Appendix II

ACTION REQUIRED AS A RESULT OF CHANGES IN THE ACCEPTABLE DAILY INTAKE (ADI) STATUS AND OTHER RECOMMEDATIONS ARISING FROM THE 96TH AND 97TH JECFA

(For information and action)

PART A: From 96TH JECFA Meeting

Table 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	Recommendation of CCFA54
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	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.

INS Number	Food additive	Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information	Recommendation of CCFA54
		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. 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.	

[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	Recommendation of CCFA54
		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 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.	

Table 2. 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.

PART B: From 97th JECFA Meeting

Table 1. 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	Recommendation of CCFA54
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	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	Recommendation of CCFA54
		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 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.	

Table 2. 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

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

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 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.