

# Evaluation of certain food additives

Ninety-sixth report of the Joint  
FAO/WHO Expert Committee on  
Food Additives



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization



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## Ninety-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Geneva, 27 June–6 July 2023

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## List of abbreviations and acronyms

ADH	alcohol dehydrogenase
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
BBN	N-butyl-N-(4-hydroxybutyl)nitrosamine
BMI	body mass index
bw	body weight
CAS	Chemical Abstracts Service
CCFA	Codex Committee on Food Additives
CI	confidence interval
DKP	diketopiperazine
FAO	Food and Agriculture Organization of the United Nations
GIT	gastrointestinal tract
GMP	Good Manufacturing Practice
GSFA	Codex Alimentarius General Standard for Food Additives
HR	hazard ratio
IARC	International Agency for Research on Cancer
INS	International Numbering System for Food Additives
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MOE	margin of exposure
MPL	maximum permitted level
MSDI	maximized survey-derived intake
NHL	non-Hodgkin lymphoma
NNS	non-nutritive sweetener
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PKU	phenylketonuria
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SPET	single portion exposure technique
T2D	type 2 diabetes
THF	tetrahydrofuran
WHO	World Health Organization



# 1. Introduction

The Ninety-sixth meeting of the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) met in Geneva from 27 June to 6 July 2023. The meeting was opened on behalf of WHO and the FAO by Dr Francesco Branca, Director of Nutrition and Food Safety Department, WHO and by Dr Markus Lipp, Senior Food Safety Officer, Food Systems and Food Safety Division, FAO, respectively.

Dr Branca welcomed the experts to the first in-person JECFA meeting since the coronavirus disease pandemic. Dr Branca highlighted the roles and responsibilities of JECFA in the international food safety standard development work of the Codex Alimentarius Commission. He emphasized the particular importance of the current meeting, given the availability of new research results on aspartame. An International Agency for Research on Cancer (IARC) Monographs Programme Working Group assessed the potential carcinogenic hazard of aspartame on 6–13 June 2023, and a risk assessment for the dietary exposure of aspartame was conducted as part of this Ninety-sixth JECFA meeting.

The sequence of these complementary evaluations, and the close collaboration between the IARC Monographs Programme Secretariat and the WHO/JECFA Secretariat, has permitted a comprehensive evaluation of aspartame based on the latest available evidence.

Dr Lipp expressed his confidence that the JECFA experts will consider all available data and scientific evidence, allowing them, in their capacity as independent scientific experts serving the FAO/WHO scientific advice programme, to draw their own conclusions on the safety of aspartame as a food additive.

The meeting agenda ([Annex 1](#)) was adopted with no modifications.

## 1.1 Declarations of interests

The Joint Secretariat informed the Committee that all experts participating in the Ninety-sixth meeting had completed declaration of interest forms. No conflicts of interest were identified.

## 1.2 Terminology

Although the publications reviewed in this report used a wide range of terminology – including intense sweeteners, high-intensity sweeteners, artificial

sweeteners and non-nutritive sweeteners (or NNS) – the Committee agreed to the use of the term “intense sweetener”.

### 1.3 Meeting summary

See [Annex 2](#) for a summary of toxicological information and specifications agreed.

## 2. Food additives (other than flavouring agents)

### 2.1 Safety evaluations

#### 2.1.1 Aspartame

##### Explanation

Aspartame was evaluated by the Committee at its Nineteenth, Twentieth, Twenty-first, Twenty-third, Twenty-fourth and Twenty-fifth meetings.<sup>1</sup> At its Twenty-fourth meeting, the Committee proposed an acceptable daily intake (ADI) of 0–40 mg/kg body weight (bw) for aspartame subject to evidence of validation for the submitted toxicological studies. For diketopiperazine (DKP), the major degradation product of aspartame, the Committee allocated an ADI of 0–7.5 mg/kg bw (1). At its Twenty-fifth meeting, the Committee confirmed the ADI of 0–40 mg/kg bw for aspartame (2). This ADI was calculated based on the no-observed-adverse-effect level (NOAEL) of 4000 mg/kg bw per day, the highest dose tested in a long-term (104-week) study in rats exposed to aspartame in the diet (3) and application of a 100-fold uncertainty factor.

The current request to re-evaluate aspartame was made by the Codex Committee on Food Additives (CCFA) at its Fifty-second Session (4). The sponsors submitted all unpublished reports of oral toxicity studies of aspartame, its metabolites and degradation products that had been previously reviewed by JECFA at its Twenty-fourth and Twenty-fifth meetings (1,2). The sponsors also provided additional unpublished study reports and articles published since JECFA's previous evaluation of aspartame as a result of searches on PubMed conducted from 2010 to 2022.

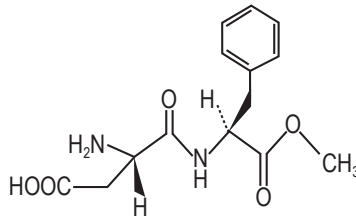
At the present meeting, the Committee was aware that IARC had evaluated the carcinogenic hazard of aspartame at its One hundred and thirty-fourth meeting in June 2023, but the report had not been published. The Committee was informed about the discussions and the outcome of the IARC meeting.

The Committee conducted a comprehensive literature search for biochemical, toxicological, epidemiological and dietary exposure data of aspartame using PubMed and/or EBSCO Discovery Service from December 1981 to May 2023. The Committee also evaluated data from unpublished toxicological studies that had become available after the Twenty-fifth JECFA meeting.

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<sup>1</sup> A full list of previous JECFA publications is provided as [Annex 3](#).

Fig. 2.1

**Structure of aspartame****Chemical and technical considerations**

Aspartame (3-amino-N-(alpha-carbomethoxy-phenethyl)-succinamic acid, N-L-alpha-aspartyl-L-phenylalanine-1-methyl ester; Chemical Abstracts Service (CAS) No. 22839-47-0; International Numbering System for Food Additives (INS) No. 951) is a dipeptide methyl ester composed of the two amino acids L-aspartic acid and L-phenylalanine. It has a molecular formula of C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> and corresponds to a molecular weight of 294.30 g/mol. Aspartame is synonymous with α-aspartame, aspartyl phenylalanine methyl ester, N-L-α-aspartyl-L-phenylalanine 1-methyl ester and L-α-aspartyl-L-phenylalanine methyl ester. The structural formula for aspartame is provided in Fig. 2.1.

Aspartame is a white crystalline powder with no odour and is approximately 200 times sweeter than sucrose. It is primarily produced via chemical synthesis by reacting L-phenylalanine or L-phenylalanine methyl ester with N-protected L-aspartic anhydride. This is followed by hydrolysis and esterification steps. Aspartame, the major component, is then separated and crystallized from its non-sweet isomer, β-aspartame. The article of commerce has a specification of not less than 98.0% and not more than 102.0% of aspartame, on a dried basis. Aspartame is stable under dry conditions; its stability is affected by moisture, pH, temperature and storage time. The major degradation product is 5-benzyl-3,6-dioxo-2-piperazineacetic acid (DKP). DKP is formed through the intramolecular reaction of the primary amine with the methyl ester group. The specification for DKP is 1.5%. The mean purity of aspartame from five batches was 99.7%, and the mean content of DKP from five batches was 0.04%.

**Biochemical aspects**

A previous Committee evaluated oral single and repeated dose studies in animals at doses of up to 4000 mg/kg bw per day and in humans at doses of up to 200 mg/kg bw per day, which showed that there was no systemic exposure to aspartame following oral exposure (1,2). Following oral exposure, aspartame is fully

hydrolysed in the gastrointestinal tract (GIT) by esterases and peptidases to form the three metabolites phenylalanine, aspartic acid and methanol, comprising (by weight) approximately 50, 40 and 10% of aspartame, respectively (5).

Phenylalanine, aspartic acid and methanol are also released from commonly consumed foods by enzymatically catalysed hydrolysis. After the pre-systemic hydrolysis of aspartame, these metabolites enter the systemic circulation at levels lower than those derived from the consumption of common foods. They are further metabolized through their respective biochemical pathways (1,2,5–7).

The present Committee evaluated data from oral single and repeated dose studies in humans of aspartame at doses of up to 50 mg/kg bw (8) and up to 75 mg/kg bw per day (9), respectively. These studies did not show any significant increases in the plasma concentrations of the metabolites above the expected postprandial range.

The Committee also evaluated the effects of oral aspartame exposure on the levels of metabolites in subpopulations such as lactating women (10), pregnant women (11) and infants (12) at doses of 50, 200 and 100 mg/kg bw, respectively. None of these studies showed any significant increases in the plasma concentrations of the metabolites.

The Committee noted that two repeated oral dosing studies of aspartame reported elevations in plasma phenylalanine levels in healthy adults (13) and individuals heterozygous for phenylketonuria (PKU) (14). Ingestion of eight successive 600-mg doses of aspartame in beverages consumed at 1-hour intervals resulted in plasma phenylalanine concentrations approximately 1.7-fold ( $P < 0.05$ ) of the baseline in healthy adults (13) and in PKU heterozygotes (14) within 30 minutes of the administration of the last dose. These concentrations were above the expected postprandial range in PKU heterozygotes. However, the plasma phenylalanine concentrations of all evaluated subjects in these studies were lower than the range associated with any neurological symptoms. These plasma concentrations also returned to the baseline 24 hours after administration of the last dose.

The Committee evaluated data from two oral repeated dose studies of aspartame in rats on hepatic microsomal enzymes, including several cytochrome P450 enzymes (15), or epoxide hydrolase, carboxylesterase and *p*-nitrophenol-uridinediphosphate-glucuronosyltransferase (16) at doses of up to 4000 mg/kg bw per day. These studies did not show any change in the activity of the evaluated hepatic microsomal enzymes.

The Committee evaluated data from metabolism studies on DKP (17–19) and a minor degradation product,  $\beta$ -aspartame (20,21), in animals and humans. None of the reviewed studies showed any accumulation of DKP or  $\beta$ -aspartame following oral exposure to aspartame.

## Toxicological studies

No new relevant toxicity data on DKP since the previous JECFA evaluation (2) were identified. A previous Committee evaluated data from acute oral toxicity studies for aspartame and DKP that reported no lethality in rats, mice and rabbits at doses of up to 5000 mg/kg bw (2).

### Short-term studies

A previous Committee evaluated data from several short-term toxicity studies of aspartame and DKP in rats, mice, monkeys and dogs at doses of up to 4000 mg/kg bw per day (2). No treatment-related effects were observed in these studies. The present Committee identified three additional short-term studies that evaluated the effects of repeated oral dosing of aspartame at dose levels of up to 1000 mg/kg bw per day for a duration of 180 days (22–24). Although some changes in blood chemistry parameters were reported, the Committee noted limitations with the study design and reporting of data in these studies, and therefore did not consider these data reliable for the present assessment (2).

### Long-term studies

Laboratory animal studies of chronic toxicity and carcinogenicity are listed in [Table 2.1](#) (3,25–37). With the exception of studies performed by one laboratory, the studies yielded negative results.

No increase in cancer incidence was observed in the studies in mice and rats that were conducted in the 1970s (25,29,30). The study designs preceded the establishment of Organisation for Economic Co-operation and Development (OECD) test guidelines and are not fully compliant with the current guideline, OECD Test Guideline No. 451 (38). Group sizes at the start of dosing were lower than the current recommendation, but survival rates meant that there were sufficient tissues available at the end of the study to meet current standards. The number of tissues was fewer than specified in OECD Test Guideline No. 451, but included all major organs and systems.

Results of dietary carcinogenicity assays using three transgenic mouse models (TgAC hemizygous, P53 haploinsufficient and Cdkn2a deficient) at doses of up to 7500 mg/kg bw per day showed no evidence of carcinogenicity (26). The TgAC mouse has a gain of oncogene function, whereas the other two models have impaired tumour suppressor function. All three strains exhibit a phenotype of increased incidence and decreased latency of cancer.

No promotion of pancreatic acinar carcinogenesis was observed using the C57BL/6 Ela1-Tag mouse model (28), and no promotion of urinary bladder carcinogenesis was observed in rats pretreated with N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) (32).



Table 2.1  
Carcinogenicity studies in laboratory animals

Animal model	Nominal doses (mg/kg bw per day)	Route	Duration	Study author conclusions	Reference(s)
<b>Mice</b>					
ICR Swiss	0, 1000, 2000 and 4000	Diet	104 weeks	Negative	Anonymous (25)
TgAC hemizygous	0, 469, 938, 1875, 3750 and 7500	Diet	9 months	Negative	NTP (26)
P53 haploinsufficient	0, 469, 938, 1875, 3750 and 7500	Diet	9 months	Negative	NTP (26)
Cdkn2a deficient	0, 469, 938, 1875, 3750 and 7500	Diet	9 months	Negative	NTP (26)
Swiss	0, 250, 1000, 2000 and 4000	Diet	Prenatal + 130 weeks	Positive	Soffritti et al. (27)
CS7BL/6 Ela1-Tag	0 and 70	Drinking water	Prenatal + 21 weeks	Negative	Dooley et al. (28)
<b>Rats</b>					
Charles River albino	0, 1000, 2000 and 4000	Diet	104 weeks	Negative	Anonymous (29)
Charles River albino	0, 2000 and 4000	Diet	Prenatal + 104 weeks	Negative	Anonymous (30)
SLC Wistar	0, 1000, 2000 and 4000	Diet	104 weeks	Negative	Ishii (31); Ishii et al. (3)
F344 pretreated with BBN	0 and 1600	Drinking water	32 weeks	Negative	Hagiwara et al. (32)
Sprague-Dawley	0, 4, 20, 100, 500, 2500 and 5000	Diet	Up to 151 weeks	Positive	Soffritti et al. (33,34); Belpoggi et al. (35)
Sprague-Dawley	0, 20 and 100	Diet	Prenatal + up to 144 weeks	Positive	Soffritti et al. (36); Chiozotto et al. (37)

BBN: N-butyl-N-(4-hydroxybutyl)nitrosamine; bw: body weight.

The study reported by Ishii and colleagues (3,31) was conducted before the adoption of OECD Test Guideline No. 451, but closely followed its requirements. Group sizes were large; 60 out of the 86 rats per sex per group at the study start were assigned to complete the 104-week study. An extensive list of organs and tissues with a few exceptions (eye, skin, peripheral nerve and skeletal muscle) from the current OECD Test Guideline was available for third-party re-examination of the tissues, using slides freshly produced from the original paraffin blocks. The lack of carcinogenic effects was confirmed by the third-party re-examination (39).

In the mouse (27) and rat (33–37) studies reported by Soffritti and colleagues animals were maintained on treatment until natural death rather than being terminated after 104 weeks of treatment. In all the studies, significant dose-related increases in haemolymphoreticular cancers, predominantly a range of lymphomas and leukaemias, were reported (40). The publications by Soffritti and colleagues have been criticized for the practice of combining the occurrences of different types of cancers, particularly lymphomas and leukaemias, that should

not be considered together. If these cancers are not added together, there are no statistically significant differences between treated rats and sex-matched controls. If those cancers that are inappropriately combined are disregarded, increases in the following cancers remain. In the mouse study (27), an increase in hepatocellular carcinoma was observed in males. At dietary concentrations of 0, 2000, 8000, 16 000 and 32 000 mg aspartame/kg feed (0, 250, 1000, 2000 and 4000 mg/kg bw per day), the percentages of males with hepatocellular carcinomas were 5.1, 11.7, 14.5, 15.6 and 18.1%, and the values for males consuming 16 000 mg aspartame/kg feed and more were statistically significantly different from those of the control males. No increases were observed in female mice (corresponding values were 0, 1.6, 0, 3.1 and 0%, respectively). It is not known whether the male mice were infected with *Helicobacter hepaticus*, which is known to be a causative agent of hepatocellular carcinoma in mice (41). In addition, all values remained within the historical control range of 0–26.3% for hepatocellular carcinoma in male mice in the test laboratory. The occurrence of bronchiolar/alveolar carcinoma at dietary concentrations of 0, 2000, 8000, 16 000 and 32 000 mg aspartame/kg feed was 6.0, 5.8, 11.3, 12.5 and 13.3%, respectively, in male mice, and 6.9, 8.2, 8.2, 10.9 and 3.2%, respectively, in female mice. The occurrence at 32 000 mg aspartame/kg feed in male mice was statistically significantly higher than that in male controls, but there was a lack of a marked dose–response relationship considering the wide interval between the lowest and highest doses. The values remained within the historical control range of 0–14.3% for these tumours in male mice in the test laboratory. For these reasons, the Committee considered that the findings on hepatocellular carcinoma and bronchiolar/alveolar carcinoma in male mice are of uncertain relevance for the evaluation of carcinogenicity.

In the rat study in which dosing commenced at approximately 8 weeks of age (34) and the numbers of different cancer types were not inappropriately combined, there were no statistically significant differences in the occurrences of cancers between treated rats and controls. Carcinomas of the renal pelvis and ureter in female rats were reported only as a combined occurrence with values of 0, 0.7, 2.0, 2.0, 3.0, 3.0 and 4.0% at doses of 0, 4, 20, 100, 500, 2500 and 5000 mg/kg bw per day, respectively, and the dose–response trend is statistically significant. Others have commented that the combination of tumours of renal pelvis and tumours of ureters is not appropriate (42).

In the rat study in which dosing commenced when the rats were in utero (36), mammary carcinomas were found in 5.3% of control females, 7.1% of females receiving 20 mg/kg bw per day and 15.7% of females receiving 100 mg/kg bw per day. The number in the high-dose group was statistically significantly higher than that in controls, and slightly higher than the historical control range of 4.0–14.2% for mammary carcinoma in female rats in the testing laboratory.

The Committee noted that these particular tumours are common in ageing Sprague-Dawley female rats.

Overall, the Committee concluded that, while some deficiencies can be identified in all of the carcinogenicity studies on aspartame, and none would meet current testing standards, the study by Ishii and colleagues was close to meeting current standards and was negative. The results of the studies by Soffritti et al. are of uncertain relevance for the risk assessment of aspartame, particularly because the use of a test protocol in which all the animals are allowed to reach natural death means that the interpretation of the findings is complicated by the known increases in cancers occurring with ageing.

### Genotoxicity

Aspartame has been tested in several *in vitro* and *in vivo* genotoxicity assays. The data indicated that aspartame does not induce gene mutations in bacteria in the presence and in the absence of liver S9 metabolic activation from rats or hamsters.

*In vitro* genotoxicity tests performed in mammalian cells had limitations related to the study design and/or the reporting of the results. Aspartame was positive only at cytotoxic concentrations in the micronucleus assay in human lymphocytes and in the  $\gamma$ H2AX assay in HepG2 (43,44). Aspartame induced both positive and negative results in the *in vitro* chromosomal aberration tests and in the *in vitro* comet assay (43,45–48). Negative results were obtained in a sister-chromatid exchange assay and in an unscheduled DNA synthesis assay in primary rat hepatocytes (43,49).

*In vivo* genotoxicity studies also yielded both positive and negative results, but well conducted *in vivo* micronucleus assays did not provide any evidence of clastogenicity and/or aneugenicity potential of aspartame in bone marrow cells after acute or long-term oral exposure. The Committee noted that these negative studies do not provide evidence of exposure of the bone marrow to aspartame, as would normally be required for conclusive negative results. However, considering that aspartame is completely hydrolysed and not absorbed intact, there is no exposure of the bone marrow to aspartame. Moreover, an *in vivo* comet assay examining site-of-contact tissue (stomach) did not show any genotoxic effect of aspartame in mice at an oral dose level of 2000 mg/kg bw per day (50). Taken together, the Committee concluded that aspartame is not a concern for genotoxicity.

### Reproductive and development toxicity

Several reproductive and developmental toxicity studies in chicken embryo, rats and rabbits were evaluated at the Twenty-fifth meeting of the Committee (2). At

that time the Committee concluded that the only treatment-related effect was significantly reduced body weight in F1A and F2A weanlings in a two-generation rat reproduction study at the highest dose level of aspartame tested (4000 mg/kg bw per day). This effect was not observed at the lower dose level (2000 mg/kg bw per day). The present Committee reviewed the data on F1A and F2A body weight at weaning (51) and noted that the numbers of pups surviving to weaning within both the control group and the high-dose group (but not the low-dose group) was very variable (F1A: 3–10 and 2–10 pups in control and high-dose groups, respectively; F2A: 3–8 and 4–8 pups in control and high-dose groups, respectively). Under these circumstances, the toxicological relevance of the reported differences in weanling body weight between the control group and high-dose group is unclear.

At the Twenty-fifth meeting, the Committee also concluded that developmental toxicity studies with rats and rabbits with either aspartame or aspartame/DKP (3:1) mixture at dose levels up to 4000 mg/kg bw per day, administered either in the diet or by gavage, showed no significant compound-related effects.

In a two-generation study in rats not previously evaluated by the Committee (52), minimal to slight hypertrophy and vesiculation of nuclei in cells of kidney tubules in the inner cortex were observed in neonatal rats of the F2 generation exposed to aspartame in utero at 2000 or 4000 mg/kg bw per day. The Committee noted that the effects, while possibly compound-related, were transient in nature and had resolved by 28 days.

In a reproductive toxicity study (53) not previously reviewed by the Committee, the effects of aspartame (0 or 4000–7800 mg/kg bw per day in the diet, administered during gestation and lactation) on peri- and postnatal development in rats were compared with those of phenylalanine, or a combination of phenylalanine and aspartic acid. Aspartame, phenylalanine and a combination of phenylalanine with aspartic acid all reduced maternal and pup body weights compared with controls.

In a developmental toxicity study in mice (54) not previously reviewed by the Committee, the NOAEL was 5700 mg/kg bw per day, the highest dose level tested.

A study in which adult mice were treated with aspartame for 90 days by gavage at a dose of 0, 40, 80 or 160 mg/kg bw per day showed dose-related reductions in sperm count, sperm motility and sperm viability, as well as an increase in sperm abnormalities at doses of 80 and 160 mg/kg bw per day. No effects were observed at 40 mg/kg bw per day (55,56). The Committee noted the relatively small group sizes used in these studies on sperm parameters, and that no effect on the reproductive capacity of male animals has been reported in one- and two-generation studies in rats that used higher-dose levels.

The Committee concluded that the NOAEL for reproductive effects in one- or two-generation studies in rats was 4000 mg/kg bw per day, the highest dose tested. In mice, the NOAEL for developmental toxicity was 5700 mg/kg bw per day, the highest dose tested.

### Special studies

The present Committee identified several recently published studies of aspartame that evaluated different toxicity end-points and mechanisms, including oxidative stress. The Committee noted limitations in the design of most studies, including inadequate controls and co-administration of methotrexate (57–60). The Committee therefore considered these studies to be of limited utility for the risk assessment of aspartame.

### Observations in humans

#### Tolerability studies

Acute, short-term and long-term repeat-dose studies have been conducted with aspartame in healthy and diabetic adults, children and adolescents, as well as in obese and non-obese subjects. Some of these studies have been described previously (61,62).

Standard safety parameters including haematology, clinical chemistry and urinalysis were evaluated in the human tolerability studies. In addition, plasma, serum and urine samples were measured for phenylalanine, tyrosine and other amino acids, as well as methanol, insulin and glucose levels. No persistent changes in vital signs, body weight and standard haematology/clinical chemistry values were reported after aspartame administration versus placebo at dose levels of up to 75 mg/kg bw per day for periods of up to 24 weeks (9). Overall, the tolerability studies conducted in children, adolescents and adults at doses of up to almost twice the current ADI, over administration periods extended up to several months, did not indicate any adverse health effects of aspartame in any population.

#### Epidemiological studies related to cancer outcomes

The studies identified involved participants from different countries; all cancers combined as well as several individual types of cancers were assessed. Numerous epidemiological studies evaluated the carcinogenic potential of intense sweeteners (often referred to as artificial sweeteners), but only a few studies assessed aspartame specifically. In addition to these, other studies were considered when it was likely that aspartame was the only or the most widely used intense sweetener.

Three case–control studies addressing brain cancers did not find any significant association between brain cancer and aspartame consumption (63–

65). The publication by Bosetti et al. (66) is an updated analysis of a hospital-based Italian case-control study (67). Neither publication found an association between aspartame consumption and the several cancer sites they investigated. A Spanish multicase-control (MCC-Spain) study (68) did not find any significant association between aspartame consumption and various cancer sites. Despite the drawbacks intrinsic to the case-control design, especially when evaluating dietary factors (such as the potential for recall and selection bias, and the use of proxies for the assessment of intense sweetener/aspartame consumption), the results as a whole indicate a lack of association between aspartame consumption and the risk of brain cancers.

Out of four cohort studies with incidence data based in the USA, two (69,70) found no association between aspartame consumption and the occurrence of haematopoietic cancers, while another reported a significant association between aspartame consumption and the occurrence of non-Hodgkin lymphoma (NHL) (relative risk (RR): 1.64; 95% confidence interval (CI): 1.17–2.29) and multiple myeloma (RR: 3.36; 95% CI: 1.38–8.19) that was limited to men. Relative risks refer to the highest quartile of aspartame consumption ( $\geq 143$  mg/day) versus no consumption (71). One study (72) reported an association between consumption of beverages containing intense sweeteners (considered by the Committee to be primarily aspartame) and liver cancer, but only in a subgroup of diabetics with up to 12 years of follow-up (hazard ratio (HR): 1.13; 95% CI: 1.02–1.25). Results in non-diabetics overall as well as in diabetics with more than 12 years of follow-up were not statistically significant. A European prospective multi-centre cohort study (73) reported a slightly but statistically significantly increased hepatocellular cancer risk. Based on 101 cases, the consumption of soft drinks containing intense sweeteners (considered by the Committee to be primarily aspartame) increased the risk of hepatocellular cancer by 6% per serving increment (330 mL) per week (HR: 1.06; 95% CI: 1.03–1.09). As in most of the other studies, dietary and lifestyle data were only collected at baseline.

A study in France involving approximately 100 000 participants during 2009–2021 (NutriNet-Santé) compared cancer risks in lower consumers (mean: 3.24 mg/day; standard deviation (SD): 4.06) and higher consumers (mean: 47.42 mg/day; SD: 60.75) with non-consumers of aspartame (74). Comparing higher consumers of aspartame versus non-consumers, increased risks were observed for all cancers (HR: 1.15; 95% CI: 1.03–1.28), breast cancer (HR: 1.22; 95% CI: 1.01–1.48) and obesity-related cancers (HR: 1.15; 95% CI: 1.01–1.32). Similar increases in cancer risk were seen in lower and higher consumers compared with non-consumers. The hazard ratios for lower consumers versus non-consumers were: 1.12 (95% CI: 1.02–1.23) for all cancers, 1.09 (95% CI: 0.92–1.29) for breast cancer and 1.08 (95% CI: 0.96–1.22) for obesity-related cancers. When analyses were restricted to participants with the best estimates of

exposure (i.e. at least four 24-hour dietary records during the first 2 years versus at least two in the main analyses), the associations were diminished and became non-significant.

Two of the cohort studies (75,76) are less informative; they do not assess the incidence of cancer but rather mortality, and the estimates of the aspartame exposure are unreliable.

The Committee noted that statistically significant increases were reported for some cancers in some studies, namely hepatocellular carcinoma, breast cancer and haematological cancers (NHL and multiple myeloma). However, a consistent association of aspartame consumption with a specific cancer type has not been observed. All these studies have limitations with respect to assessment of exposure and, in many studies, particularly with respect to aspartame versus intense sweeteners. Reverse causality, chance, bias and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components cannot be ruled out. Overall, the Committee did not find convincing evidence of an association between aspartame consumption and cancer in humans.

#### Epidemiological studies related to non-cancer outcomes

The evidence linking aspartame consumption to glycaemic responses and markers of type 2 diabetes (T2D) – blood glucose and insulin, insulinemic index, insulin sensitivity, HbA1c, GLP-1, leptin, cholesterol and body mass index (BMI) – is inconclusive. The studies linking aspartame consumption and T2D and its markers yielded different results depending on whether they were randomized controlled trials (RCTs) or epidemiological studies. Several clinical studies in both diabetic and non-diabetic subjects found no significant effects of aspartame consumption on blood glucose, HbA1c, insulin or levels of other markers of glycaemic response (77–81). Other studies linked aspartame consumption with reduced glycaemic response and other markers of T2D (82–87).

Epidemiological studies showed different results. Using data reported in the United States Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) III, Kuk and Brown (88) found that in 2856 Americans surveyed during 1988–1994 for demographics, dietary practices, blood glucose, oral glucose tolerance and anthropometrics, aspartame consumption was associated with greater glucose intolerance in obese individuals. Reverse causation in this study is also possible. In the NutriNet-Santé cohort, aspartame consumption was associated with increased T2D incidence after a median follow-up of 9.1 years (HR: 1.63; 95% CI: 1.38–1.93) (89). The results may be biased by how T2D cases were identified in this study, that is, specific medications and self-reported physician diagnosis.



Studies linking aspartame consumption to changes in gut or oral microbiota have shown inconsistent results. One study in 17 healthy individuals showed no significant changes in gut microbiota measured in stool samples from consumers versus non-consumers of an aspartame-containing beverage, for two periods of 14 days each separated by a 4-week washout period (90). Another study of 31 subjects who regularly consumed aspartame and/or acesulfame-K found that those who consumed aspartame had a different microbiome profile – different proportions of certain bacteria in stool – compared with non-consumers of aspartame (91). One RCT consisted of 120 subjects who had previously not consumed intense sweeteners regularly, divided into six groups: four consuming sachets of different intense sweeteners and two control groups (one of sucrose and one with no sweeteners) for 2 weeks. It was found that the four intense sweeteners altered oral microbiomes and microbiome function compared with baseline measurements in these subjects and with the two control groups. Specifically, aspartame consumption was linked to changes in polyamine metabolism. However, unlike other intense sweeteners examined in this study, aspartame was not shown to impair glycaemic response, despite microbiome changes (92). The health implications of alterations in microbiomes and metabolome are not known.

The prospective NutriNet-Santé cohort study in France linked aspartame consumption to a statistically significant increase in incidence of cerebrovascular events (HR: 1.17; 95% CI: 1.03–1.33) (93). Another study (94) showed that in HIV-positive subjects, but not in HIV-negative subjects, aspartame consumption was associated with vascular plaque burden and inflammation, which may be correlated with higher risk of cardiovascular disease. This study may have been confounded by dietary, medical and lifestyle factors, including that the HIV-positive subjects in this study consumed significantly more sweeteners of all types than HIV-negative subjects.

In case reports from the 1980s, subjects reported seizures following aspartame consumption; however, in following clinical and observational studies, no evidence was found linking aspartame consumption to seizures (95–97). Similarly, no consistent significant impacts were detected in clinical trials linking aspartame consumption to mood disorders (98); learning ability measured by modified intelligence quotient (IQ) tests, and learning and arithmetic tests; children's behaviours as assessed by actometers and video recordings (99–103); or headaches (104). In many cases, study interpretations were limited by small sample sizes, that is, either case reports of individuals or studies including 20 or fewer subjects (102,105–108).

Overall, the Committee did not find convincing evidence that aspartame consumption was associated with specific non-cancer health end-points.



## Assessment of dietary exposure

The Committee has not previously evaluated the dietary exposure to aspartame. Information related to the use of or dietary exposure to aspartame was provided to the Committee for Australia and New Zealand (109), Chile (110) and Germany (111), as well as for Europe (112) and other countries, by the sponsors. As the Committee has not evaluated the dietary exposure to aspartame in the past, the scope of this assessment included all studies or assessments available. The Committee also considered aspartame-acesulfame salt (INS No. 962) in its assessment. The Committee noted that, in most of the world, the use of aspartame-acesulfame salt was limited. The Committee therefore noted that dietary exposure to aspartame-acesulfame salt specifically would also be minimal.

### Use of aspartame

Within the Codex Alimentarius General Standard for Food Additives (GSFA) (113), aspartame is permitted for use as a flavour enhancer and sweetener in a range of food categories at maximum permitted levels (MPLs) between 300 and 10 000 mg/kg, and in accordance with Good Manufacturing Practice (GMP) for table-top sweeteners. It is permitted for use both on its own in food products, as well as in combination with other sweeteners. Aspartame has been reported to be used in food products with other sweeteners (114–117).

Concentrations of aspartame in food products were reported from food labels, food industry use levels or analytical results. Overall, the most reported use of aspartame is in non-alcoholic beverages, with use also reported for a range of other food groups, as summarized in [Table 2.2](#). Some reported concentrations were not included in the summary where they were not considered to be robust, or where their basis could not be determined.

There were a small number of concentrations for some food categories that were reported to exceed the GSFA MPLs (e.g. non-alcoholic beverages, confectionery, dietary supplements/special dietary foods, chocolate and cocoa products, desserts, chewing gum), but it is noted that there are higher MPLs or GMP permissions for some food categories for some countries (e.g. chewing gum). These concentrations were evaluated further by the Committee. In some cases these may have been for powdered or concentrated foods, and are therefore not directly comparable to the MPL. In other instances they were foods produced specifically in local areas. The range of mean concentrations fell within the GSFA MPLs, except for dietary supplements/special-purpose foods. For dietary supplements the exceedance was only observed at the mean for one study for a vitamin preparation.

Table 2.2  
**Summary of reported concentrations of aspartame by food category**

Food category	MPL in the GSFA (mg/kg)	Range of reported mean concentrations (mg/kg) <sup>a</sup>	Range of reported concentrations (mg/kg) <sup>a</sup>
Non-alcoholic beverages	600	ND and 0–450	ND and 0–7 235
Alcoholic beverages	600	24–126	ND–600
Confectionery	3 000	74–1 295	ND–5 132
Chocolate and cocoa products	1 000–3 000	11–269	ND–5 649
Bread and bakery	1 700–4 000	62	ND–416
Snack foods	500	18–28	ND–310
Dairy products	600–2 000	16–234	ND–1 000
Fruit and vegetable products	300–2 500	294	ND–1 000
Table-top sweeteners	GMP	306–243 000	ND and 0–500 000
Desserts	1 000	10–270	ND–1 575
Chewing gum	10 000	59–5 158	ND–13 000
Jams and preserves	1 000	4–415	ND–725
Sauces and condiments	350–3 000	NR	ND–473
Dietary supplements	800–5 500	4–6 365	ND–6 615

GMP: Good Manufacturing Practice; GSFA: Codex Alimentarius General Standard for Food Additives; MPL: maximum permitted level; ND: not detected; NR: not reported.

<sup>a</sup> Food industry use levels or analytical data. ND results are relevant to studies where analysis was undertaken, and zeros relate to food industry use levels.

### Estimates of dietary exposure to aspartame

The estimates reviewed were prepared using a range of different dietary exposure assessment methodologies, including those that captured different combinations of foods, different population and/or subpopulation groups, and different types of consumption and concentration data. The estimates that have been analysed were prepared and published between 1981 and 2023. There were many estimates of dietary exposure available from around the world, including five out of six of the WHO regions: Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and Western Pacific Region. The Committee noted that there were no estimates from the WHO African Region, only two estimates from the South-East Asia Region and only one estimate from the Eastern Mediterranean Region.

Estimates of dietary exposure to aspartame based on screening methods (budget method, sugar replacement models or disappearance data) were reviewed by the Committee. The Committee also reviewed many studies based on individual dietary records derived using a variety of methods and data.

The Committee established some criteria to determine the most suitable dietary exposure estimates for use in the Evaluation. These criteria included that the estimate was based on individual dietary records collected via food frequency

Table 2.3

**Range of reported estimates of dietary exposure to aspartame for consumers only that are appropriate for the Evaluation (mg/kg bw per day)**

Population group	Mean or median	High <sup>a</sup>
General population	< 0.1–7.5	< 0.2–19.8
Children	< 0.1–10.1	0.1–20.2
Adults	< 0.1–4.4	0.1–11.5
Diabetics (all)	0.1–5.3	0.3–10.6
Diabetics (children)	0.7–4.1	1.4–7.8
Diabetics (adults)	1.4–2.5	2.5–7.9

<sup>a</sup> Range of high percentiles reported including 75th to 99th percentile and high estimates calculated by the Committee.

questionnaire, 24-hour recall or food diary. Multiple days of data were preferred; however, if the estimate was based on 1 day of consumption data, only mean exposures could be included, not high estimates. Only estimates based on food industry use levels or analytical levels were used. Estimates that were based on a broad range of foods as well as those based on beverages only were included. Mean (or median) and high percentile (excluding maximum) estimates of dietary exposure were included. For studies for which there was no high estimate, an unreliable high estimate or only a maximum, an estimate based on mean exposure multiplied by 2 was applied by the Committee (118). Estimates with insufficient methodological details and/or data were not included in the Evaluation.

A summary of the estimates of dietary exposure relevant to the Evaluation are shown in Table 2.3. In summary, the mean dietary exposures to aspartame ranged from < 0.1 to 7.5 mg/kg bw per day for the general population, from < 0.1 to 10.1 mg/kg bw per day for children (aged < 18 years) and from < 0.1 to 4.4 mg/kg bw per day for adults (aged ≥ 18 years). Estimates of high dietary exposure to aspartame ranged from < 0.2 to 19.8 mg/kg bw per day for the general population, from 0.1 to 20.2 mg/kg bw per day for children and from 0.1 to 11.5 mg/kg bw per day for adults.

Despite there being no, or only a small number of, estimates of dietary exposure for some WHO regions, given the large number of estimates and combinations of data and methodologies reviewed, the Committee noted that it is unlikely that dietary exposures for these WHO regions would be outside the estimates reviewed for other WHO regions.

Diabetics or overweight people, or those on a weight control diet, were included in a number of studies as potential higher consumers of intensely sweetened products. The estimates were reviewed to determine if this was the case. Other subpopulation groups, such as pregnant women and those with PKU

and cow's milk protein allergy, were also included in some assessments. These were reviewed by the Committee but not considered for the Evaluation.

No consistent patterns were observed in the estimates of dietary exposure to aspartame for consumers with diabetes where comparisons were made with the general or non-diabetic population. Where studies met the criteria established for estimates that could be used for the Evaluation, estimated dietary exposures for people with diabetes ranged from 0.1 to 5.3 mg/kg bw per day at the mean and from 0.3 to 10.6 mg/kg bw per day for the high estimates (Table 2.3).

Although not the case in all studies, there were more estimates of dietary exposures to aspartame that were higher for overweight subjects or those on a calorie-controlled diet than compared with the general population. Estimated dietary exposures for this population group ranged from < 1 to 2.0 mg/kg bw per day at the mean and from 1.3 to 14.6 mg/kg bw per day for the high estimates.

The most common food contributing the highest proportion (from 6 to 100%) of the dietary exposure to aspartame was non-alcoholic beverages, depending on the assessment and population groups assessed. The majority (75%) of the studies reviewed reported contributions of 50% or more for non-alcoholic beverages. Table-top sweeteners were also reported as a major contributor in many studies, ranging from < 1 to 66%, although mostly < 20%. Where a range of population groups were assessed, table-top sweeteners contributed more to dietary exposures for older adults. Other foods that contributed to dietary exposure in a number of studies included dairy products at < 1–72%, desserts at < 1–44%, edible ices at 5–29%, confectionery at < 1–27%, alcoholic beverages at 6–15% and chewing gum at 1–50%. Foods with 10% or less contribution to dietary exposure included cocoa and chocolate products, chocolate/coffee beverage bases, cereals and cereal products, cakes and cookies, snack foods, condiments/sauces/jams, special-purpose foods and dietary supplements.

Overall, the Committee concluded that dietary exposures to aspartame worldwide for the general population including specific subgroups (e.g. diabetics and overweight/on weight control diet) would range at the mean from < 0.1 to 10.1 mg/kg bw per day for children and from < 0.1 to 4.4 mg/kg bw per day for adults. High dietary exposures would range from 0.1 to 20.2 mg/kg bw per day for children and from 0.1 to 11.5 mg/kg bw per day for adults.

## Evaluation

At its Twenty-fifth meeting, the Committee established an ADI of 0–40 mg/kg bw for aspartame (2). This ADI was based on the NOAEL of 4000 mg/kg bw per day, the highest dose tested, in a 104-week study in rats exposed to aspartame in the diet (3), and the application of a 100-fold uncertainty factor. At the present meeting, the Committee evaluated biochemical, toxicological and epidemiological

studies on aspartame, its metabolites and degradation products that had become available since the previous Committee's evaluation. The Committee 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. The Committee 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 the consumption of common foods. The Committee 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.

The Committee concluded that there was no concern for genotoxicity of oral exposure to aspartame.

The Committee evaluated data from 12 oral carcinogenicity studies of aspartame and identified deficiencies with all of them. The Committee noted that all the studies apart from those by Soffritti et al. (27,33,34,36) showed negative results. The Committee 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. The Committee reached the view that the results of the Soffritti et al. studies are of uncertain relevance and therefore cannot be used for the risk assessment of aspartame. The Committee concluded that the carcinogenicity study by Ishii et al. (3) was close to meeting the current testing guidelines and showed negative results. The Committee 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. The Committee 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 for genotoxicity and a lack of a plausible mechanism by which oral exposure to aspartame could induce cancer, the Committee 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. The Committee therefore concluded that aspartame was not a reproductive or developmental toxicant in animals.

The Committee evaluated data from RCTs and epidemiological studies to examine the association between aspartame consumption and certain health effects, such as cancer, T2D and other non-cancer health end-points in humans.

The Committee noted that statistically significant increases were reported for some cancers, such as hepatocellular, breast and haematological (NHL 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, the Committee 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. The Committee noted that the results of the epidemiological studies may be biased by how T2D cases were identified (either specific medications or self-reported physician diagnosis). The Committee therefore concluded that the evidence of an association between aspartame consumption and the evaluated non-cancer health end-points is not convincing.

Overall, the Committee 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 GIT into metabolites that are identical to those absorbed after the consumption of common foods, and that no aspartame enters the systemic circulation. The Committee 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. The Committee therefore reaffirmed the ADI of 0–40 mg/kg bw for aspartame at the present meeting.

The Committee determined that dietary exposure estimates to aspartame at the mean of up to 10 mg/kg bw per day for children and 5 mg/kg bw per day

for adults, and for high dietary exposures up to 20 mg/kg bw per day for children and 12 mg/kg bw per day for adults, were appropriate for the present assessment.

The Committee noted that these dietary exposure estimates do not exceed the ADI. The Committee therefore concluded that dietary exposure to aspartame does not pose a health concern.

After review of the data submitted, the Committee made the following modifications to the specifications monograph for aspartame that was previously revised at the Eighty-second meeting (119):

- updated the description to include details on manufacturing;
- added flavour enhancer to the functional uses;
- replaced the method of assay with a high-performance liquid chromatography method;
- added a test and specification for “other related impurities”; and
- removed the test and specification for “other optical isomers”.

An addendum to the toxicology and dietary exposure monograph was prepared. The specifications were revised.

## 2.2 Revision of specifications

### 2.2.1 Lycopene (synthetic); and lycopene from *Blakeslea trispora*

The Committee recalled that at its Eighty-second, Eighty-sixth and Eighty-seventh meetings (120–122) there was a recommendation to replace the solvent chloroform with less hazardous solvents. Upon request from the CCFA, the Committee revised the specifications for lycopene (synthetic) (INS No. 160d(i)) and lycopene from *Blakeslea trispora* (INS No. 160d(iii)) as follows:

- replaced “freely soluble in chloroform” with “sparingly soluble in tetrahydrofuran (THF)” in the solubility test; and
- replaced the “solution in chloroform” test with a “solution in THF” test requirement.

### 2.2.2 Pentasodium triphosphate

At the request of the CCFA, the Committee revised the specifications for pentasodium triphosphate (INS No. 451(i)) as follows:

- revised the assay value for P<sub>2</sub>O<sub>5</sub> to not less than 56% and not more than 59% of P<sub>2</sub>O<sub>5</sub>; and
- revised the pH value to 9.1–10.2 (1% solution).



Table 2.4

**Revision to the specifications monograph for (Framework for) steviol glycosides, annex 4 (Enzyme modified glucosylated steviol glycosides) (123)**

Substance	Original text	Revised text	Additional information
Steviol glycosides Annex 4: Enzyme modified glucosylated steviol glycosides	Cyclomaltodextrin glucanotransferase (EC 2.4.1.19) and $\alpha$ -amylase (EC 3.2.1.1) from non-toxicogenic nonpathogenic strains of <i>Bacillus stearothermophilus</i> , <i>Bacillus licheniformis</i> and <i>Bacillus subtilis</i> are used to facilitate the transfer of glucose to steviol glycosides.	Cyclomaltodextrin glucanotransferase (EC 2.4.1.19) and $\alpha$ -amylase (EC 3.2.1.1) from non-toxicogenic nonpathogenic strains of <i>Anoxybacillus caldiproteoliticus</i> , <i>Bacillus licheniformis</i> and <i>Bacillus subtilis</i> are used to facilitate the transfer of glucose to steviol glycosides.	The production strain of the enzyme used to facilitate the transfer of glucose to steviol glycosides was incorrectly identified as <i>Bacillus stearothermophilus</i> . The revised identification is <i>Anoxybacillus caldiproteoliticus</i> .

The Committee also revised the level of lead from 4 mg/kg to not more than 2 mg/kg based on information available to the Committee.

### 2.2.3 Steviol glycosides

At its Ninety-fifth meeting the Committee was requested to make a correction to the specifications monograph for (Framework for) steviol glycosides, annex 4 (Enzyme modified glucosylated steviol glycosides) (123). The Committee at that meeting decided to defer the request. Based on the information provided, the Ninety-sixth Committee made the revision as reported in Table 2.4.

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## 3. Flavouring agents

### 3.1 Safety evaluation

#### 3.1.1 Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids

##### Introduction

At the request of the CCFA at its Fifty-second session (1), the Committee evaluated an additional six flavouring agents in the group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids for the first time. In addition, the Committee considered new data on 10 previously evaluated flavouring agents in this group; data on isoamyl isovalerate (No. 50), a structurally related substance; and data on the hydrolysis products from three (Nos 2282, 2284 and 2285) of the six additional flavouring agents, namely 2-ethylhexanoic acid, 2-ethylbutyric acid (No. 257) and isovaleric acid (No. 259).

The Committee previously evaluated 32 members of this group of flavouring agents at its Forty-ninth meeting (2). The Committee concluded that none of the 32 flavouring agents had any safety concerns at the estimated dietary exposures.

The additional flavouring agents in this group are 4-methylpentyl 4-methylvalerate (No. 2280), 5-methylhexyl acetate (No. 2281), 4-methylpentyl isovalerate (No. 2282), ethyl 4-methylpentanoate (No. 2283), ethyl 2-ethylbutyrate (No. 2284) and ethyl 2-ethylhexanoate (No. 2285). Three of the additional six flavouring agents (Nos 2280, 2282 and 2283) in this group have been reported to occur naturally in some foods such as beer, capsicum, cheese, cocoa, litchi, rum, sake or wine (3).

The six additional members of this group were evaluated according to the revised Procedure for the Safety Evaluation of Flavouring Agents (4).

The Committee reviewed unpublished study reports and scientific publications that were submitted. Study summaries from a database of the European Chemicals Agency (<https://echa.europa.eu/nl/information-on-chemicals/registered-substances>) were submitted, as well as English summaries of study reports submitted in other languages. The Committee could not assess these studies in the absence of the original full study reports. Further, some study reports not in English could not be assessed by the Committee.

A comprehensive literature search for absorption, distribution, metabolism and elimination (ADME) and toxicological data was performed in Google Scholar, PubMed, Embase and Web of Science using the names and CAS numbers of the flavouring agents under evaluation in this group, including

articles published from 1 January 1998 to 10 May 2023; 10 additional relevant references were identified.

### Assessment of dietary exposure

The total annual volume of production of the six additional flavouring agents belonging to the group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids is 96 kg in Japan and 4 kg in the USA (5,6). More than 99% of the annual production volume in Japan is accounted for by ethyl 2-ethylbutyrate (No. 2284), and more than 75% of the production volume in the USA is accounted for by 4-methylpentyl 4-methylvalerate (No. 2280).

Dietary exposures were estimated by both the single portion exposure technique (SPET) and the maximized survey-derived intake (MSDI) method; the highest values are reported in Table 3.1 (2,5–8). The SPET and MSDI method values are in the range of 40–3000 µg/day and 0.01–25 µg/day, respectively. The estimated daily dietary exposure was highest for 5-methylhexyl acetate (No. 2281) (the SPET value obtained for non-alcoholic soft beverages).

### Absorption, distribution, metabolism and elimination

Information on the ADME of the flavouring agents belonging to the group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids is available in the monograph from the Forty-ninth meeting (9). No additional information on the ADME of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids was available for this meeting.

In mammals, 4-methylpentyl 4-methylvalerate (No. 2280), 5-methylhexyl acetate (No. 2281), 4-methylpentyl isovalerate (No. 2282), ethyl 4-methylpentanoate (No. 2283), ethyl 2-ethylbutyrate (No. 2284) and ethyl 2-ethylhexanoate (No. 2285) are expected to be hydrolysed by esterases to their corresponding carboxylic acids and alcohols, including those of branched carbon chains and other products including ethanol (No. 41) and acetic acid (No. 81). The resulting branched-chain alcohols and carboxylic acids are expected to undergo further oxidation prior to entering the fatty acid pathway to ultimately yield CO<sub>2</sub>. Acids with a methyl substituent located at an even-numbered carboxylic acid (e.g. 4-methylpentanoic acid) are extensively metabolized to CO<sub>2</sub> via β-oxidation. Branched-chain acids with α-ethyl substituents undergo ω- and ω-1-oxidation to produce polar metabolites excreted in the urine. ω-Oxidation rather than β-oxidation is expected in acids with a methyl group at the 3-position, and yields polar, acidic metabolites that either undergo further oxidation or are conjugated and excreted in the urine. Generally, saturated linear primary alcohols such as ethanol (No. 41) are rapidly oxidized in vivo to the corresponding aldehyde in the presence of alcohol dehydrogenase (ADH), and are then further oxidized to

the corresponding carboxylic acid (e.g. acetic acid, No. 81) prior to undergoing normal fatty acid metabolism.

### Application of the revised Procedure for the Safety Evaluation of Flavouring Agents

**Step 1.** There are no structural alerts for genotoxicity of the additional six flavouring agents (Nos 2280–2285) in this group. Chemical-specific genotoxicity data on previously evaluated flavouring agents in this group and on one additional flavouring agent (No. 2285) do not indicate any genotoxic potential.

**Step 2.** In applying the revised procedure for the safety evaluation of flavouring agents to the additional six flavouring agents, the Committee assigned all additional six flavouring agents (Nos 2280–2285) to structural class I (10).

**Step 3.** Dietary exposures determined with the MSDI method and SPET are presented in [Table 3.1](#).

**Step 4.** The highest estimated dietary exposures for five flavouring agents (Nos 2280, 2282, 2283, 2284 and 2285) in structural class I are below the threshold of concern (i.e. 1800 µg/person per day). The Committee therefore concluded these five flavouring agents would not raise safety concerns at current estimated dietary exposures.

The highest estimated dietary exposure for 5-methylhexyl acetate (No. 2281) in structural class I is above the threshold of concern (i.e. 1800 µg/person per day for structural class I), and its evaluation proceeded to Step 5 of the revised procedure.

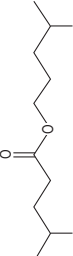

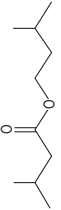
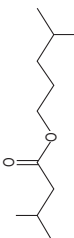
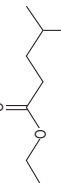
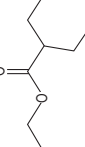
**Step 5.** For 5-methylhexyl acetate (No. 2281), the NOAEL of 220 mg/kg bw per day for the structurally related substance isoamyl isovalerate (No. 50) in a 90-day dietary feeding study in rats (8) provides an adequate margin of exposure (MOE) (4400) relative to the SPET estimate of 3000 µg/day (50 µg/kg bw per day) when it is used as a flavouring agent.

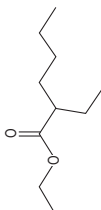
[Table 3.1](#) summarizes the evaluations of the additional six flavouring agents belonging to this group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids (Nos 2280–2285).

### Consideration of combined intakes from use as flavouring agents

The Committee previously considered the potential combined intake of this group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids at its Forty-ninth meeting (2) and concluded that the combined intake would not raise safety concerns. As the MSDI values for the six additional flavouring agents in this group (Nos 2280–2285) are low (0.01–25 µg/day), they would make a negligible contribution to the combined intake of this group.

**Table 3.1**  
**Summary of the results of safety evaluations of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids used as flavouring agents<sup>a,b,c,d</sup>**

Flavouring agent	No.	CAS No. and structure	Step 4 Does intake exceed the threshold of human intake? <sup>e</sup>	Step 5 Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate margin of exposure? <sup>f</sup>	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
4-Methylpentyl 4-methylvalerate	2280	35852-42-7 	No	NR	– <sup>g</sup>	–	No safety concern
5-Methylhexyl acetate	2281	180348-60-1; 72246-17-4 	Yes; SPET: 3000 µg/day	Yes; the NOAEL of 220 mg/kg bw per day for structurally related isoamyl isovalerate (No. 50) in a 90-day study in rats (♂) is 4400 times the estimated dietary exposure of No. 2281 when used as a flavouring agent	– <sup>h</sup>	Isoamyl isovalerate (No. 50) 	No safety concern
4-Methylpentyl isovalerate	2282	850309-45-4 	No	NR	–	–	No safety concern
Ethyl 4-methylpentanoate	2283	25415-67-2 	No	NR	–	–	No safety concern
Ethyl 2-ethylbutyrate	2284	2983-38-2 	No	NR	– <sup>k</sup>	–	No safety concern

Flavouring agent	No.	CAS No. and structure	Step 4		Step 5		Conclusion based on current estimated dietary exposure
			Does intake exceed the threshold of human intake? <sup>a</sup>	Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate margin of exposure? <sup>b</sup>	Comments on predicted metabolism	Structural relative name (No.) and structure	
Ethyl 2-ethylhexanoate	2285	2983-37-1 	No	NR	–	–	No safety concern

bw: body weight; CAS: Chemical Abstracts Service; MSDI: maximized survey-derived intake; No.: number; NOAEL: no-observed-adverse-effect level; NR: not relevant; SPET: single portion exposure technique.

<sup>a</sup> In total, 32 flavouring agents in this group were previously evaluated by the Committee at its Forty-ninth meeting (2).

<sup>b</sup> Step 1: There are no structural alerts for genotoxicity for the additional six flavouring agents, and data on genotoxicity of No. 2285 do not indicate potential for genotoxicity.

<sup>c</sup> Step 2: All six flavouring agents are in structural class 1.

<sup>d</sup> Step 3: Dietary exposures were estimated with both the SPET and the MSDI method; the higher of the two values for each flavouring agent is reported. SPET gave the higher estimate for each flavouring agent.

<sup>e</sup> Step 4: The threshold of toxicological concern for structural class 1 is 1800 µg/day.

<sup>f</sup> The margin of exposure was calculated based on the higher daily per capita intake calculated either by SPET or MSDI.

<sup>g</sup> 4-Methylpentyl 4-methylvalerate is expected to be hydrolysed to 4-methylpentanoic acid and 4-methylpentanol. Acids with a methyl substituent located at an even-numbered carboxylic acid (e.g. 4-methylpentanoic acid) are extensively metabolized to CO<sub>2</sub> via  $\beta$ -oxidative cleavage in the fatty acid pathway.

<sup>h</sup> 5-Methylhexyl acetate is expected to be hydrolysed to acetic acid and 5-methylhexanol. The carboxylic acid resulting from ester hydrolysis enters cellular fatty acid metabolism. Even-numbered carboxylic acids (e.g. acetic acid) continue to be cleaved to acetyl CoA. Acetyl CoA enters the citric acid cycle directly.

<sup>i</sup> 4-Methylpentyl isovalerate is expected to be hydrolysed to isovaleric acid and 4-methylpentanol. For resulting branched-chain alcohols and acids, the position of the methyl substituent plays a role in metabolism. If the methyl group is located at the 3-position (e.g. isovaleric acid),  $\beta$ -oxidation is inhibited and  $\omega$ -oxidation predominates, primarily leading to polar, acidic metabolites capable of being further oxidized, or conjugated and excreted in the urine.

<sup>j</sup> Ethyl 4-methylpentanoate is expected to be hydrolysed to 4-methylpentanoic acid and ethanol. For resulting branched-chain alcohols and acids, the position of the methyl substituent plays a role in metabolism. Acids with a methyl substituent located at an even-numbered carboxylic acid (e.g. 4-methylpentanoic acid) are extensively metabolized to CO<sub>2</sub> via  $\beta$ -oxidative cleavage in the fatty acid pathway. In general, saturated linear primary alcohols are rapidly oxidized in vivo to the corresponding aldehyde in the presence of ADH. The resulting aldehyde undergoes rapid in vivo oxidation to the corresponding carboxylic acid, which participates in normal fatty acid metabolism.

<sup>k</sup> Ethyl 2-ethylbutyrate is expected to be hydrolysed to 2-ethylbutyric acid and ethanol. Resulting branched-chain alcohols and carboxylic acids with  $\alpha$ -ethyl substituents are metabolized by  $\omega$ - and  $\omega$ -1-oxidation to yield polar metabolites capable of excretion in the urine. In general, saturated linear primary alcohols are rapidly oxidized in vivo to the corresponding aldehyde in the presence of ADH. The resulting aldehyde undergoes rapid in vivo oxidation to the corresponding carboxylic acid, which participates in normal fatty acid metabolism.

<sup>l</sup> Ethyl 2-ethylhexanoate is expected to be hydrolysed to 2-ethylhexanoic acid and ethanol. Resulting branched-chain alcohols and carboxylic acids with  $\alpha$ -ethyl substituents are metabolized by  $\omega$ - and  $\omega$ -1-oxidation to yield polar metabolites capable of excretion in the urine. In general, saturated linear primary alcohols are rapidly oxidized in vivo to the corresponding aldehyde in the presence of ADH. The resulting aldehyde undergoes rapid in vivo oxidation to the corresponding carboxylic acid, which participates in normal fatty acid metabolism.

### Consideration of secondary components

One flavouring agent in this group (No. 2281) has a minimum assay value of < 95% (Annex 4). The major secondary components hexyl acetate (No. 128), present at 5–6%, and heptyl acetate (No. 129), present at 3–4%, were both previously evaluated by the Committee and found to have no safety concerns at the estimated dietary exposures when used as flavouring agents (2). These secondary components are not considered to present a safety concern when consumed as components of No. 2281 used as a flavouring agent at their current estimated dietary exposure.

### Consideration of additional data on previously evaluated flavouring agents

The Committee considered additional data on 10 of the 32 previously evaluated flavouring agents in this group. Studies of acute toxicity (Nos 206 and 213), short-term toxicity (No. 213) and genotoxicity (Nos 186, 188, 189, 195, 196, 205, 206, 210 and 214) were available. Since no updated exposure data were submitted for the previously evaluated flavouring agents (Nos 186, 188, 189, 195, 196, 205, 206, 210, 213 and 214) for which toxicological data were submitted, a re-evaluation including an updated exposure assessment should be conducted for these flavouring agents at a future meeting.

The new information does not affect the conclusions on the other flavouring agents previously evaluated in this group.

### Conclusion

In the previous evaluations of 32 substances in this group of esters of aliphatic acyclic primary alcohols, studies of ADME, acute toxicity, short-term toxicity, reproductive and developmental toxicity, and genotoxicity were evaluated in the monographs from the Eleventh, Thirty-fifth, Forty-fourth, Forty-ninth, Fifty-seventh and Sixty-ninth JECFA meetings (9,11–15). None raised safety concerns.

For one (No. 2285) of the six additional flavouring agents, studies of acute toxicity and genotoxicity were available. In addition, studies of genotoxicity were available for the hydrolysis products from Nos 2282 and 2284, namely isovaleric acid (No. 259) and 2-ethylbutyric acid (No. 257), respectively. Short-term toxicity studies were available for the structurally related substance No. 50 and the hydrolysis products from Nos 2284 and 2285, namely No. 257 and 2-ethylhexanoic acid, respectively. In addition, studies on reproductive and developmental toxicity were available for 2-ethylhexanoic acid.

The Committee concluded that the six additional flavouring agents (Nos 2280–2285) would not give rise to safety concerns at the current estimated dietary exposures.

The Committee concluded that a re-evaluation including an updated exposure assessment should be undertaken for the previously evaluated flavouring agents ethyl isobutyrate (No. 186), butyl isobutyrate (No. 188), hexyl isobutyrate (No. 189), methyl isovalerate (No. 195), ethyl isovalerate (No. 196), methyl 2-methylbutyrate (No. 205), ethyl 2-methylbutyrate (No. 206), isopropyl 2-methylbutyrate (No. 210), methyl 2-methylpentanoate (No. 213) and ethyl 2-methylpentanoate (No. 214). The additional data presented do not give rise to safety concerns, and further support the safety of the other 22 previously evaluated flavouring agents in this group.

An addendum to the monograph was prepared.

## Recommendations

The Committee requests that updated exposure data (including both MSDI and SPET values) be provided for the flavouring agents ethyl isobutyrate (No. 186), butyl isobutyrate (No. 188), hexyl isobutyrate (No. 189), methyl isovalerate (No. 195), ethyl isovalerate (No. 196), methyl 2-methylbutyrate (No. 205), ethyl 2-methylbutyrate (No. 206), isopropyl 2-methylbutyrate (No. 210), methyl 2-methylpentanoate (No. 213) and ethyl 2-methylpentanoate (No. 214) within 2 years (i.e. by July 2025) so that a re-evaluation of these previously evaluated compounds can be conducted.

The Committee asks the JECFA Secretariat to urge sponsors and Codex Members to ensure that all required information is available for evaluation of flavouring agents prior to requesting inclusion in the CCFA JECFA Priority List, including updated exposure data (both SPET and MSDI values) for previously evaluated flavouring agents for which new toxicological data are submitted.

### 3.1.2 Hydroxy- and alkoxy-substituted benzyl derivatives

#### Introduction

At the request of the CCFA at its Fifty-first session (16), the Committee evaluated an additional nine flavouring agents in the group of hydroxy- and alkoxy-substituted benzyl derivatives for the first time. In addition, the Committee considered new data for 22 previously evaluated flavouring agents in this group and data on gallic acid, a structurally related substance.

The Committee evaluated 52 members of this group at previous meetings. Ethyl vanillin (No. 893) was evaluated by the Committee at its Eleventh meeting (17), and a conditional ADI<sup>2</sup> of 0–10 mg/kg bw was established. At its Thirty-fifth meeting (18), the Committee converted the conditional ADI to a temporary

<sup>2</sup> The term “conditional ADI” was previously used by JECFA to signify a range above the “unconditional ADI”, which may signify an acceptable intake when special problems, different patterns of dietary intake and special groups of the population that may require consideration are taken into account.



ADI of 0–5 mg/kg bw. At its Thirty-ninth meeting (19), the Committee extended the temporary ADI of 0–5 mg/kg bw. At its Forty-fourth meeting (20), the Committee established an ADI of 0–3 mg/kg bw. Vanillin (No. 889) was evaluated by the Committee at its Eleventh meeting and an ADI of 0–10 mg/kg bw was established. Methyl salicylate (No. 899) was evaluated by the Committee at its Eleventh meeting, and an ADI of 0–0.5 mg/kg bw was established. Piperonal (No. 896) was evaluated at the Eleventh meeting of the Committee and an ADI of 0–2.5 mg/kg bw was established. The Committee evaluated 46 members of this group at its Fifty-seventh meeting (21) and concluded that 45 of these flavouring agents were of no safety concern at the estimated dietary exposures. The ADIs for ethyl vanillin (No. 893), vanillin (No. 889), methyl salicylate (No. 899) and piperonal (No. 896) were maintained.

For butyl-*p*-hydroxybenzoate (No. 870), the evaluation was not finalized at the Fifty-seventh meeting because further information was required to confirm whether the substance was in current use as a flavouring agent. This information was available at the Fifty-ninth meeting (22), where it was concluded that this flavouring agent was of no safety concern at the estimated dietary exposure.

The structurally related substance propyl paraben (propyl-*p*-hydroxybenzoate) was on the agenda of the Sixty-seventh meeting for re-evaluation as a food additive. Toxicological data on butyl-*p*-hydroxybenzoate (No. 870) were also evaluated at that meeting. The Committee concluded that “in view of the adverse effects in male rats, propyl paraben (propyl-*p*-hydroxybenzoate) should be excluded from the group ADI for the parabens used in food” (23). The Committee also noted that the “reproductive toxicity of the parabens appears to increase with increasing length of the alkyl chain, and there are specific data showing adverse reproductive effects in male rats of butyl paraben”.

The Committee evaluated six members of this group at its Sixty-ninth meeting (24) and concluded that these flavouring agents were of no safety concern at the estimated dietary exposures.

The additional flavouring agents in this group are 2-ethoxy-4-(hydroxymethyl)phenol (No. 2271), 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate (No. 2272), 3-phenylpropyl 2-(4-hydroxy-3-methoxyphenyl)acetate (No. 2273), ethyl-2-(4-hydroxy-3-methoxyphenyl)acetate (No. 2274), *cis*-3-hexenyl salicylate (No. 2275), 4-formyl-2-methoxyphenyl 2-hydroxypropanoate (No. 2276), 2-hydroxy-4-methoxybenzaldehyde (No. 2277), 3,4-dihydroxybenzoic acid (No. 2278) and 3-hydroxybenzoic acid (No. 2279). Three of the nine flavouring agents (Nos 2275, 2278 and 2279) in this group have been reported to occur naturally in apple brandy, apple juice, beer, blackcurrants, bourbon whisky, buckwheat honey, Canadian whisky, cognac, dates, defatted soybean, fermented cocoa beans, grape brandy, malt whisky,



mulberry, honey, peanuts, red wine, roasted cocoa beans, rum, sake, sherry, white wine, wort, kumazasa (bamboo), cornmint oil and/or mango (3).

The nine additional members of this group were evaluated according to the revised Procedure for the Safety Evaluation of Flavouring Agents (4).

The Committee reviewed unpublished study reports and scientific publications that were submitted. Study summaries from a database of the European Chemicals Agency (ECHA) (<https://echa.europa.eu/nl/information-on-chemicals/registered-substances>) were submitted, as well as English summaries of study reports submitted in other languages. The Committee could not assess these studies in the absence of the original full study reports. Further, some study reports not in English could not be assessed by the Committee.

A literature search for toxicokinetic and toxicological data was performed in Google Scholar, PubMed, Embase and Web of Science using the names and CAS numbers of the flavouring agents under evaluation in this group up to 3 April 2023; three additional relevant references were identified.

### Assessment of dietary exposure

The total annual volume of production of the nine additional flavouring agents in the group of hydroxy- and alkoxy-substituted benzyl derivatives is 12 kg in Japan, 12 680 kg in the USA, 0.1 kg in Europe and 1 kg in Latin America (5,6). The entire volume of production in Europe and Latin America is accounted for by *cis*-3-hexenyl salicylate (No. 2275). More than 99% of the annual volume of production in Japan is accounted for by ethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate (No. 2274). More than 75% of the volume of production in USA is accounted for by 3,4-dihydroxybenzoic acid (No. 2278) and 3-hydroxybenzoic acid (No. 2279).

Dietary exposures were estimated with both the SPET and the MSDI method; the higher of the two values for each flavouring agent is reported in Table 3.2 (17,18,20,21,24–27). The SPET and MSDI method values have a range of 100–20 000 µg/day and 0.008–518 µg/day, respectively. The estimated daily dietary exposure was highest for 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate (No. 2272) (20 000 µg/day), with the SPET yielding the higher estimates (5–7).

### Absorption, distribution, metabolism and elimination

Information on the ADME of the flavouring agents in the group of hydroxy- and alkoxy-substituted benzyl derivatives was provided in the monographs from the Eleventh, Thirty-fifth, Forty-fourth, Fifty-seventh and Sixty-ninth meetings (11–15). Further information on two of the additional flavouring agents (Nos 2278 and 2279) evaluated at this meeting and on four previously evaluated flavouring agents (Nos 870, 878, 899 and 904) was available.

The aromatic esters in this group are expected to be hydrolysed to their corresponding alcohols and carboxylic acids, which are completely metabolized. *cis*-3-Hexenyl salicylate (No. 2275) is expected to be hydrolysed to salicylic acid and *cis*-3-hexenol. Salicylic acid (No. 958) undergoes a well understood metabolic pathway that was previously reviewed for methyl salicylate (No. 899) (28), where the metabolites are conjugated and excreted. Benzyl salicylate (No. 904) is rapidly hydrolysed to yield salicylic acid in rat and human microsomes and tissues (29). Minor metabolic pathways for these esters may include O-demethylation, reduction and/or decarboxylation. The hydroxy-substituted benzyl derivatives, including 3,4-dihydroxybenzoic acid (No. 2278), 3-hydroxybenzoic acid (No. 2279) and *p*-methoxybenzaldehyde (No. 878), are expected to be excreted unchanged as O-methylated products, or as the sulfate, glycine and/or glucuronide conjugates (30–35). These compounds can also undergo oxidation; for example, 2-ethoxy-4-(hydroxymethyl)phenol (No. 2271) is expected to either directly form glucuronic acid conjugates, or undergo oxidation to ethyl vanillic acid that will form sulfate and glucuronic acid conjugates. In vitro and in vivo data in rodents and humans show that butyl-*p*-hydroxybenzoate (No. 870) is expected to be primarily metabolized to 4-hydroxybenzoic acid (No. 957), followed by 4-hydroxyhippuric acid, as well as sulfate or glucuronide conjugates of these metabolites and a ring hydroxylation catechol product (36–39).

### Application of the revised Procedure for the Safety Evaluation of Flavouring Agents

**Step 1.** There are no structural alerts for genotoxicity for the nine additional flavouring agents (Nos 2271–2279) in this group. Chemical-specific genotoxicity data on previously evaluated flavouring agents in this group and on the additional flavouring agents do not indicate any genotoxic potential.

**Step 2.** In applying the revised Procedure for the Safety Evaluation of Flavouring Agents to the additional nine flavouring agents, the Committee assigned all nine flavouring agents (Nos 2271–2279) to structural class I (10).

**Step 3.** Dietary exposures were estimated with both the MSDI method and the SPET, and are presented in Table 3.2.

**Step 4.** The highest estimated dietary exposure for two flavouring agents (Nos 2273 and 2275) in structural class I are below the threshold of concern for the class (i.e. 1800 µg/person per day). The Committee therefore concluded these two flavouring agents are not a safety concern at the current estimated dietary exposures.

The highest estimated dietary exposures for the remaining seven flavouring agents (Nos 2271, 2272, 2274 and 2276–2279) in structural class I are above the threshold of toxicological concern for that class (i.e. 1800 µg/person per day). Evaluation of these flavouring agents therefore proceeded to Step 5.

**Step 5.** The NOAEL of 1000 mg/kg bw per day for the structurally related substance vanillin (No. 889) from a 2-year dietary study in male and female rats (25) provides adequate MOEs of 8000, 3000, 12 000, 30 000 and 20 000 (relative to the SPET estimates of 7500, 20 000, 5000, 2000 and 3000 µg/day, respectively) for the flavouring agents 2-ethoxy-4-(hydroxymethyl)phenol (No. 2271), 2-phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate (No. 2272), ethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate (No. 2274), 4-formyl-2-methoxyphenyl 2-hydroxypropanoate (No. 2276) and 2-hydroxy-4-methoxybenzaldehyde (No. 2277), respectively. The SPET estimates of 7500, 20 000, 5000, 2000 and 3000 µg/day correspond to 125, 333, 83, 33 and 50 µg/kg bw per day, respectively, for a 60-kg person. For 3,4-dihydroxybenzoic acid (No. 2278) the NOAEL in a 90-day dietary study in rats (26) of 119 mg/kg bw per day for the structurally related substance gallic acid provides an adequate MOE of 714 relative to the SPET estimate of 10 000 µg/day (167 µg/kg bw per day for a 60-kg person).<sup>3</sup>

For 3-hydroxybenzoic acid (No. 2279), the NOAEL in a 2-year dietary study in rats (27) of 50 mg/kg bw per day for the structurally related substance methyl salicylate (No. 899) provides an adequate MOE of 300 relative to the SPET estimate of 10 000 µg/day (167 µg/kg bw per day for a 60-kg person).

Table 3.2 summarizes the evaluations of the nine flavouring agents (Nos 2271–2279) in the group of hydroxy- and alkoxy-substituted benzyl derivatives that were considered at the present meeting.



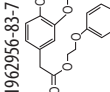


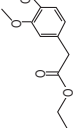

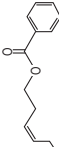
### Consideration of combined intakes from use as flavouring agents

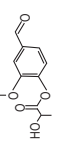

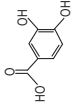

The Committee considered the potential combined intake for this group of hydroxy- and alkoxy-substituted benzyl derivatives at its Sixty-ninth meeting (24) and concluded that combined intake would not raise safety concerns. Vanillin (No. 889), for which the Committee had maintained the ADI of 0–10 mg/kg bw at its Fifty-seventh meeting (21), accounted for most of the potential combined intake. At that time, the estimated per capita intake was 150 000 and 55 000 µg/day for the USA and Europe, respectively (21).

The nine additional flavouring agents in this group (Nos 2271–2279) have much lower MSDI values ranging from 0.008 to 518 µg/day. According to the screening assessment for combined intake recommended by the Committee at its Seventy-third meeting (40), the Committee concluded that consideration of combined intakes is not necessary because the additional flavouring agents would not contribute significantly to the combined intake of this group.

<sup>3</sup> The Committee reviewed two subchronic studies for No. 2278 but, since these two studies covered only limited toxicological end-points, a NOAEL for a related substance was used to calculate the MOE.

**Table 3.2. Summary of the results of safety evaluations of hydroxy- and alkoxy-substituted benzyl derivatives used as flavouring agents<sup>a,b,c,d</sup>**

Flavouring agent	No.	CAS No. and structure	Step 4	Step 5	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
			Does intake exceed the threshold of toxicological concern? <sup>e</sup>	Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate MOE? <sup>f</sup>			
<b>Structural class I</b>							
2-Ethoxy-4-(hydroxymethyl) phenol	2271	4912-58-7 	Yes; SPET: 7500 µg/day	Yes; the NOAEL of 1000 mg/kg bw per day for structurally related vanillin (No. 889) in a 2-year study in rats (25) is 8000 times the estimated dietary exposure of No. 2271 when used as a flavouring agent.	— <sup>g</sup>	Vanillin (No. 889) 	No safety concern
2-Phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl) acetate	2272	1962956-83-7 	Yes; SPET: 20 000 µg/day	Yes; the NOAEL of 1000 mg/kg bw per day for structurally related vanillin (No. 889) in a 2-year study in rats (25) is 3000 times the estimated dietary exposure of No. 2272 when used as a flavouring agent.	— <sup>h</sup>	Vanillin (No. 889) 	No safety concern
3-Phenylpropyl 2-(4-hydroxy-3-methoxy-phenyl)acetate	2273	105025-99-8 	No	NR	—		No safety concern
Ethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate	2274	60563-13-5 	Yes; SPET: 5000 µg/day	Yes; the NOAEL of 1000 mg/kg bw per day for structurally related vanillin (No. 889) in a 2-year study in rats (25) is 12 000 times the estimated dietary exposure of No. 2274 when used as a flavouring agent.	—	Vanillin (No. 889) 	No safety concern
cis-3-Hexenyl salicylate	2275	65405-77-8 	No	NR	— <sup>k</sup>		No safety concern

Step 4		Step 5		Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
Flavouring agent	Does intake exceed the threshold of toxicological concern? <sup>a</sup>	Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate MOE? <sup>b</sup>	Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate MOE? <sup>b</sup>			
4-Formyl-2-methoxyphenyl	Yes; SPET: 2000 µg/day	Yes; the NOAEL of 1000 mg/kg bw per day for structurally related vanillin (No. 889) in a 2-year study in rats (25) is 30 000 times the estimated dietary exposure of No. 2276 when used as a flavouring agent.	– <sup>c</sup>	Vanillin (No. 889)	No safety concern	
2-hydroxypropanoate						
2-Hydroxy-4-methoxybenzaldehyde	Yes; SPET: 3000 µg/day	Yes; the NOAEL of 1000 mg/kg bw per day for structurally related vanillin (No. 889) in a 2-year study in rats (25) is 20 000 times the estimated dietary exposure of No. 2277 when used as a flavouring agent.	– <sup>m</sup>	Vanillin (No. 889)	No safety concern	
						
3,4-Dihydroxybenzoic acid	Yes; SPET: 10 000 µg/day	Yes; the NOAEL of 119 mg/kg bw per day for structurally related gallic acid in a 90-day study in rats (26) is 714 times the estimated dietary exposure of No. 2278 when used as a flavouring agent.	– <sup>n</sup>	Gallic acid	No safety concern	
						
3-Hydroxybenzoic acid	Yes; SPET: 10 000 µg/day	Yes; the NOAEL of 50 mg/kg bw per day for structurally related methyl salicylate (No. 899) in a 90-day study in rats (27) is 300 times the estimated dietary exposure of No. 2279 when used as a flavouring agent.	– <sup>o</sup>	Methyl salicylate (No. 899)	No safety concern	
						

bw: body weight; CAS: Chemical Abstracts Service; MSDI: maximized survey-derived intake; No.: number; NOAEL: no-observed-adverse-effect level; NR: not relevant; SPET: single portion exposure technique.

<sup>a</sup> Fifty-two flavouring agents in this group were previously evaluated by the Committee (17,18,20,21,24).

<sup>b</sup> Step 1: There are no structural alerts for genotoxicity for the additional nine flavouring agents, and data on genotoxicity of Nos 2273, 2274 and 2277 do not indicate potential for genotoxicity.

<sup>c</sup> Step 2: All nine flavouring agents are in structural class 1.

<sup>d</sup> Step 3: Dietary exposures were estimated with both the SPET and the MSDI method; the higher of the two values for each flavouring agent is reported. SPET gave the higher estimate for each flavouring agent.

<sup>e</sup> Step 4: The thresholds of toxicological concern for structural class 1 is: 1800 µg/day.

<sup>f</sup> The margin of exposure was calculated based on the higher daily per capita intake calculated either by SPET or MSDI.

<sup>g</sup> 2-Ethoxy-4-(4-hydroxy-3-methoxyphenyl)phenol is expected to either directly form glucuronic acid conjugates, or undergo oxidation to ethyl vanillic acid that will form sulfate and glucuronic acid conjugates followed by elimination in the urine.

<sup>h</sup> 2-Phenoxyethyl 2-(4-hydroxy-3-methoxyphenyl)acetate is expected to undergo hydrolysis to form the corresponding 4-hydroxy-3-methoxyphenyl acetic acid, which would form a glycine conjugate and be excreted in the urine. The 2-phenoxyethanol would likely undergo glucuronic acid or conjugation of sulfation, and be excreted primarily in the urine.

<sup>i</sup> 3-Phenylpropyl 2-(4-hydroxy-3-methoxy-phenyl)acetate is expected to readily undergo hydrolysis to homovanillic acid and 3-phenylpropanol. Homovanillic acid could be excreted in the urine unchanged or undergo conjugation at the phenolic moiety or the acid moiety, and be excreted. 3-Phenylpropanol could be conjugated with sulfate or glucuronic acid and excreted, or undergo further oxidative steps and be excreted in the urine.

<sup>j</sup> Ethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate is expected to be rapidly hydrolysed to the corresponding carboxylic acid, which would be expected to undergo conjugation with glycine (rodent species) and with glutamine (humans) and be excreted as such. Additionally, conjugation with glucuronic acid at the hydroxyl functionality is expected.

Table 3.2. (continued)

<sup>k</sup> *cis*-3-Hexenyl salicylate is expected to be hydrolysed by esterases to salicylic acid and *cis*-3-Hexenol. *cis*-3-Hexenol is expected to be oxidized to the corresponding carboxylic acid, which would be completely metabolized in the fatty acid and tricarboxylic acid pathways. Salicylic acid undergoes a well understood metabolic pathway, primarily in the liver, in which it is conjugated with glycine to form salicylic acid. Salicylic acid also undergoes glucuronide conjugation to form acyl and phenolic glucuronides. A small amount of salicylic acid is oxidized to gentisic acid, which is subsequently subject to glucuronide conjugation and excretion in the urine.

<sup>l</sup> Vanillin esters are expected to be hydrolysed to their corresponding alcohols and carboxylic acids. The vanillin would be expected to be conjugated and excreted or, in an alternative pathway, the aldehyde moiety could be oxidized or reduced to the carboxylic acid and alcohol, respectively, and either conjugated and excreted or excreted directly.

<sup>m</sup> 2-Hydroxy-4-methoxybenzaldehyde is expected to metabolize primarily by oxidation of the aldehyde moiety to the corresponding carboxylic acid, resulting in 2-hydroxy-4-methoxybenzoic acid. This acid would be expected to be excreted unchanged, conjugated with glycine at the carboxylic acid moiety, or conjugated with glucuronic acid or sulfate at the hydroxyl position before excretion.

<sup>n</sup> 3,4-Dihydroxybenzoic acid is expected to be metabolized by catechol O-methyl transferase into 3-hydroxy-4-methoxybenzoic acid (isovanillic acid) and 4-hydroxy-3-methoxybenzoic acid (vanillic acid). These substances, including the parent acid, would be excreted either unchanged or after formation of the corresponding glucuronide, sulfate or glycine conjugates.

<sup>o</sup> 3-Hydroxybenzoic acid is expected to be excreted mainly as the glycine conjugate. A small amount of 3-hydroxybenzoic acid may be excreted unchanged or as the glucuronide conjugate.

### Consideration of secondary components

One flavouring agent in this group (No. 2276) has a minimum assay value of < 95% (Annex 4). The secondary component lactic acid (No. 930), present at 3%, was previously evaluated by the Committee to be of no safety concern at the estimated dietary exposure when used as a flavouring agent (21). This secondary component is therefore not considered to present a safety concern at current estimated dietary exposure.

### Consideration of additional data on previously evaluated flavouring agents

The Committee considered additional data on 22 of the 52 previously evaluated flavouring agents in this group. Studies of ADME (Nos 870, 878, 899 and 904), acute toxicity (Nos 873, 877, 888 and 959), short-term toxicity (Nos 870, 873, 877, 878, 888, 891, 899, 904, 959 and 1882), reproductive and developmental toxicity (Nos 870, 873, 891, 899, 904, 958 and 959), genotoxicity (Nos 870–873, 876–878, 880, 883, 888, 889, 891, 899, 900, 902–905, 956 and 1882) and special studies (Nos 870 and 904) were considered.

The additional data on reproductive toxicity submitted for butyl-*p*-hydroxybenzoate (No. 870), as well as the data available in the monograph on the re-evaluation of the related substance propyl-*p*-hydroxybenzoate (propylparaben) for its use as a food additive (23), warrant a re-evaluation for No. 870 including an updated exposure assessment. Since no updated exposure data were submitted for the current meeting, this should be done at a future meeting. Additionally, since no updated exposure data were submitted for all other flavouring agents (Nos 870–873, 876–878, 880, 883, 888, 889, 891, 899, 900, 902–905, 956, 958, 959 and 1882) for which toxicological data were submitted, a re-evaluation including an updated exposure assessment should be done for these flavouring agents at a future meeting.

The new information does not affect the conclusions on the other flavouring agents previously evaluated in this group.

### Conclusion

In the previous evaluations of 52 substances in this group of hydroxy- and alkoxy-substituted benzyl derivatives, studies of ADME, acute toxicity, short-term and long-term toxicity, reproductive and developmental toxicity, and genotoxicity were evaluated in the monographs from the Eleventh, Thirty-fifth, Forty-fourth, Fifty-seventh and Sixty-ninth meetings (11–15). None raised safety concerns. In a re-evaluation of the food additive propylparaben (propyl-*p*-hydroxybenzoate, structurally related to butyl-*p*-hydroxybenzoate, No. 870), a flavouring agent evaluated previously in this group, concerns related to reproductive toxicity of parabens were raised. In combination with the newly submitted data on reproductive toxicity of No. 870, these concerns warrant a re-evaluation of this flavouring agent at a future meeting (see section above).

Studies of ADME (Nos 2278 and 2279), acute toxicity (No. 2275), short-term toxicity (No. 2278) and genotoxicity (Nos 2273, 2274 and 2277), as well as special studies (No. 2278), were available for the nine additional flavouring agents. In addition, a short-term toxicity study was available for the structurally related substance gallic acid.

The Committee concluded that the nine additional flavouring agents (Nos 2271–2279) would not give rise to safety concerns at the current estimated dietary exposures.

The Committee concluded that, as well as for butyl-*p*-hydroxybenzoate (No. 870), a re-evaluation including an updated exposure assessment should be undertaken for the previously evaluated flavouring agents anisyl alcohol (No. 871), anisyl formate (No. 872), anisyl acetate (No. 873), anisyl phenylacetate (No. 876), veratraldehyde (No. 877), *p*-methoxybenzaldehyde (No. 878), methyl *o*-methoxybenzoate (No. 880), 4-methoxybenzoic acid (No. 883), vanillyl butyl ether (No. 888), vanillin (No. 889), vanillin isobutyrate (No. 891), methyl salicylate (No. 899), ethyl salicylate (No. 900), isobutyl salicylate (No. 902), isoamyl salicylate (No. 903), benzyl salicylate (No. 904), phenethyl salicylate (No. 905), 4-hydroxybenzaldehyde (No. 956), 2-hydroxybenzoic acid (No. 958), 4-hydroxy-3-methoxybenzoic acid (No. 959) and vanillin propylene glycol acetal (No. 1882). The additional data presented do not give rise to safety concerns and further support the safety of the other 30 previously evaluated flavouring agents in this group.

An addendum to the monograph was prepared.



## Recommendations

The Committee requests that updated exposure data (including both MSDI and SPET values) be provided for the flavouring agents anisyl alcohol (No. 871), anisyl formate (No. 872), anisyl acetate (No. 873), anisyl phenylacetate (No. 876), veratraldehyde (No. 877), *p*-methoxybenzaldehyde (No. 878), methyl *o*-methoxybenzoate (No. 880), 4-methoxybenzoic acid (No. 883), vanillyl butyl ether (No. 888), vanillin isobutyrate (No. 891), methyl salicylate (No. 899), ethyl salicylate (No. 900), isobutyl salicylate (No. 902), isoamyl salicylate (No. 903), benzyl salicylate (No. 904), phenethyl salicylate (No. 905), 4-hydroxybenzaldehyde (No. 956), 2-hydroxybenzoic acid (No. 958), 4-hydroxy-3-methoxybenzoic acid (No. 959) and vanillin propylene glycol acetal (No. 1882) within 2 years (i.e. by July 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

The Committee asks the JECFA Secretariat to urge sponsors and Codex Members to ensure that all required information is available for the evaluation of flavouring agents prior to requesting inclusion in the CCFA JECFA Priority List, including updated exposure data (both SPET and MSDI values).

### 3.2 Specifications of identity and purity

#### 3.2.1 New specifications (from Sections 3.1.1 and 3.1.2)

The Committee received information in support of the establishment of full specifications for 15 flavourings: six flavouring agents of the group of esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids (Nos 2280–2285) and nine flavouring agents of the group hydroxy- and alkoxy-substituted benzyl derivatives (Nos 2271–2279) that were on the agenda of the present meeting.

The Committee noted that no odour has been reported for flavouring agents Nos 2274, 2277, 2278, 2279 and 2280.

The Committee discussed the most appropriate way to report molecular weight for flavourings. It was recalled that at the Eighty-ninth meeting the best approach for assigning molecular weights to flavourings was determined to be the use of the molecular weight reported by CAS SciFinder, when available. The Committee agreed that this was still the most practical approach.

#### 3.2.2 Revised specifications

The Committee received information in support of revision of the full specifications for eight flavouring agents that were on the agenda of the present meeting (Nos 1383, 1170, 1233, 1166, 1411, 1416, 808 and 810).



The Committee revised specifications for (*E*)-2-hexenal diethyl acetal (No. 1383) based on data from 72 lots of the commercial product. The assay minimum was revised to 97% (sum of isomers), with a change of isomeric compositions to 94–99% (*E*) and 0.4–3.2% (*Z*). The chemical name was also revised to (2*E*)-1,1-diethoxy-2-hexene and the molecular weight was revised to 172.26.

For 3-butylidenephthalide (No. 1170), the Committee revised the specifications based on data from 14 lots of the commercial product. The assay minimum was revised from 99% to 95% (sum of isomers). The isomeric composition was also established as follows: 86–96% (*Z*) and 2–14% (*E*). The refractive index was revised to 1.554–1.592, and the specific gravity was revised to 1.080–1.117. The molecular weight was also revised to 172.26.

For 1,4-cineole (No. 1233), the Committee revised the assay minimum from 75% to 95% (sum of isomers with > 75% 1,4-cineole) based on data from 18 lots of the commercial product. The isomeric composition was also established as follows: not less than 75% of 1,4-cineole with the remainder being 1,8-cineole (No. 1234). The refractive index was revised to 1.400–1.500 and the specific gravity was revised to 0.850–0.908.

The Committee revised the specific gravity for octahydrocoumarin (No. 1166) to 1.089–1.096 based on data from six lots of the commercial product.

For 3-(*l*-methoxy)-2-methylpropane-1,2-diol (No. 1411), the Committee revised the specific gravity to 0.978–0.987 (20 °C) based on data from four lots of the commercial product. The molecular weight was revised to 244.37.

For *p*-methane-3,8-diol (No. 1416), the Committee revised the assay minimum from 99% to 95% (sum of isomers) based on data from three lots of the commercial product. The isomeric composition was also established as follows: 55–61% (1*S*,2*S*,4*R*) (CAS No. 107133-84-6), 34–39% (1*S*,2*R*,4*R*) (CAS No. 238748-68-0), 1.5–3.5% (1*R*,2*S*,4*R*) (CAS No. 92471-23-3, 3564-95-2) and 1–2% (1*R*,2*R*,4*R*) (CAS No. 91739-72-9, 3564-98-5). The molecular weight was revised to 172.26.

For *p*-isopropylacetophenone (No. 808), the Committee revised the assay minimum from 98% (sum of isomers) to 95% (*p*-isomer) based on information contained in certificates of analysis from at least four lots of the commercial product provided to the Committee.

For acetanisole (No. 810), the Committee revised the specifications based on data from eight lots of the commercial product. The assay minimum was revised from 97% (sum of *o*,*m*,*p*-isomers) to 97% (sum of isomers). The isomeric composition was also established as follows: 97% (*o*-, *m*-, *p*- isomers) and > 95% (*p*-isomer). The molecular weight was revised to 150.17.

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## 4. Corrigenda

The Committee discussed the tentative errata. One request was for the amendment of the CAS number for the flavouring agent ethyl levulinate propyleneglycol ketal (No. 1973) for which specifications were prepared at the Seventy-third JECFA meeting, but a full safety evaluation was not completed. The Committee did not consider the request to revise the CAS number; instead, the Committee withdrew the specifications for No. 1973 as information to allow the completion of the safety review of the flavouring agent had not been provided to the Committee in a timely manner. A recommendation for future work was made to compile a list of flavourings for which a full safety evaluation has not been completed, with a view to withdraw such specifications.

The requests for corrections in [Table 4.1](#), submitted to the CCFA, were evaluated at the Ninety-sixth meeting of JECFA and found to be necessary. Corrections will be made only in the online database for flavouring specifications.

## References

1. Compendium of food additive specifications. Rome: Food and Agriculture Organization of the United Nations. FAO Food and Nutrition Paper, No. 52, addendum 8; 2000.
2. Compendium of food additive specifications. Rome: Food and Agriculture Organization of the United Nations; 2004 (FAO Food and Nutrition Paper, No. 52, addendum 12, <https://www.fao.org/publications/card/en/c/Y5777E>, accessed 28 July 2023).
3. Evaluation of certain food additives and contaminants: sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 2004 (WHO Technical Report Series, No. 922, <https://apps.who.int/iris/handle/10665/42849>, accessed 28 July 2023).
4. Evaluation of certain food additives and contaminants: fifty-third report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization; 2000 (WHO Technical Report Series, No. 896, <https://apps.who.int/iris/handle/10665/42378>, accessed 28 July 2023).

Table 4.1  
Requests for corrections submitted to the CCFA

Flavouring	Original text	Revised text	Additional information
S-Methyl hexanethioate (No. 489)	CAS No. 20756-86-9 Chemical formula: $C_7H_{14}O_2S$ ; molecular weight: 162.24	CAS No. 2432-77-1 Chemical formula: $C_7H_{14}OS$ ; molecular weight: 146.25	Correction to CAS number, chemical formula and molecular weight.
Isopulegol (No. 755)	CAS No. 89-79-2	CAS Nos 7786-67-6 and 89-79-2	According to the specifications from the Fifty-fifth JECFA meeting (1), No. 755 is a mixture of isomers. CAS No. 89-79-2 is specifically for the L isomer. CAS No. 7786-67-6 does not specify stereochemistry, and represents the mixture of isomers. Both CAS numbers will be included in the updated specification.
Farnesene ( $\alpha$ and $\beta$ ) (No. 1343)	CAS No. 502-61-4	CAS Nos: 502-61-4 ( $\alpha$ ), 18794-84-8 ( $\beta$ ) and 688330-26-9 (mixture)	According to specifications from the Sixty-third JECFA meeting (2), No. 1343 is a mixture of 3,7,11-trimethyldodeca-1,3,6,10-tetraene and 3-methylene-7,11-dimethyldodeca-1,6,10-triene. CAS No. 688330-26-9 is for a mixture of the two compounds. CAS No. 502-61-4 only represents 3,7,11-trimethyldodeca-1,3,6,10-tetraene. CAS No. 18794-84-8 represents 3-methylene-7,11-dimethyldodeca-1,6,10-triene. All three CAS numbers will be included in the updated specification.
1-Butanethiol (No. 511)	CAS No. 61122-71-2	CAS No. 109-79-5	Original CAS number is incorrect and not related to 1-butanethiol. The correct CAS number is 109-79-5.
8-Ocimenyl acetate (No. 1226)	Missing CAS number	CAS No. 197098-61-6	CAS number missing from specifications. Correct CAS number (197098-61-6) was originally included in table 4 of the report from the Sixty-first JECFA meeting (3).
Methylthio 2-(propionyloxy) propionate (No. 493)	Missing CAS number	CAS No. 827024-53-3	Added missing CAS number.
2, 3 or 10-Mercaptopinane (No. 520)	Missing CAS number	CAS Nos 23832-18-0, 72361-41-2 and 6588-78-9	CAS No. 23832-18-0 corresponds to 2-mercaptopynane; CAS No. 72361-41-2 corresponds to 3-mercaptopynane; CAS No. 6588-78-9 corresponds to 10-mercaptopynane.
Methyl 3-methyl-1-butenyl disulfide (No. 571)	Missing CAS number	CAS No. 233666-09-6	Added missing CAS number.
Potassium 2-(1'-ethoxy) ethoxypropanoate (No. 933)	Missing CAS number; chemical formula: $C_7H_{13}O_4$	CAS No. 100743-68-8 Chemical formula: $C_7H_{13}O_4K$	Added missing CAS number and revised formula to include potassium.
(-)-Menthol 1- and 2-propylene glycol carbonate (No. 444)	CAS No. 156329-82-2	No CAS No. included	The original CAS No. (156329-82-2) is no longer in the CAS registry. A proposal was made to JECFA to replace it with CAS No. 30304-82-6. However, CAS No. 30304-82-6 does not match the flavouring reviewed by JECFA.
Lactic acid (No. 930)	CAS No. 598-82-3	CAS Nos 10326-41-7, 79-33-4 and 50-21-5	The original CAS No. (598-82-3) is no longer valid. The following CAS numbers have been added: CAS No. 10326-41-7 for D-lactic acid; CAS No. 79-33-4 for L-lactic acid; and CAS No. 50-21-5 for the mixture of isomers.



Flavouring	Original text	Revised text	Additional information
Allyl 10-undecenoate (No. 9)	CAS No. 7439-76-7	CAS No. 7493-76-7	Typographical error.
Geranyl formate (No. 54)	CAS No. 1005-86-2	CAS No. 105-86-2	Typographical error.
Allyl heptanoate (No. 4)	CAS No. 142-91-8	CAS No. 142-19-8	Typographical error.
Allyl propionate (No. 1)	CAS No. 2408-70-0	CAS No. 2408-20-0	Typographical error.
3-Hexenyl formate ( <i>cis</i> and <i>trans</i> mixture) (No. 1272)	CAS No. 151824	CAS Nos 33467-73-1, 56922-80-6 and 2315-09-5	The original CAS number is no longer valid. The following CAS numbers were added: CAS No. 33467-73-1 for the <i>cis</i> isomer; CAS No. 56922-80-6 for the <i>trans</i> isomer; and CAS No. 2315-09-5, which is not specific to double bond geometry.
<i>trans</i> -3-Heptenyl acetate (No. 135)	CAS No. 34942-91-1	CAS No. 1576-77-8	The original CAS number is not specific to the double bond geometry. CAS No. 1576-77-8 is specific to the <i>trans</i> isomer.
Methyl 4-methylvalerate (No. 216)	CAS No. 2412-24-1	CAS No. 2412-80-8	Typographical error.
2,6-Dimethyloctanal (No. 273)	CAS No. 1321-89-7 Synonyms: isodecylaldehyde; isodecanal; 2,6-dimethyl octanoic aldehyde	CAS No. 7779-07-9 Synonyms: 2,6-dimethyl octanoic aldehyde	Replacement of incorrect CAS number. Removal of two incorrect synonyms.
Menthone-8-thioacetate (No. 506)	CAS No. 109-79-5 Flavouring name: menthone-8-thioacetate	Flavouring name: menthone-8-thioacetate ( <i>cis</i> - and <i>trans</i> -) CAS No.: 94293-57-9	Revision of name to match the flavouring evaluated at the Fifty-third JECFA meeting (4) and replacement of incorrect CAS number.



## 5. Recommendations

### 5.1 Withdrawal of specifications without full safety review

The Committee noted that several flavourings have full specifications but are not accompanied by a full safety evaluation. The Ninety-sixth Committee recommends the compilation of a list of such flavourings with a view to withdrawing their specifications.





# Annex 1

## Meeting agenda



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

### 96th JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA) 27 June to 6 July 2023

1. Opening
2. Declarations of Interests (information by the Secretariat on any declared interests and discussion, update by experts)
3. Election of Chairperson and Vice-Chairperson, appointment of Rapporteurs
4. Adoption of the agenda
5. Matters of interest arising from previous Sessions of the Codex Committee on Food Additives
6. Update from IARC on their aspartame hazard identification
7. Critical issues and questions from Working Papers (first brief round of discussion on all subjects to inform the full committee)
8. Evaluations
  - 8.1. Safety evaluations
    - 8.1.1. Aspartame
  - 8.2. Revision of specifications
    - 8.2.1. Lycopene (synthetic); and lycopene from *Blakeslea trispora*
    - 8.2.2. Pentasodium triphosphate
    - 8.2.3. Steviol glycosides
9. Flavouring agents
  - 9.1. Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids
  - 9.2. Hydroxy- and alkoxy-substituted benzyl derivatives
10. Errata

11. Other matters brought forward by the Committee during discussions at the meeting
12. Adoption of the report

## Annex 2

### Toxicological information and information on specifications

Table A2.1

#### Food additives considered for specifications only

Food additive	Specifications	Details
Lycopene (synthetic); and lycopene from <i>Blakeslea trispora</i>	R	Upon request from the CCFA, the Committee revised the specifications for lycopene (synthetic) (INS 160d(ii)) and lycopene from <i>Blakeslea trispora</i> (INS 160d(iii)) by replacing “freely soluble in chloroform” with “sparingly soluble in tetrahydrofuran (THF)” in the solubility test, and replacing the “solution in chloroform” test with a “solution in THF” test requirement.
Pentasodium triphosphate	R	At the request of the CCFA, the Committee revised the specifications for pentasodium triphosphate (INS 451(i)) by revising: the assay value for P <sub>2</sub> O <sub>5</sub> to not less than 56% and not more than 59% of P <sub>2</sub> O <sub>5</sub> ; the pH value to 9.1–10.2 (1% solution); and the level of lead from 4 mg/kg to not more than 2 mg/kg.
Steviol glycosides	R	The Committee was requested to change the list of non-toxicogenic nonpathogenic strains used to facilitate the transfer of glucose to steviol glycosides to: <i>Anoxybacillus caldiproteoliticus</i> , <i>Bacillus licheniformis</i> and <i>Bacillus subtilis</i> in <a href="#">annex 4</a> : Enzyme modified glucosylated steviol glycosides of the Ninety-fifth JECFA meeting report. The following text was also added: “The production strain of the enzyme used to facilitate the transfer of glucose to steviol glycosides was incorrectly identified as <i>Bacillus stearothermophilus</i> . The revised identification is <i>Anoxybacillus caldiproteoliticus</i> .”

CCFA: Codex Committee on Food Additives; R: revised specification; THF: tetrahydrofuran.

Table A2.2

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

Table A2.3

**Flavouring agents evaluated by the revised Procedure for the Safety of Evaluation of Flavouring Agents: 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
<i>cis</i> -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.

Table A2.4

**Flavouring agents considered for specifications only**

Food additive	No.	Specifications
( <i>E</i> )-2-hexenal diethyl acetal	1383	R
3-Butylidenephthalide	1170	R
1,4-Cineole	1233	R
Octahydrocoumarin	1166	R
3-( <i>I</i> -Methoxy)-2-Methylpropane-1,2-diol	1411	R
<i>p</i> -Methane-3,8-diol	1416	R
<i>p</i> -Isopropylacetophenone	808	R
Acetanisole	810	R

R: revised specification.



## Annex 3

### Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. General principles governing the use of food additives (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. Procedures for the testing of intentional food additives to establish their safety for use (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants) (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. I. Antimicrobial preservatives and antioxidants, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. Evaluation of the carcinogenic hazards of food additives (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants (Eighth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).
10. Specifications for identity and purity and toxicological evaluation of food colours. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.
11. Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.
13. Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.
14. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.
15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
16. Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
18. Specifications for the identity and purity of some antibiotics. FAO Nutrition Meetings Series, No. 45A, 1969; WHO/Food Add/69.34.
19. 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). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.
20. Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.
21. Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.
22. Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents (Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.
23. Toxicological evaluation of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.
24. Specifications for the identity and purity of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.
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## Annex 4

### Secondary components of flavouring agents with revised specifications with minimum assay values of less than 95%

Table A4.1

#### Secondary components of flavouring agents with revised specifications with minimum assay values of less than 95%

No.	Flavouring agent	Minimum assay value	Secondary components	Comments on secondary components
<b>Hydroxy- and alkoxy-substituted benzyl derivatives</b>				
2276	4-Formyl-2-methoxyphenyl 2-hydroxypropanoate	> 93%	Secondary component: 3% lactic acid (No. 930)	This secondary component was previously evaluated by the Committee and found to have no safety concerns at the estimated dietary exposure when used as a flavouring agent
<b>Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids</b>				
2281	5-Methylhexyl acetate	> 87%	Secondary component: 5–6% hexyl acetate (No. 128); 3–4% heptyl acetate (No. 129)	These secondary components were both previously evaluated by the Committee and found to have no safety concerns at the estimated dietary exposures when used as flavouring agents

## Evaluation of certain food additives

This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of various food additives, including flavouring agents, to identify safety concerns and to prepare specifications for the identity and purity of the food additives.

The report provides a summary of the Committee's evaluations of technical, toxicological and dietary exposure data for the food additive aspartame. Specifications for several other food additives, namely lycopene (synthetic) and lycopene from *Blakeslea trispora*, pentasodium triphosphate and steviol glycosides, were revised.

Summaries are also provided of the safety evaluations of two groups of flavouring agents: esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids, and hydroxy- and alkoxy-substituted benzyl derivatives. New specifications were prepared for six and nine flavouring agents from these groups, respectively. Specifications were revised for eight other flavouring agents, namely: (*E*)-2-hexenal diethyl acetal, 3-butylidene-phthalide, 1,4-cineole, octahydrocoumarin, 3-(*l*-methoxy)-2-methylpropane-1,2-diol, *p*-methane-3,8-diol, *p*-isopropyl-acetophenone and acetanisole.

Annexed to the report are tables summarizing the Committee's recommendations for dietary exposures to all of the food additives as well as toxicological information, dietary exposures and information on specifications.

