CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 3(a) **CX/FA 24/54/3**

February 2024

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD ADDITIVES

Fifty-fourth Session

MATTERS OF INTEREST ARISING FROM FAO/WHO AND FROM THE 96TH AND 97TH MEETINGS OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA) RESPECTIVELY

Matters for information from WHO

1. Assessments of the health impacts of the non-sugar sweetener aspartame has been evaluated both by the International Agency for Research on Cancer (IARC) and the FAO/WHO Joint Expert Committee on Food Additives (JECFA) in 2023. Citing "limited evidence" for carcinogenicity in humans, IARC classified aspartame as possibly carcinogenic to humans (IARC Group 2B) and JECFA reaffirmed the acceptable daily intake of 40mg/kg body weight.

2. IARC and JECFA carried out independent but complementary scientific reviews. IARC has limited scope to analyse the potential carcinogenic hazard, whereas JECFA's scope includes all possible health impacts related to aspartame consumption. This was the first time that IARC has evaluated aspartame and the third time for JECFA. After reviewing the available scientific literature, both evaluations noted limitations in the available evidence for cancer (and other health effects). IARC classified aspartame as possibly carcinogenic to humans (Group 2B) because of limited evidence for cancer in humans (specifically, for hepatocellular carcinoma, which is a type of liver cancer). There was also limited evidence for cancer in experimental animals and limited evidence related to the possible mechanisms for causing cancer. This classification should be understood as an appeal for more research to reduce uncertainty about the possible link between cancer and the consumption of aspartame.

3. JECFA also examined the evidence for cancer in humans and concluded that there is no convincing evidence linking aspartame to cancer in humans. In addition, JECFA found that several studies examining the effects of aspartame consumption on type 2 diabetes and other non-cancer health outcomes for humans but the data showed inconsistent results.

4. JECFA concluded that the data evaluated indicated no sufficient reason to change the previously established acceptable daily intake (ADI) of 0–40 mg/kg body weight for aspartame. JECFA therefore reaffirmed that it is safe for a person to consume within this limit per day.

5. Earlier in 2023, WHO released a guideline on the use of non-sugar sweeteners in which WHO recommends against the use of non-sugar sweeteners as a means of achieving weight control or reducing the risk of noncommunicable diseases. The recommendation covers all non-sugar sweeteners except for sugar alcohols (i.e. polyols) and low calorie sugars and is based primarily on evidence suggesting lack of long-term benefit in terms of weight loss and increased risk of type 2 diabetes, cardiovascular diseases and premature mortality. Evidence for a link between non-sugar sweetener use and cancer was not observed. The WHO recommendation is therefore in line with the conclusions reached by IARC and JECFA.

Matters for information from the 96th and 97th meetings of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

6. The results of the 96th meeting (Geneva, 27June - 6 July 2023) and the 97th meeting (Rome, 31 October - 9 November 2023) of JECFA on certain food additives will be available as follows: the meeting reports (WHO Technical Report Series 1050 and 1051 respectively) and the toxicological and dietary exposure monographs (WHO Food Additive Series No 87 and No 88 respectively) will be accessible through the WHO JECFA publications website: https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/publications. The specification monographs resulting from the 96th JECFA meeting are published as FAO JECFA Monographs 31, 2023. The publication is available on the FAO JECFA website at: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/. The specification monographs resulting from the 97th JECFA meeting will be published as FAO JECFA Monographs 32, 2024 and will be accessible via the FAO JECFA Resources webpage: www.fao.org/food-safety/resources/publications/en/.

Requests for scientific advice

7. Both organizations continue to jointly prioritize the requests for scientific advice taking into consideration the criteria proposed by Codex as well as the requests for advice from Member Countries and the availability of resources. A list of all pending requests for scientific advice by JECFA will be posted on the respective FAO and WHO websites.

8. In scheduling the JECFA meetings and developing the agenda, the Joint Secretaries have to take into account the priorities requested by CCFA, CCCF, CCFO and CCRVDF. Due to the increasing requests for scientific advice to JECFA, not all requests can be addressed in the subsequent meeting. In prioritizing the work, the JECFA Secretariat takes into account existing criteria, on-going Codex work and available resources.

9. To facilitate provision of extra-budgetary resources for scientific advice activities, please contact Dr Markus Lipp, FAO Food Systems and Food Safety Division (jecfa@fao.org) and Kim Petersen Department of Nutrition and Food Safety, WHO (jecfa@who.int).

Actions required as a result of changes in acceptable daily intake (ADI) status and other toxicological recommendations from JECFA

10. At its 96th meeting, JECFA evaluated the safety of one food additive, revised the specification for three food additives, evaluated the safety of two groups of flavouring agents and revised the specifications for eight flavouring agents. Toxicological recommendations or other scientific advice for these food additives are provided in Annex 1 to this document. For the new and revised specifications please see CX/FA 24/54/4, Annex 1. CCFA54 **is invited** to consider the recommended actions (presented in Annex 1 to this document) which might be required following the evaluations of these food additives.

11. At its 96th meeting, JECFA also noted that several flavourings have full specifications but are not accompanied by a full safety evaluation. JECFA recommends the compilation of a list of such flavourings with a view to withdrawing their specifications.

12. At its 97th meeting, JECFA evaluated the safety of one food additive, including revising its specifications, and evaluated the safety of three groups of flavouring agents. Toxicological recommendations or other scientific advice for these food additives are provided in Annex 2 to this document. For the new and revised specifications please see CX/FA 24/54/4, Annex 2. CCFA54 **is invited** to consider the recommended actions (presented in Annex 2 to this document) which might be required following the evaluations of these food additives.

13. At its 97th meeting**, JECFA asked 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. JECFA 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 evaluated at the 97th JECFA meeting are provided below.

14. At its 97th meeting, JECFA requests that for aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups 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.

15. At its 97th meeting, JECFA requests that for linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters 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), cis3-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.

16. At its 97th meeting, JECFA recommended that for saturated aliphatic acyclic linear primary alcohols, aldehydes and acids that the use of acetaldehyde (No. 80) as a structural analogue in the safety assessment of flavouring substances would require further evaluation. Furthermore, JECFA concluded that the use of acetaldehyde (No. 80) as a flavouring agent requires re-evaluation. JECFA 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 1

Food additives evaluated toxicologically and/or considered for specifications at the 96th JECFA meeting

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommended action by CCFA
951	Aspartame	JECFA evaluated biochemical, toxicological and epidemiological studies on aspartame, its metabolites and degradation products that had become available since the previous JECFA evaluation. JECFA also assessed estimates of dietary exposure to aspartame for the first time. Following oral exposure, aspartame is fully hydrolysed in the gastrointestinal tract of humans and animals into three metabolites: phenylalanine, aspartic acid and methanol. JECFA therefore reaffirmed that there is no systemic exposure to aspartame after dietary exposure. Phenylalanine, aspartic acid and methanol are also released from commonly consumed foods by enzymatically catalysed hydrolysis. After the pre-systemic hydrolysis of aspartame, these substances enter the systemic circulation at levels lower than those derived from consumption of common foods. JECFA noted that in oral aspartame exposure studies in humans at doses up to the current ADI, there were no increases in the plasma concentrations of the metabolites of aspartame. JECFA concluded that there was no concern for genotoxicity of oral exposure to aspartame. JECFA evaluated data from twelve oral carcinogenicity studies of aspartame and identified deficiencies with all of them. JECFA noted that all the studies apart from those by Soffritti et al. (1–4) [1] showed negative results. JECFA considered the positive findings of Soffritti and colleagues, noting that there were limitations in the study design, execution, reporting and interpretation of these studies. In particular, this was because of the use of a test protocol in which most animals were allowed to reach natural death. As a result, the interpretation of these studies was complicated by the known increases in cancer occurrence with ageing. JECFA reached the view that the results of the Soffritti et al[2]. studies are of uncertain relevance and therefore cannot be used for the risk assessment of aspartame. JECFA concluded that the carcinogenicity study by Ishii et al.	Note the JECFA conclusion that it **reaffirmed its previously established ADI** of 0–40mg/kg bw for aspartame. Note the revised specifications for aspartame, (see CX/FA 24/54/4).

[1] Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L. Aspartame induces lymphomas and leukaemias in rats. Eur J Oncol. 2005;10:107–16.
Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E, Rigano A. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. Environ Health Perspect. 2006;114:379–85. doi:10.1289/ehp.8711.
Soffritti M, Belpoggi F, Tibaldi E, Esposti DD, Lauriola M. Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. Environ Health Perspect. 2007;115:1293–7. doi:10.1289/ehp.10271.
Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L, Bua L. Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice. Am J Ind Med. 2010;53:1197–206. doi:10.1002/ajim.20896.

[2] Ishii H, Koshimizu T, Usami S, Fujimoto T. Toxicity of aspartame and its diketopiperazine for Wistar rats by dietary administration for 104 weeks. Toxicology. 1981;21(2):91–4. doi:10.1016/0300-483x(81)90119-0.

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommended action by CCFA
		was close to meeting the current testing guidelines and showed negative results. JECFA reviewed several recently published studies that investigated possible mechanisms that may be relevant to the induction of cancer, including oxidative stress. The studies that reported changes in markers of oxidative stress had limitations in their design. JECFA noted that histopathological changes that would be expected from prolonged oxidative stress were not observed in other short- and long-term toxicity studies of aspartame. Based on the negative results of the Ishii et al. study as well as the other negative carcinogenicity studies, no concern of genotoxicity, and a lack of a plausible mechanism by which oral exposure to aspartame could induce cancer, JECFA concluded that there was no concern for carcinogenicity in animals from oral exposure to aspartame. The NOAEL in one- or two-generation reproductive and developmental toxicity studies in rats was 4000 mg/kg bw per day, the highest dose tested. The NOAEL for developmental toxicity in mice was 5700 mg/kg bw per day, the highest dose tested. JECFA therefore concluded that aspartame was not a reproductive or developmental toxicant in animals. JECFA evaluated data from randomized controlled trials (RCTs) and epidemiological studies to examine the association between aspartame consumption and certain health effects, such as cancer, type 2 diabetes (T2D) and other non-cancer health end-points in humans. JECFA noted that statistically significant increases were reported for some cancers, such as hepatocellular, breast and haematological (non-Hodgkin lymphoma and multiple myeloma) cancers, in some cohort studies conducted with aspartame or beverages containing aspartame as an intense sweetener. However, a consistent association between aspartame consumption and a specific cancer type was not observed. All studies have limitations with respect to their assessment of exposure and, in many studies, particularly with respect to aspartame versus intense sweeteners in general. Reverse causality, chance, bias and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components cannot be ruled out. Overall, JECFA concluded that the evidence of an association between aspartame consumption and cancer in humans is not convincing. Several studies assessing the effects of aspartame consumption on T2D and other non-cancer health end-points in humans showed inconsistent results. For example, RCTs showed reduced glycaemic responses after aspartame consumption, whereas in epidemiological studies aspartame consumption was associated with a greater T2D risk. JECFA noted that the results of the epidemiological studies may be	

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommended action by CCFA
		biased by how T2D cases were identified (either specific medications and self-reported physician diagnosis). JECFA therefore concluded that the evidence of an association between aspartame consumption and the evaluated non-cancer health end-points is not convincing. Overall, JECFA concluded that there was no convincing evidence from experimental animal or human data that aspartame has adverse effects after ingestion. This conclusion is underpinned by the information that aspartame is fully hydrolysed in the gastrointestinal tract into metabolites that are identical to those absorbed after consumption of common foods, and that no aspartame enters the systemic circulation. JECFA concluded that the data evaluated at the present meeting indicated no reason to change the previously established ADI of 0–40 mg/kg bw for aspartame. **JECFA therefore reaffirmed the ADI of 0–40mg/kg bw for aspartame at the present meeting**. JECFA determined that dietary exposure estimates to aspartame at the mean of up to 10mg/kg bw per day for children and 5mg/kg bw per day for adults, and for high dietary exposures up to 20mg/kg bw per day for children and 12mg/kg bw per day for adults, were appropriate for the present assessment. JECFA noted that these dietary exposure estimates do not exceed the ADI. JECFA therefore concluded that dietary exposure to aspartame does not pose a health concern.	

Flavouring agents evaluated at the 96th JECFA meeting

The flavouring agents were evaluated by the revised Procedure for the Safety Evaluation of Flavouring Agents.

A. Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
4-Methylpentyl 4-methylvalerate	2280	N	No safety concern
5-Methylhexyl acetate	2281	N	No safety concern
4-Methylpentyl isovalerate	2282	N	No safety concern
Ethyl 4-methylpentanoate	2283	N	No safety concern
Ethyl 2-ethylbutyrate	2284	N	No safety concern
Ethyl 2-ethylhexanoate	2285	N	No safety concern

N: new specifications.

B. Hydroxy- and alkoxy-substituted benzyl derivatives

Flavouring agent	No.	Specifications	Conclusion based on current estimated dietary exposure
Structural class I			
2-Ethoxy-4-(hydroxymethyl)phenol	2271	N	No safety concern
2-Phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate	2272	N	No safety concern
3-Phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate	2273	N	No safety concern
Ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate	2274	N	No safety concern
cis-3-Hexenyl salicylate	2275	N	No safety concern
4-Formyl-2-methoxyphenyl 2-hydroxypropanoate	2276	N	No safety concern
2-Hydroxy-4-methoxybenzaldehyde	2277	N	No safety concern
3,4-Dihydroxybenzoic acid	2278	N	No safety concern
3-Hydroxybenzoic acid	2279	N	No safety concern

N: new specifications.

Annex 2

Food additives evaluated toxicologically and/or considered for specifications at the 97th JECFA meeting

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommended action by CCFA
171	Titanium dioxide (TiO_2)	JECFA 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. JECFA identified a number of TiO_2 test materials that were considered representative of INS 171. Further, JECFA 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 JECFA, but it was concluded that they were not relevant to the safety assessment of INS 171. JECFA noted that 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. JECFA 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, JECFA 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. JECFA 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	Note the JECFA conclusion that it **reaffirmed the previously established ADI "not specified" for titanium dioxide.** Note the revised specifications for titanium dioxide, (see CX/FA 24/54/4).

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommended action by CCFA
		171 and human health effects. At the 97th JECFA meeting JECFA estimated the dietary exposure to INS 171. Based on the estimates considered, JECFA 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, JECFA reaffirmed the ADI "not specified" established at the Thirteenth meeting.	

Flavouring agents evaluated at the 97th JECFA meeting

The flavouring agents were 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

JECFA decided not to review succinic acid (No. 2307) because it had previously been evaluated as a food additive at the Twenty-ninth meeting; at that meeting, JECFA 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.

JECFA 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 i*n vitro*, which did not allow the evaluation to be completed at this meeting. JECFA 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, JECFA considered that the use of acetaldehyde (No. 80) as a structural analogue in this safety assessment would require further evaluation. JECFA was therefore unable to complete the evaluation of Nos 2299, 2303 and 2306. JECFA 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.