrochalcone	2208	N	No safety concern
1-(2,4-Dihydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)propan-1-one	2209	N	No safety concern
(−)-Matairesinol	2210	N	No safety concern

N: new specifications

G. Phenyl-substituted aliphatic alcohols and related aldehydes and esters

The Committee concluded that the Procedure could not be applied to (±)-2-phenyl-4-methyl-2-hexenal (No. 2069) until concerns regarding genotoxicity are resolved. In addition, the evaluations of the other α,β-unsaturated aldehydes in this group (Nos 1472–1494 and 1476) should be reconsidered at a future meeting, given the potential genotoxicity of 2-phenyl-2-butenal (No. 1474).

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
Ethyl 3-(2-hydroxyphenyl)propanoate	2202	N	No safety concern

N: new specifications

H. Sulfur-containing heterocyclic compounds

The Committee concluded that 2,5-dimethyl-3-acetylthiophene (No. 1051) is mutagenic in vitro and in vivo and considered that it is inappropriate for such a compound to be used as a flavouring agent or for any other food additive purpose. It therefore withdrew the previous conclusion of the Committee. The Committee is also aware that the flavouring industry has already taken steps to remove this compound from the market. Specifications established at the fifty-ninth meeting for No. 1051 were also withdrawn based on toxicological concerns.

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class II			
Triethylthialdine	2205	N	No safety concern
Structural class III			
2-Isopropyl-4-methyl-3-thiazoline	2206	N	No safety concern

N: new specifications

Annex 1

Seventy-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Geneva, 17–26 June 2014

Members

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Mrs I. Meyland, Birkerød, Denmark (*Vice-Chairperson*)
Dr U. Mueller, Food Standards Australia New Zealand, Barton, ACT, Australia
Dr G. Pascal, Le Breuil, Saint Alyre d'Arlanc, France
Dr J. Schlatter, Zurich, Switzerland
Dr M. Veerabhadra Rao, Quality Control Department, Department of the President's Affairs, Al Ain, United Arab Emirates
Mrs H. Wallin, Helsinki, Finland (*Joint Rapporteur*)

Secretariat

Mr D. Arcella, Evidence Management, European Food Safety Authority, Parma, Italy (*WHO Expert*)
Dr S. Barlow, Brighton, East Sussex, England, United Kingdom (*WHO Expert*)
Dr A. Bruno, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy (*Codex Secretariat*)
Dr R. Cantrill, AOCS, Urbana, IL, USA (*FAO Expert*)
Dr J. Chen,[1] Chairman of the Codex Committee on Food Additives (CCFA), Institute of Nutrition and Food Safety, Chinese Centers for Disease Control and Prevention, Beijing, China (*CCFA Chairman*)
Mr P. Cressey, ESR (Institute of Environmental Science and Research Ltd), Christchurch, New Zealand (*FAO Expert*)
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Mr J. Kim, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland (*WHO Secretariat*)
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Professor O.E. Orisakwe, Faculty of Pharmacy, University of Port Harcourt, Choba, Rivers State, Nigeria (*WHO Expert*)
Professor S. Rath, Department of Analytical Chemistry, University of Campinas, São Paulo, Brazil (*FAO Expert*)

[1] Invited but unable to attend.

Mr J. Reeve, Biosecurity Science, Food Science and Risk Assessment Directorate, Regulation and Assessment Branch, Ministry for Primary Industries, Wellington, New Zealand (*WHO Expert*)
Ms M. Sheffer, Orleans, Ontario, Canada (*WHO Technical Editor and Co-Rapporteur*)
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Annex 2

General considerations

An edited version of this section will appear in the report of the seventy-ninth 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.

Threshold of toxicological concern (TTC) principle: update on WHO project and implications for the Procedure for the Safety Evaluation of Flavouring Agents

The Committee was informed about a project that WHO is undertaking in collaboration with the European Food Safety Authority (EFSA) on a review of the application of the threshold of toxicological concern (TTC) in the risk assessment of chemicals, based on the current state-of-the-science and building on existing work. A draft report was presented reviewing the Cramer classification scheme, with a focus on how metabolism is taken into account and a review of class thresholds and the underlying science.

A revised JECFA decision-tree for the evaluation of flavours was proposed. After a brief discussion, the Committee recommended that further considerations are necessary and that a proposal should be drafted for consideration at the next JECFA meeting at which flavouring agents will be evaluated.

The Committee was also informed about a new decision-tree under development by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for the evaluation of pesticide metabolites using the TTC principle.

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

The Committee at the present meeting considered four additives for use in infant formula and formula for special medical purposes intended for infants – namely, carrageenan; citric and fatty acid esters of glycerol (CITREM); pectin; and starch sodium octenyl succinate (octenyl succinic acid (OSA)–modified starch). The Committee noted that the Eighth Session of the Codex Committee on Contaminants in Foods (CCCF) agreed to a maximum level (ML) of 0.01 mg/kg for lead in infant formula (as consumed). The Committee also noted that with the exception of carrageenan, use of the other three food additives at proposed use levels could result in an exceedance of the ML of lead in infant formula. This situation was estimated to occur if lead were present in the additive at the specified limit – i.e. 2 mg/kg in CITREM and starch sodium octenyl succinate (OSA-modified starch) and 5 mg/kg in pectin. This estimation was calculated without considering the contribution of other ingredients to the overall lead level in infant formulas.

The Committee noted that the responsibility for ensuring that the final infant formulas comply with the ML for lead remains with infant formula producers. Furthermore, the Committee noted that data provided at the present meeting by the sponsors indicate that individual food additives can be produced with lead levels below the specified limits as listed above. Considering this, the Committee noted that lower lead limits in the specifications – for instance, 0.1 mg/kg for starch sodium octenyl succinate (OSA-modified starch), 1 mg/kg for pectin and 0.5 mg/kg for CITREM – would result in none of the additives exceeding the ML for lead in the final infant formula (i.e. 0.01 mg/kg). The specifications monographs for some of the food additives for use in infant formulas that were considered for safety review at this meeting are also used in the manufacture of other foods. Thus, the Committee agreed that it would be necessary to confirm with manufacturers that the lower lead limits would also be

achievable for the intended use of these food additives in products other than infant formulas.

The Committee refers back to the CCFA on whether specific purity criteria for additives for use in infant formulas should be considered and appropriate ways to present these criteria (e.g. establishing specifications for additives for use in infant formulas only; establishing different purity limits for additives for use in infant formulas in existing specifications).

As an additional consideration, the Committee noted that if separate specifications for additives in infant formulas were considered necessary, microbiological criteria should also be included.

The use of the margin of exposure (MOE) for the evaluation of additives used in infant formula

The acceptable daily intake (ADI) concept does not apply to infants up to the age of 12 weeks because they might be at risk at lower levels of exposure compared with older age groups. This is due to special considerations, such as their immature metabolic capacities, the greater permeability of the immature gut, and their rapid growth and development. Therefore, risk characterization for very young infants has to be considered on a case-by-case basis.

Toxicological testing strategies for additives to be used in infant formulas require approaches that differ from those generally adopted for food additives. For example, evaluation of food additives to be used in infant formulas requires consideration of safety studies involving exposure of very young animals. The reproductive and developmental toxicity studies commonly available for evaluations of chemicals in food address the possible impact on neonatal animals arising through in utero and lactational exposure. However, they frequently do not incorporate direct oral administration to neonatal animals, and such studies are required for the evaluation of food additives in infant formula. If the additive is proposed for use in infant formula at relatively high levels (e.g. 0.1% or greater), then conducting toxicological studies in neonatal animals at doses two or more orders of magnitude greater than the anticipated human exposure, which is the approach commonly taken for food additives, may not be feasible.

The Committee noted that for three of the four food additives on its current agenda, proposed for use in infant formulas, the margins of exposure (MOE) between the no-observed-adverse-effect level (NOAEL) and the estimated daily exposures to the food additives were in the range of 0.8–12 for infants. Interpretation of the MOE needs to take into account uncertainties or conservatisms that may exist in the toxicological point of departure or in the exposure estimates.

Considerations related to the toxicological point of departure to be taken into account in interpreting the MOE include:

- absorption, distribution, metabolism and excretion – for example, whether or not the additive is absorbed, comparison of potential for metabolic activation and detoxication in the neonatal organism compared with the adult;
- the overall toxicological profile of the substance, including identification of critical effects;
- the potential effects of exposure during life stages in experimental animals of relevance to human infants;
- the relevance for the human infant of the neonatal animal models used in toxicological testing;
- whether adverse effects have been identified in the toxicological studies in neonatal animals, or if the NOAELs are the highest doses tested;

- the design and outcome of any clinical studies conducted with infants (e.g. total number and age of infants tested, growth, tolerance, types of adverse reaction examined); and
- reports of adverse reactions in post-marketing surveillance, where the infant formula is already in use in some countries.

Factors related to the dietary exposure assessments that should be taken into account for the interpretation of an MOE include the following assumptions and considerations:

- Formula is the only source of nutrition for the first 12 weeks of life.
- The additive will be used at the maximum proposed level.
- An energy density of 67 kcal/100 mL (280 kJ/100 mL) is used to convert energy to the volume of formula ingested daily.
- High infant formula consumption is derived from 95th percentile energy intakes.
- Variability of exposure among infants is small.
- Duration of exposure is for a limited time, and exposure decreases on a body weight basis during the exposure period.

The Committee concluded that when the above issues have been taken into account, an MOE in the region of 1–10 could be interpreted as indicating low risk for the health of infants aged 0–12 weeks consuming the food additive in infant formula.

Need for an approach for prioritizing flavouring agents for re-evaluation

At this meeting, the Committee held a preliminary discussion concerning the fact that the submission of additional toxicology data, including genotoxicity data, and/or exposure data for new or previously evaluated flavouring agents may trigger the need for re-evaluation of previously evaluated flavouring agents.

Three examples encountered at the present meeting are described. In the first example, 3-acetyl-2,5-dimethylthiophene (No. 1051) was on the agenda for reconsideration at this meeting because new data suggested genotoxic potential. Positive in vitro and in vivo genotoxicity data raised concerns about No. 1051 and previously evaluated thiophenes that are metabolized to thiophene epoxides, indicating that reconsideration of the Committee's conclusions regarding the safety of the previously evaluated thiophenes is warranted.

Second, 2-phenyl-2-butenal (No. 1474) was evaluated earlier as a flavouring agent, and it is structurally related to (±)-2-phenyl-4-methyl-2-hexenal (No. 2069), under consideration at this meeting. Genotoxicity data for No. 1474, used as a structural analogue for No. 2069, were equivocal, raising concerns about the potential genotoxicity of No. 1474 and possibly other previously evaluated compounds with similar structures in this group, in addition to No. 2069. The Committee noted that No. 2069 should not be evaluated for use as a flavouring agent until the concerns related to genotoxicity are resolved, and the safe use of No. 1474 and structurally related substances as flavouring agents should be reconsidered.

Third, *trans*-α-damascone (No. 2188) was submitted for evaluation at the current meeting of the Committee. Several isomers of No. 2188 were evaluated previously by the Committee, including β-damascone (No. 384), α-damascone (No. 385) and δ-damascone (No. 386), and each was found to be of no safety concern based on dietary exposures estimated by the maximum survey-derived intake (MSDI) method. At this meeting, the same toxicological database used for the evaluation of Nos 384–386 was used for No. 2188. However, the NOAEL for No. 384, used as a structural analogue for No. 2188, was only 200 times the single-portion exposure technique (SPET) estimate for exposure to No. 2188 (600 µg/day). If the SPET estimate of exposure for use of No. 384, No. 385 or No. 386 as a flavouring agent is similar to that for No. 2188, the safety of each of these compounds for use as a flavouring agent could be called into question.

Based on the evaluations conducted on these flavouring agents at the present meeting, the Committee recommended that an approach be developed for prioritizing flavouring agents for re-evaluation based on all available toxicological data and updated exposure estimates.

Annex 3

Future work and recommendations

General considerations

Threshold of toxicological concern (TTC) principle: update on a WHO project and implications for the Procedure for the Safety Evaluation of Flavouring Agents

The Committee recommended that a proposal regarding a revised JECFA decision-tree for the evaluation of flavours based on application of the threshold of toxicological concern (TTC) in the risk assessment of chemicals should be further considered and a proposal prepared for consideration at the next JECFA meeting at which flavours will be evaluated.

Need for an approach for prioritizing flavouring agents for re-evaluation

The Committee held a preliminary discussion concerning the fact that the submission of additional toxicology data, including genotoxicity data, and/or exposure data for new or previously evaluated flavouring agents may trigger the need for re-evaluation of previously evaluated flavouring agents. The Committee recommended that an approach be developed for prioritizing flavouring agents for re-evaluation based on all available toxicological data and updated exposure estimates.

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

The Committee referred back to the Codex Committee on Food Additives (CCFA) on whether specific purity criteria for additives for use in infant formulas should be considered and appropriate ways to present these criteria (e.g. establishing specifications for additives for use in infant formulas only; establishing different purity limits for additives for use in infant formulas in existing specifications).

Specific food additives (other than flavouring agents)

Citric and fatty acid esters of glycerol (CITREM)

The Committee noted that the test method for the determination of total citric acid in the specifications monograph for CITREM currently employs a gas chromatographic method using a packed column. The Committee recommended the submission of data for a suitable method using a capillary/wide-bore column to replace the current method for consideration at a future meeting.

Gardenia yellow

The Committee noted that it is not clear whether the material tested toxicologically was representative of gardenia yellow. In addition, the available toxicity studies have not been conducted following internationally recognized guidelines, and a number of studies were performed using non-relevant routes of administration. Finally, there are no long-term toxicity, carcinogenicity, reproductive toxicity or developmental toxicity studies available.

In order to establish specifications, the Committee requires:

- information on the manufacturing process, including purification steps;
- analytical data on the composition of the substance, including the total amount of colouring matter and relevant compounds of known biological activity, such as geniposide and genipin;
- data on loss on drying;
- information on a method of assay;
- analytical data on at least five different batches of commercial materials supporting the specifications; and
- data on stability in food.

Lutein esters from **Tagetes erecta**

New tentative specifications were prepared. The Committee requested the following information, **by the end of 2015**, to complete the safety assessment:

- details on the manufacturing process, including purification steps;
- detailed analytical data on the full composition of at least five different batches of commercially available product to support the specifications;
- method of analysis to determine carotenoid composition; and
- method of analysis to determine the composition of the non-carotenoid lipidic fraction.

Octenyl succinic acid (OSA)–modified gum arabic

The existing specifications were revised and their tentative status was maintained, pending the submission of the following information, **by the end of 2015**:

- data on the manufacturing process, including purification steps;
- chemical characterization of the product in commerce;
- updated analytical methods for the determination of esterified (bound) and residual (free) OSA;
- results of the analysis of at least five batches of product in commerce; and
- applicability of the high-performance liquid chromatographic method for the determination of residual OSA.

Modified starches

The existing specifications monograph for modified starches includes 16 different modified starches, which complicates revisions of the specifications for any individual modified starch. Therefore, the Committee recommended that the specifications monograph for the modified starches be split into 16 individual specifications monographs.

The Committee, as noted at its seventy-sixth meeting, considered that it would also be necessary to revise the specifications for all the modified starches, including test methods, at future meetings.

Pectin

The Committee requested additional data to support the safety evaluation of pectin in infant formula, including an explanation for the decreased feed intake and body weight gain in neonatal pigs.

Flavouring agents

Phenyl-substituted aliphatic alcohols and related aldehydes and esters

The Committee concluded that the Procedure for the Safety Evaluation of Flavouring Agents could not be applied to (±)-2-phenyl-4-methyl-2-hexenal (No. 2069) until concerns regarding genotoxicity are resolved. In addition, the evaluations of the other α,β-unsaturated aldehydes in this group (Nos 1472–1494 and 1476) should be reconsidered at a future meeting, given the potential genotoxicity of 2-phenyl-2-butenal (No.1474).

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 one flavouring agent (No. 2188). The Committee was aware of additional genotoxicity data reporting equivocal results for a structurally related compound; therefore, information to address any concerns regarding potential genotoxicity should also be provided.