Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninety-seventh meeting (Safety evaluation of certain food additives)
31 October–9 November 2023

SUMMARY AND CONCLUSIONS

Issued on 24 November 2023

The Ninety-seventh meeting of the Joint FAO/WHO Executive Committee on Food Additives was held in Rome from 31 October to 9 November 2023. The purpose of the meeting was to evaluate the safety of certain food additives and flavourings. The present meeting was the Ninety-seventh in a series of similar meetings. The tasks before the Committee were to (a) further elaborate principles governing the evaluation of food additives; (b) undertake safety evaluations of certain food additives; (c) review and prepare specifications for certain food additives; and (d) establish specifications for certain flavouring agents.

Dr R. Cantrill served as Chairperson and Dr D. Bedford served as Vice-chairperson. Ms A. Vlachou and Mr K. Petersen served as joint secretaries.

The Committee evaluated the safety of one food additive, including revising its specifications, and evaluated the safety of three groups of flavouring agents.

The report of the meeting will be published in the WHO Technical Report Series (TRS 1051). The report will summarize the main conclusions of the Committee in terms of acceptable daily intakes (ADIs) and other toxicological, dietary exposure and safety recommendations. Information on deliberations and conclusions with regards to the specifications for the identity and purity of certain food additives examined by the Committee, and on specifications for the flavouring agents, will also be included.

The participants are listed in Annex 1. Future work and recommendations arising from the summary report of the Ninety-seventh JECFA meeting are summarized in Annex 2. Finally, Annex 3 includes requests for corrections that were reported to the JECFA Secretariat, evaluated by the Committee and found to be necessary (note that these corrections will only be made in the electronic versions available in the online database).

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 88. New and revised specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs No. 32.

More information on the work of JECFA is available at: http://www.fao.org/food-safety/scientific-advice/jecfa/en/ and https://www.who.int/foodsafety/en/.

Toxicological and dietary exposure information and conclusions

Food additive evaluated toxicologically and assessed for dietary exposure

Titanium dioxide (TiO_2)

The Committee evaluated TiO_2 (INS 171) at its Thirteenth meeting *(1)* and assigned an ADI "not specified"[1] based on an absence of significant absorption and a lack of toxicological effects in the available experimental animal and human studies at the time.

At the present meeting, the Committee considered additional toxicological studies relevant to the safety assessment of INS 171 that investigated the toxicokinetics, acute toxicity, short-term toxicity, long-term toxicity and carcinogenicity, genotoxicity, and reproductive and developmental toxicity, as well as special studies addressing the short-term initiation/promotion potential for colon cancer.

The Committee identified a number of TiO_2 test materials that were considered representative of INS 171. Further, the Committee recognized that a large number of toxicological studies have been conducted using test materials, including nanoparticles, having size distributions and physico-chemical properties not comparable to INS 171. These studies on non-representative materials were evaluated by the Committee, but it was concluded that they were not relevant to the safety assessment of INS 171.

INS 171 was poorly absorbed from the gastrointestinal tract of mice and rats. No adverse effects were observed in short-term studies in mice and rats receiving INS 171 in the diet, with NOAELs of 15 000 mg/kg bw per day and 5000 mg/kg bw per day in mice and rats, respectively, the highest doses tested. The Committee noted that the available data did not provide convincing evidence of genotoxicity for INS 171, but recognized the limitations in current methodologies with respect to the testing of poorly soluble particulate materials. Although there were uncertainties in the genotoxicity data, the Committee took into account the fact that INS 171 was not carcinogenic in adequately conducted 2-year studies in mice and rats at doses of up to 7500 mg/kg bw per day for mice and 2500 mg/kg bw per day for rats, the highest doses tested. There was no evidence of reproductive or developmental toxicity in studies in rats at INS 171 doses up to 1000 mg/kg bw per day, the highest doses tested.

Available studies in humans and postmortem analysis of tissues suggested that the oral bioavailability of TiO_2 in humans is very low. The Committee noted that there are currently no epidemiological studies that allow any conclusions to be drawn with respect to an association between dietary exposure to INS 171 and human health effects.

At the present meeting, the Committee evaluated estimates of dietary exposure to INS 171. Based on the estimates considered, the Committee selected a high P95 estimate of exposure to INS 171 of 10 mg/kg bw per day for the evaluation.

Considering the very low oral absorption of INS 171, and in the absence of any identifiable hazard associated with INS 171 in the diet, the Committee reaffirmed the ADI "not specified" established at the Thirteenth meeting.

A toxicological and dietary exposure monograph addendum was prepared.

The specifications monograph was revised. Specifications for the content of alumina and silica were removed, as TiO_2 coated with alumina or silica is not used as a food additive. The specification for the level of Pb soluble in 0.5 N HCl was reduced from 10 mg/kg to 5 mg/kg and the level of Cd soluble in 0.5 N HCl was reduced from 1 mg/kg to 0.5 mg/kg.

The chemical and technical assessment was revised.

[1] The Committee used the term "not limited", a term that is no longer used by JECFA and that has the same meaning as ADI "not specified".

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

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

The Committee decided not to review succinic acid (No. 2307) because it had previously been evaluated as a food additive at the Twenty-ninth meeting *(2)*; at that meeting, the Committee concluded that succinic acid does not represent a hazard at the levels at which it is likely to be used as a food additive, due to its normal role in metabolism.

The Committee could not evaluate flavouring agents Nos 1973 and 1988. Only study summaries without the original full study reports had been submitted for evaluation for No. 1973, and no data were submitted for No. 1988.

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
(±)-6-Methoxy-2,6-dimethylheptanal	2308	N	No safety concern
Ethyl 5-formyloxydecanoate	2309	N	No safety concern
Mixture of ricinoleic acid, linoleic acid and oleic acid	2310	N	No safety concern
Ethyl 3-methyl-2-oxopentanoate	2311	N	No safety concern

N: new specifications.

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

The studies of genotoxicity available for 4,7-decadienal (mixture of isomers) (No. 2298) indicated positive results in vitro, which did not allow the evaluation to be completed at this meeting. The Committee concluded that further investigation is required to demonstrate the absence of clastogenicity.

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
(4*Z*,7*Z*)-Trideca-4,7-dienal	2286	N	No safety concern
cis-5-Dodecenyl acetate	2287	N	No safety concern
trans-5-Dodecenal	2288	N	No safety concern
cis-6-Dodecenal	2289	N	No safety concern
cis-9-Dodecenal	2290	N	No safety concern
(*E*)-3-Methyl-4-dodecenoic acid	2291	N	No safety concern
trans-5-Octenal	2292	N	No safety concern
trans-Tetradec-4-enal	2293	N	No safety concern
2,6-Dimethylheptenyl formate	2294	N	No safety concern
(*Z*)-9-Dodecenoic acid	2295	N	No safety concern
cis-Tridec-5-enal	2296	N	No safety concern
(*Z*)-8-Pentadecenal	2297	N	No safety concern

N: new specifications.

C. Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids

Flavouring agents Nos 2299, 2303 and 2306 all exceeded their respective thresholds of toxicological concern. The structural analogue proposed to complete the evaluation of these three flavouring agents was acetaldehyde (No. 80) *(3)*; however, the Committee considered that the use of acetaldehyde (No. 80) as a structural analogue in this safety assessment would require further evaluation. The Committee was therefore unable to complete the evaluation of Nos 2299, 2303 and 2306. The Committee also concluded that the use of acetaldehyde (No. 80) as a flavouring agent requires to be re-evaluated.

Flavouring agent	**No.**	**Specifications**	**Conclusion based on current estimated dietary exposure**
Structural class I			
Pentadecanoic acid	2300	N	No safety concern
Tridecanal	2301	N	No safety concern
Tridecanoic acid	2302	N	No safety concern
Acetaldehyde di-isobutyl acetal	2304	N	No safety concern
Acetaldehyde ethyl isobutyl acetal	2305	N	No safety concern

N: new specifications.

References

1. Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances: thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 1970 (WHO Technical Report Series, No. 445, https://iris.who.int/handle/10665/40773, accessed 9 November 2023).

2. Evaluation of certain food additives and contaminants: twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 1986 (WHO Technical Report Series, No. 733, https://iris.who.int/handle/10665/37285, accessed 15 November 2023).

3. Evaluation of certain food additives and contaminants: forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 1999 (WHO Technical Report Series, No. 884, https://apps.who.int/iris/handle/10665/42142, accessed 26 July 2023).

Annex 1. List of participants

Members

Dr A. Agudo, Unit of Nutrition and Cancer, Catalan Institute of Oncology, Barcelona, Spain

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Dr R. Cantrill, Bedford, Nova Scotia, Canada *(Chairperson)*

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Annex 2. Recommendations and future work

The Committee asks the JECFA Secretariat to urge sponsors and Codex Members to ensure that all information is available for the evaluation of additional flavouring agents, including an updated literature search, a rationale for the choice of a comparator compound, and exposure data (both SPET and MSDI values) for all previously evaluated flavouring agents prior to requesting inclusion in the CCFA JECFA Priority List.

The Committee discussed the importance of receiving data in support of the establishment of specifications for flavouring agents. For future meetings, data should be provided by the sponsor in support of any parameter for which a numerical value is specified.

Specific recommendations for the three different groups of flavouring agents are provided below.

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

The Committee requests that updated exposure data (including both MSDI and SPET values) be provided for the flavouring agents citronelloxyacetaldehyde (No. 592), 1,3-nonanediol acetate (No. 605), levulinic acid (No. 606), hydroxycitronellal diethyl acetal (No. 613), diethyl malonate (No. 614), diethyl tartrate (No. 622) and triethyl citrate (No. 629) within 2 years (i.e. by December 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

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

The Committee requests that updated exposure data (including both MSDI and SPET values) be provided for the flavouring agents *cis*-3-hexen-1-ol (No. 315), 10-undecenal (No. 330), 10-undecenoic acid (No. 331), *cis*-3-hexenyl cis-3-hexenoate (No. 336), 5-hexenol (No. 1623) and methyl 10-undecenoate (No. 1639) within 2 years (i.e. by December 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

C. Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids

The Committee considered that the use of acetaldehyde (No. 80) as a structural analogue in the safety assessment of flavouring substances would require further evaluation. Furthermore, the Committee concluded that the use of acetaldehyde (No. 80) as a flavouring agent requires re-evaluation.

The Committee requests that updated exposure data (including both MSDI and SPET values) be provided for the flavouring agents acetaldehyde (No. 80), butyl alcohol (No. 85), butyraldehyde (No. 86), hexanoic acid (No. 93) and lauric aldehyde (No. 110) within 2 years (i.e. by December 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

Annex 3. Corrigenda

The requests for corrections in the table below, reported to the JECFA Secretariat, were evaluated at the Ninety-seventh JECFA meeting and found to be necessary. Corrections will be made only in the online database for specifications.

Requests for corrections submitted to the JECFA Secretariat

Substance	Original text	Revised text	Additional information
Modified starches	Table on page 3 of specifications *(1)*	See revised table below	Revised table is in alignment with specifications
	Page 13 CAS numbers 601464-73-0 (Amylopectin, acetate)	CAS numbers 60164-73-0 (Amylopectin, acetate)	
	Page 22 Increase temperature to 250 °C at a rate of 14.5 °C/s. Hold at 250 °C for 1 min	Increase temperature to 250 °C at a rate of 14.5 °C/min, hold at 250 °C for 1 min	
	Page 22 Split/splitless injector settings Injector temperature: 250 °C Injection mode: splitless for 0.8 min	Split/splitless injector settings Injector temperature: 250 °C Injection mode: splitless for 0.8 min Recommended liner of at least: 870 µL	
Pullulan	Chemical formula: $(C_6H_{10}O_5)_x$	Chemical formula: $(C_{36}H_{60}O_{30})_n$	
	Characteristics: Mono-, di- and oligosaccharides Not more than 10% (expressed as glucose)	Characteristics: Mono-, di- and oligosaccharides Not more than 10% (expressed as glucose), on the dried basis	
	Purity tests: Mono-, di- and oligosaccharides Procedure – Weigh accurately 0.8 g sample and dissolve in water to make 100 ml (stock solution).	Purity tests: Mono-, di- and oligosaccharides Procedure – Weigh accurately 0.8 g sample previously dried and dissolve in water to make 100 ml (stock solution).	
	Method of assay: P(%) = 100 – (L+C) where L is loss on drying; and C is taken from the calculation for mono-, di- and oligosaccharides.	Method of assay: P(%) = [100 – C] where C is taken from the calculation for mono-, di- and oligosaccharides.	
Spirulina extract (INS 134)	Method of assay: Calculate the allophycocyanin content (percent, w/w) as follows: TaPC = [(0.180 x A620) – (0.042 x A650) x V1 x 100] / W1	Method of assay: Calculate the allophycocyanin content (percent, w/w) as follows: TaPC = [(0.180 x A650) – (0.042 x A620) x V1 x 100] / W1	

Modified starches *(1)*; revised table

Summary table							
GENERAL REQUIREMENTS							
IDENTIFICATION				**PURITY**			
Solubility	**Microscopy**	**Iodine Stain**	**Copper Reduction**	**Loss on Drying**	**Lead**	**Microbiological Criteria**	**Sulfur dioxide**
Insoluble in cold water, **if not pre-gelatinised.**	Granular structure typical of the starch source	Colour from dark blue to orange-red after addition of iodine TS	Red precipitate after addition of hot alkaline cupric tartrate to a test sample refluxed under acidic condition	Cereal starch ≤15.0%; Potato starch: ≤21.0%; Other starches: ≤18.0%	≤0.2mg/kg d.w. Pb (≤0.1 mg/kg) for starch sodium octenylsuccinate for infant formula	Aerobic Plate Count: ≤100,000 CFU/g; Yeasts and molds: ≤1,000 CFU/g; Total Coliforms: ≤100 CFU/g;	Modified cereal starches: ≤50 mg/kg d.w.; Other modified starches ≤10 mg/kg d.w.

SPECIFIC REQUIREMENTS			
Modified Starch	Annex	**IDENTIFICATION**	**PURITY**
Dextrin roasted starch (INS 1400)	1	Dispersion test	No additional
Acid treated starch (INS 1401)	1	Dispersion test	No additional
Alkaline treated starch (INS 1402)	1	Dispersion test	No additional
Bleached starch (INS 1403)	2	No additional	Carboxyl groups (≤0.1% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2
Oxidized starch (INS 1404)	5	Hypochlorite oxidized starch	Carboxyl groups (≤1.3% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2
Enzyme-treated starch (INS 1405)	1	Dispersion ~~index (Information Required); Reducing sugars (Information Required)~~ **test**	No additional
Monostarch phosphate (INS 1410)	3	Phosphate groups	Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w for other starches)
Distarch phosphate (INS 1412)	3	Crosslinking	Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w. for other starches)
Phosphated distarch phosphate (INS 1413)	3	Crosslinking	Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w. for other starches)
Acetylated distarch phosphate (INS 1414)	3, 4	Acetyl group; Ester group; Crosslinking	Phosphate (≤0.14% d.w. for potato or wheat starches; ≤0.04% d.w. for other starches) Acetyl groups (≤2.5% d.w.); ~~Ester groups (≤0.5% d.w.)~~
Starch acetate (INS 1420)	4	Acetyl group; Ester group	Acetyl groups (≤2.5% d.w.); ~~Ester groups (≤0.5% d.w.)~~
Acetylated distarch adipate (INS 1422)	4, 8	Acetyl group; Ester group; Crosslinking	Acetyl groups (≤2.5% d.w.); Vinyl acetate (≤0.1 mg/kg); ~~Ester groups (≤0.5%d.w.)~~ Adipate groups (≤0.135% d.w.); Residual free adipic acid (≤0.025% d.w.)
Hydroxypropyl starch (INS 1440)	7	Hydroxypropyl ether groups	Hydroxypropyl groups (≤7.0% d.w.); Propylene chlorohydrins (≤1 mg/kg d.w.)
Hydroxypropyl distarch phosphate (INS 1442)	3, 7	Hydroxypropyl ether groups; Crosslinking	Phosphate (≤0.14% d.w. for potato or wheat starches; ≤0.04% d.w. for other starches) Hydroxypropyl groups (≤7.0% d.w.); Propylene chlorohydrins (≤1 mg/kg d.w.)
Starch sodium octenylsuccinate (INS 1450)	6	No additional	Octenylsuccinyl groups (≤3% d.w.); Residual free octenylsuccinic acid (≤0.3% d.w.);
Acetylated oxidized starch (INS 1451)	4, 5	Acetyl group	Acetyl groups (≤2.5% d.w.); Vinyl acetate (≤0.1 mg/kg); ~~Ester groups (≤0.5% d.w.)~~ Carboxyl groups (≤1.3% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2

Reference

1. Online edition. Modified starches Monograph 27; 2021 (https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/, accessed 15 November 2023).