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1051

Evaluation of certain food additives

Ninety-seventh 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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Rome, 31 October–9 November 2023

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List of abbreviations and acronyms

ACF	aberrant crypt foci
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
bw	body weight
CAS	Chemical Abstracts Service
CCFA	Codex Committee on Food Additives
DMH	1,2-dimethylhydrazine
FDA	United States Food and Drug Administration
ECHA	European Chemicals Agency
EDX	energy-dispersive X-ray
EFSA	European Food Safety Authority
EOGRT	one-generation reproductive toxicity
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GMP	Good Manufacturing Practices
GSFA	General Standard for Food Additives
IARC	International Agency for Research on Cancer
IL	interleukin
INS	International Numbering System for Food Additives
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
MOE	margin of exposure
MSDI	maximized survey-derived intake
NCI	United States National Cancer Institute
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
pg	pigment grade
SEM	scanning electron microscopy
SDG	Sustainable Development Goals
SPET	single portion exposure technique
TEM	transmission electron microscopy
Ti	titanium
TiO_2	titanium dioxide
TNF	tumour necrosis factor
TTC	threshold of toxicological concern
WHO	World Health Organization

Glossary

Agglomerate: a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components *(1)*; assemblage of particles that are loosely coherent (ISO 14887:2000)

Aggregate: a particle comprising strongly bound or fused particles *(1)*; assemblage of particles that are rigidly joined together (ISO 14887:2000)

Anatase: a metastable mineral form of titanium dioxide (TiO_2) with a tetragonal crystal structure, colourless to white when pure; most common polymorph used as the food additive (note that the terms anatase and rutile refer to both the ore/mineral forms of TiO_2 as it occurs in nature and to crystalline forms or polymorphs) *(2)*; transforms irreversibly to rutile form at high temperatures (> 600 °C) *(3)*

Constituent particle: an identifiable, integral component of a larger particle (ISO 80004-1:2023); part of a larger ensemble and can be an aggregate itself that can form even larger agglomerates *(4)*

Dynamic light scattering (DLS): an analytical technique used to measure particle size and the broadness of the size distribution of submicron particles dispersed in a liquid; enables characterization of colloidal systems based on the scattering of visible light resulting from the difference in refractive index between the dispersed colloids and the dispersion medium; measurement of fluctuations in laser light scattered by vibrating particles suspended in a liquid as a function of time *(5)*

Energy-dispersive X-ray (EDX) analysis: analytical technique, complementary to electron microscopy, used to identify the elemental composition of materials; based on the generation of X-rays characteristic of the elements present in a sample

P25 TiO_2: photocatalytic grade of TiO_2 produced by flame hydrolysis ($TiCl_4$ hydroxy-oxygen flame hydrolysis); exists as a mixture of anatase and rutile forms (nominally 85:15) with a particle size of approximately 20–23 nm

Particle: minute piece of matter with defined physical boundaries *(1)*; smallest discrete identifiable entity *(6)*; may be generated by top-down manufacturing processes (e.g. milling of larger starting entities) or by bottom-up processes (e.g. growing from gases, solutions or plasmas) *(4)*

Primary particle: original source particle of agglomerates or aggregates or mixtures of the two; constituent particles of agglomerates or aggregates at a certain actual state may be primary particles, but often the constituents are aggregates; agglomerates and aggregates are also termed secondary particles (ISO 26824:2013)

Rutile: a stable mineral form of TiO_2 and the most common natural form of TiO_2; tetragonal unit cell; range of colours from brown, red, green and yellow (exhibits pleochroism); much less commonly used as food additive *(3)*

Scanning electron microscopy (SEM): an electron microscopy technique that produces images of a sample by scanning the surface with a focused beam of electrons; the electrons interact with atoms in the sample, producing various signals that contain information about the surface topography and composition of the sample

Single-particle inductively coupled plasma–mass spectrometry (spICP-MS): an analytical technique used to measure highly diluted nanoparticle dispersions by ICP-MS operated in time-resolved mode for a pre-selected mass-to-charge ratio (*m/z*) value; individual particles enter the ion source and are atomized and ionized in the plasma torch to produce a plume of elemental ions that is transferred to the mass spectrometric detector; the discrete dwell time of the MS is set to a value that allows the detection of a single ion particle from the ion plume *(5)*

Transmission electron microscopy (TEM): an electron microscopy technique in which a beam of electrons is transmitted through a specimen to form an image; an image is formed from the interaction of the electrons with the sample as the beam is transmitted through the specimen, allowing particle size to be calculated

X-ray fluorescence (XRF): analysis technique based on the measurement of the energies and intensities of characteristic X-rays emitted by a test portion during irradiation with electromagnetic radiation *(6)*

X-ray photoelectron spectroscopy (XPS): a photoemission spectroscopy technique in which a sample is bombarded with X-rays; photoelectrons produced by the sample are detected as a function of their energy *(6)*

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1. Introduction

The Ninety-seventh 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 Rome from 31 October to 9 November 2023. The meeting was opened on behalf of the FAO by Dr Divine Njie, deputy Director of Food Systems and Food Safety Division, and on behalf of WHO by Dr Moez Sanaa, Head of Standards and Scientific Advice on Food and Nutrition, Department on Nutrition and Food Safety.

Dr Njie welcomed the experts to the Ninety-seventh meeting, and thanked them for their valuable time and expertise at the disposal of JECFA and for the effort put into the preparation for this meeting. He emphasized that the scientific advice provided by JECFA is a cornerstone of the process of providing guidance on food safety. It ultimately ensures that food safety and quality measures and food standards are indeed based on sound scientific principles and provide the necessary protection of consumers' health. Dr Njie highlighted that food safety plays a pivotal role in the 2030 Agenda for Sustainable Development and its Sustainable Development Goals (SDGs). Without food safety, many SDGs will remain out of reach, including eliminating hunger (SDG2) and achieving health and well-being (SDG3). The FAO Strategic Framework 2022–2031 *(1)* explicitly lists "Safe food for everyone" (BN3) as one of the Programme Priority Areas. The Strategic Priorities are based on an agrifood systems approach, in which food safety takes on a central role in the development of more efficient, inclusive, resilient and sustainable agrifood systems. The Strategic Priorities connect FAO's normative and programmatic work. The normative work includes the provision of scientific advice to support the Codex Alimentarius standard-setting process and the development of food safety guidance materials for FAO Members. The programmatic work supports initiatives by FAO Members to strengthen official food control systems and food safety, and quality management along the food chain, as well as enhancing intersectoral coordination.

Dr Sanaa welcomed all attendees to the meeting and noted that the re-evaluation of titanium dioxide (TiO_2) as a food additive and the safety evaluation of certain flavouring agents are the subjects of this meeting. The activities of JECFA are governed by the principles of risk analysis specified in the Codex Alimentarius document. Risk management and risk assessment should be kept as distinct as possible to safeguard the scientific rigour of risk assessment and reduce any potential conflicts of interest. It is imperative that the risk assessment conducted by JECFA experts is carried out in an unbiased manner in accordance with the FAO/WHO framework for the provision of scientific advice on food safety and nutrition. Dr Sanaa emphasized the need to thoroughly evaluate and record constraints, uncertainties and assumptions that may have an impact on

the result at every phase of the risk assessment procedure. He further stressed the need for the experts to include in the risk assessment report any limitations, ambiguities or assumptions that were present, along with an explanation of their impact on the outcomes. He reminded the experts of the importance to reach a consensus and of the opportunity to explicitly express a minority opinion or point of view should the need arise. He concluded with highlighting that risk managers, not risk assessors, are tasked with resolving the impact that ambiguity or uncertainty has on the risk management decision, and that the objective of the full process of food safety risk analysis within the Codex Alimentarius is to protect the health of the consumers.

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

1.1 Declarations of interest

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

1.2 Meeting summary

See Annex 2 for a summary of toxicological information and specifications agreed.

Reference

1. FAO strategic framework 2022-31. Rome: Food and Agriculture Organization of the United Nations; 2023 (https://www.fao.org/strategic-framework/en, accessed 14 November 2023).

2. Food additives (other than flavouring agents)

2.1 Safety evaluation (toxicological assessment and specifications)

2.1.1 Titanium dioxide

Explanation

TiO_2 (International Numbering System for Food Additives (INS) No. 171) is a food additive that is included in table 3 of the General Standard for Food Additives (GSFA) *(1)* and may be used in a wide range of foods under conditions of Good Manufacturing Practices (GMP).

The Committee evaluated TiO_2 at its Thirteenth meeting and assigned an ADI "not specified"[1] based on an absence of significant absorption and a lack of toxicological effects in the available experimental animal and human studies at that time *(2)*.[2]

The Committee was asked by the Fifty-second session of the Codex Committee on Food Additives to conduct a safety assessment and, if necessary, to revise the specifications of INS 171 *(3)*.

The Committee received submissions that included studies on toxicokinetics, acute and short-term toxicity, long-term toxicity and carcinogenicity, genotoxicity, reproductive and developmental toxicity, special studies and dietary exposure.

Systematic searches of the information available in the literature of relevance to the toxicological assessment of TiO_2 as a food additive were also conducted. Searches were conducted for literature published from 1946 to May 2023 in Embase and Medline and included the following search strings: titanium dioxide OR 13463-67-7 AND short-term toxicity; titanium dioxide OR 13463-67-7 AND (reproductive OR developmental toxicity); titanium dioxide OR 13463-67-7 AND genotoxicity; titanium dioxide OR 13463-67-7 AND (long-term toxicity OR carcinogenicity); titanium dioxide OR 13463-67-7 AND allergenicity.

An additional literature search was conducted to consider any further studies on dietary exposure from 2010 onwards that were not included in the submission. The databases Embase, Scopus and PubMed were searched using the terms (titanium dioxide, TiO_2, E 171, E171, INS 171 OR INS171) AND (food, gum*, confecti*, chocolat*, diet* OR nutrition) AND (intake, expos*, consum*, concentr* OR eat*).

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

[2] A full list of JECFA publications is provided as Annex 3.

Chemical and technical considerations

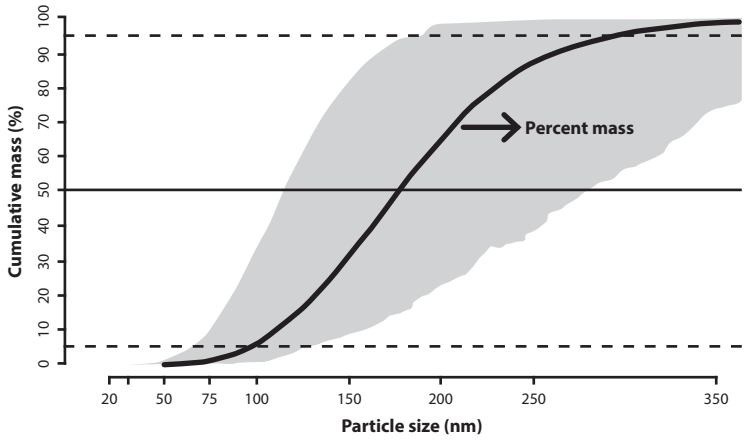
TiO_2 (Chemical Abstracts Service (CAS) No. 13463-67-7, INS 171, molecular weight 79.87) is a white insoluble crystalline powder with a high refractive index; it is used as a colour in various food categories. INS 171 consists of uncoated TiO_2 particles. In the European Union (EU), food-grade TiO_2 is identified and labelled as E171. INS 171 and E171 are equivalent except that INS 171 does not include the TiO_2 coating of pearlescent pigments (INS 176). Potassium aluminium silicate-based pearlescent pigments (INS 176) are formed by depositing titanium (Ti) and/or iron salts onto mica or potassium aluminium silicate, followed by calcination at high temperatures. The resulting pigment consists of potassium aluminium silicate or mica coated with TiO_2, iron oxide and, potentially, mixed oxides; the Committee did not consider INS 176 in its evaluation.

Anatase and rutile, or a mixture of these, are the crystal forms of TiO_2 that are used in foods. Food-grade TiO_2 is produced from Ti-containing ores by either the sulfate or chloride process. In the sulfate process, sulfuric acid is used to digest ilmenite ($FeTiO_3$) or ilmenite and Ti slag. Purification steps include removal of the iron sulfate and crystallization of the TiO_2. Anatase or rutile are formed based on processing conditions. The isolated TiO_2 is washed with water, calcined and milled to a powder. In the chloride process, Ti-containing ore is reacted either with chlorine gas or concentrated hydrochloric acid to form titanium tetrachloride, which is then oxidized or hydrolysed at high temperature to produce TiO_2. The resulting compound crystallizes into the rutile form and is filtered, washed and calcined. The majority of food-grade TiO_2 is produced by the sulfate process in the anatase crystal structure.

The functional effect of TiO_2 is attributed to particles (including aggregates and agglomerates) with sizes that range between 200 and 300 nm in diameter. TiO_2 particles of sizes less than 100 nm are transparent to visible light and are not of functional significance in food. Small TiO_2 particles have a greater tendency to agglomerate and/or aggregate than large particles *(4)*. The reported particle size distribution of food-grade TiO_2 is broad with samples shown to contain particles that range from approximately 30 to 400 nm. Based on data submitted to the Committee or available in published literature *(5)*, the reproducibility between individual laboratories is widely divergent (Fig. 2.1). Within-lab precision for the measurement of particle size distribution was considered to be acceptable. An internationally agreed upon method for determination of particle size distribution that has been standardized and validated through collaborative testing is currently not available. Such a method must include suitable preparation steps such that the TiO_2 retains its size and surface chemistry properties. Similarly, there are no harmonized methods available for the extraction and characterization of TiO_2 particles in food matrices. Despite the uncertainty in the determination of

Fig. 2.1

Intra-laboratory variability of particle size measurement of TiO_2 samples representative of INS 171. Data were generated using transmission electron microscopy (TEM) and converted to cumulative distribution of mass %; the grey area indicates the extent of particle size distributions. Observed inter-laboratory variability was larger than between-sample variability, for data from the same laboratory. The percent mass is also shown as a black solid curve.



particle size distribution, based on available data, particles smaller than 30 nm, if present, are only expected to be present at trace levels. As shown in Fig. 2.1, even though the reported cumulative mass distribution per particle size varies within the grey area, the percent mass of particles smaller than 30 nm tends to zero.

The Committee noted that the test articles used in the safety assessment are representative of food-grade TiO_2 based on production process, particle size distribution and the percentage of particles smaller than 100 nm.

The Committee noted that TiO_2 is also manufactured for non-food applications using methods that differ from the sulfate and chloride processes; these include sol-gel, microemulsion, precipitation, hydrothermal, solvothermal, electrochemical and enzymatic methods. These methods utilize different precursors, additives and size control agents, which impart specific sizes, narrow size distributions and unique geometries. TiO_2 obtained from such manufacturing processes are not intended for use as food additives. The subject of the current evaluation is food-grade TiO_2 as defined by INS 171.

The mean purity of food-grade TiO_2 (INS 171) from five batches was reported to be 99.3%. From data provided to the Committee, the highest levels of

impurities soluble in 0.5 N hydrochloric acid were reported as: As at 1 mg/kg, Cd at 0.5 mg/kg, Pb at 5 mg/kg, Hg at 0.5 mg/kg and Sb at 2 mg/kg.

TiO_2 materials considered in the Evaluation. The Committee considered that toxicological studies that used E171 as the test substance are representative of the article of commerce and the most relevant for assessment of the safety of INS 171 in food (including beverages). INS 171 has been manufactured using the sulfate or chloride processes for many years, and the resulting commercial products have been demonstrated to have TiO_2 particle size distributions that fall within a relatively consistent range of 30–400 nm (Fig. 2.1). The Committee recognized that a large number of toxicological studies have been conducted using engineered TiO_2 nanoparticles as the test material, and that such test materials have been manufactured using methods other than the sulfate or chloride processes that are described in the specification monograph for INS 171. These nanoparticle test materials generally have significantly lower particle size distribution ranges and different physicochemical properties, such that while some may overlap with the lower end of the distribution range for INS 171, they are not representative of INS 171. The Committee also noted that use of E171 as a test material in biological studies should allow the identification of possible hazards from the fraction of particles within INS 171 that are in the nanoscale range (i.e. those between 30 and 100 nm).

Based on data provided by the sponsor, the range of median particle size for E171 is 104–166 nm with 11.4–45% by number less than 100 nm. In addition to E171 (anatase, rutile or a mixture of both), the following test items were considered by the Committee to be representative of INS 171.

- Unitane 0–220 (anatase) was used in the United States National Cancer Institute (NCI) short-term toxicity studies and carcinogenicity studies in mice and rats *(6)*. The mean particle size range is 106–135 nm with 20–44% by number less than 100 nm.
- Pigment-grade (pg) TiO_2 was used in developmental toxicity studies *(7)*. Median particle sizes were: pg-1 100% anatase, 120 nm; pg-2 and pg-3 100% rutile, 165 nm and 132 nm, respectively.

Unless otherwise specified, percent particles smaller than 100 nm is reported by number in the individual toxicological studies.

Overall, the Committee considered the existing toxicological database was sufficient for the evaluation of the safety of INS 171.

Biochemical aspects

In mammals, the intestinal epithelium is poorly permeable to insoluble particulate material. This low permeability means that most insoluble particulate

material has poor oral bioavailability, passes through the gastrointestinal tract and is eliminated from the body. Nevertheless, evidence has accumulated in the literature over the past 40 years demonstrating some, albeit generally low, absorption of certain nanoscale and microscale particulates across the intestinal mucosa via M-cells to underlying lymphoid follicles (Peyer's patches), and also through normal columnar epithelial cells. Tissue disposition studies have also found low concentrations of insoluble particulates distributed to the mesenteric lymph nodes, and phagocytic cells in the liver and spleen, following oral exposure. This tissue distribution profile is consistent with that for insoluble particles administered intravenously, in which blood pharmacokinetic parameters are dominated by interaction with the mononuclear phagocytic system *(8–12)*.

The extent of absorption of TiO_2 is difficult to measure because of the variability in background concentrations of Ti in tissue, and concentrations of Ti in blood and tissue that are close to the detection limits. It is also difficult to compare the extent of absorption between studies due to the different vehicles used to suspend the TiO_2 (which may affect the size of aggregates), the methods of preparation (e.g. sonication) and the methods of detection.

A study was conducted to investigate the uptake of TiO_2 from the intestinal lumen in mice *(13)*. TiO_2 (described as food grade; diameter 50–350 nm) was administered in the diet up to a dose of 100 mg/kg bw per day for up to 18 weeks. A dose-related increase in the number of TiO_2 particles seen in the base of Peyer's patches was observed using reflectance confocal microscopy. Scanning electron microscopy (SEM) and energy-dispersive X-ray (EDX) analyses confirmed that the particles contained Ti. Systemic bioavailability was not assessed.

A study in mice *(14)* used a non-standard method of administration of E171 (anatase, mean diameter 201.2 ± 8.5 nm, 35% < 100 nm); E171 (freshly dispersed in water) was slowly dripped with a pipette into the mouth, providing a dose of 5 mg/kg bw per day for 3 days per week for 3 weeks. A significant increase in Ti concentration in the large intestine (1.07 ± 0.38 μg/g) and the liver (0.94 ± 0.57 μg/g) was demonstrated, 1.8 and 3.6 times higher than for vehicle-treated animals, respectively. In the brain, kidney and testes of the treated group, Ti concentrations were below the limit of detection (LOD) (0.03 μg/g). Ti concentrations in the lungs, stomach, small intestine and spleen were not significantly different from those in the control group.

E171 (anatase, 36% by mass < 100 nm) was administered in the diet to rats for 7 days at a dose of 24–30 mg/kg bw per day in a study conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline No. 417 *(15)*. No Ti was detected for whole blood and urine (LOD 0.04 μg/mL) or for most of the tissue samples (liver, kidney and muscle) (LOD 0.1–0.2 μg/g wet weight). Ti was found in large amounts in the faeces *(16)*.

In an extended one-generation reproductive toxicity (EOGRT) study in rats, conducted according to OECD Test Guideline No. 443 *(17)*, E171 (anatase, mean 112–117 nm) was administered in the diet at doses up to 1000 mg/kg bw per day for up to 18 weeks *(18)*. Ti concentrations in blood and urine from the treated adult animals of the F0 and F1 generations were similar to those in the control groups, ranging from less than 0.001 (LOD) to 0.008 µg/g for blood and from 0.007 to 0.033 µg/g for urine.

In a study conducted according to OECD Test Guideline No. 417 *(15)*, a single dose of E171 (median diameter 100 nm) was administered to rats by oral gavage (1000 mg/kg bw); no uptake of Ti in blood was detected over the 4-day post-dosing period *(19)*. The absorption of TiO_2 was estimated to be less than 0.000 75% based on a limit of quantification (LOQ) between 0.000 007 and 0.000 054 µg/mL using inductively coupled plasma–mass spectrometry (ICP-MS)/MS.

Distribution of TiO_2 particles in the gut and liver was examined in rats following administration of sonicated E171 (anatase, 20–340 nm, 44.7% < 100 nm) via gavage at a dose of 10 mg/kg bw per day for 7 days *(20)*. At the end of the study, some TiO_2 particles were detected in the Peyer's patches of the small intestine, the colonic mucosa and the liver of the treated group but not in the control animals, based on confocal and fluorescence reflection microscopy; micro X-ray fluorescence (µXRF) mapping confirmed the presence of particles containing Ti.

Vignard et al. *(21)* examined the translocation of E171 (anatase, mean 105 nm) suspended in water through the buccal mucosa in piglets by deposition under the tongue; four doses of 10 µg each were administered over 3 hours. TiO_2 particles (72–199 nm) and small aggregates (117–550 nm) were observed in the buccal mucosa 30 minutes after sublingual deposition, and were recovered in the submandibular lymph nodes 4 hours post-dosing, in samples analysed by transmission electron microscopy (TEM)/EDX. No TiO_2 particles were detected in the control pig (exposed to water only).

Absorption studies in humans

Reported basal Ti concentrations in blood (26 subjects) ranged from less than 0.001 to 0.0137 µg/mL *(22–25)*. Analysis of 22 human placentae collected after full-term births showed a wide range of Ti content (0.01–0.48 µg/g) *(26)*. In postmortem analysis of adults aged 56–104 years, no Ti was detected in 8/30 livers (LOD 0.01 µg/g). In the remaining livers the range was 0.02–0.09 µg/g, which does not suggest there is potential for bioaccumulation *(27,28)*.

A human study measured increased concentrations of Ti in the blood following ingestion of capsules containing TiO_2. Following ingestion of one

capsule containing 22.9 mg of TiO_2 (mean diameter 160 nm) in the capsule wall material, blood Ti concentrations increased in five subjects from 0.012 (mean of baseline values) to 0.058 µg/mL (mean as calculated by the Committee), and the time of peak concentration varied from 30 minutes up to 12 hours. When two capsules were administered (a total of 45.8 mg of TiO_2), the maximum Ti blood concentrations were 0.110 and 0.062 µg/mL (two volunteers only). In two volunteers who received a gelatine capsule containing 22.9 mg of TiO_2 (mean diameter 380 nm) as powder, Ti blood concentrations increased but to a lesser extent (maximum concentrations of 0.047 and 0.031 µg/mL) *(22)*.

In a human study (nine subjects) that included separate experiments with the same subjects, 5 mg/kg bw of TiO_2 of different particle diameters (15, 100 or < 5000 nm) was administered in a glass of drinking-water. No increased concentrations of Ti in the blood above the baseline concentration of 0.013 µg/mL up to 48 hours post-ingestion was reported *(24)*.

In another study with seven subjects *(25)*, the baseline Ti blood concentration was approximately 0.001–0.002 µg/mL. Following ingestion of two gelatine capsules, each containing 50 mg of TiO_2 (anatase, median 260 nm), the maximum peak concentration occurred at 6 hours post-dosing (approximately 0.011 µg/mL). At 10 hours post-dosing, the Ti concentration had decreased to approximately 0.005 µg/mL.

The Committee concluded that when TiO_2 is administered to animals, absorption is very low (e.g. < 0.000 75%). Absorption in humans is also very low.

Toxicological studies

Acute toxicity

There are no acute oral toxicity studies on test materials clearly defined as INS 171 or E171.

Short-term studies

Mice received an average daily dose of 2 mg/kg bw of E171 (anatase, mean diameter 201.2 ± 8.5 nm, 35% < 100 nm) by dropping water/E171 into the mouth for 3 days a week for 3 weeks. The test article was not sonicated prior to administration. No effects on body weight, feed intake or organ weights were observed *(14)*. Some inflammatory biomarkers (increase in interleukin (IL)-1β liver and stomach, and decrease in intestinal tumour necrosis factor (TNF)-α and liver IL-10) were altered but, given the magnitude of the changes, were probably the result of an adaptive rather than toxic response. There was no evidence regarding liver enzyme changes indicative of injury to support these findings. The Committee noted that this study had a number of deficiencies including use

of a single dose group, male mice only and very low numbers used to evaluate liver histopathology, meaning that statistical power was reduced.

The NCI *(6)* performed 90-day range-finding studies in mice and rats given TiO_2 (anatase, Unitane 0–220) in the diet. Food consumption, body weight, and gross and microscopic pathology of tissues and organs were examined, but no haematology or clinical chemistry parameters were investigated. Doses of Unitane 0–220 up to 15 000 mg/kg bw per day in mice were well tolerated, with no treatment-related adverse effects reported. In rats, doses of Unitane 0–220 up to 5000 mg/kg bw per day were well tolerated with no treatment-related adverse effects reported. The Committee concluded that the NOAELs were 15 000 mg/kg bw per day in mice and 5000 mg/kg bw per day in rats, the highest doses tested.

In a study by Bettini et al. *(20)*, rats were dosed with 10 mg/kg bw per day of E171 (anatase, mean diameter 118 ± 53 nm, range 20–340 nm, 44.7% < 100 nm) for 7 days by gavage. The test article was ultrasonicated in water prior to administration. Tissue imaging, flow cytometry, and cytokine assays and markers for tissue inflammation and gut permeability measurements were conducted. No changes were noted in myeloperoxidase (MPO) activity or in the content of basal cytokines (i.e. TNF-α, IL-10, IL-1β, interferon (IFN)-γ and IL-17) in mucosa of the small and large intestine relative to the control rats.

In a study by Blevins et al. *(29)*, rats were fed a diet containing E171 (mean diameter 110–115 nm, 36% < 100 nm) at 0, 40, 400 or 5000 mg/kg feed for 7 days (1.81 (basal diet), 4.76, 31.4 or 374 mg/kg bw per day) or 100 days (1.1–1.5 (basal diet), 3.0–4.1, 19.0–25.7 or 236–300 mg/kg bw per day). Histopathology and immunological markers (cytokine production; anti-rat CD3/CD28 activation) were evaluated. E171 caused no adverse effects on any tissue histopathology or immune parameters up to the highest dose given for 7 or 100 days.

Han et al. *(30)* conducted a 90-day oral toxicity study according to OECD Test Guideline No. 408 *(31)*. Male and female rats received E171 (anatase, average diameter 150 nm) suspended in water at doses of 0, 10, 100 or 1000 mg/kg per day by gavage; the control group received the water vehicle. No treatment-related adverse effects were observed. Ti concentration was increased in the colon compared with controls at the maximum dose tested. The Committee concluded that the NOAEL was 1000 mg/kg bw per day, the highest dose tested.

Long-term toxicity and carcinogenicity

In a carcinogenicity bioassay, groups of mice and rats of each sex received Unitane 0–220 in the diet at concentrations of 0, 25 000 or 50 000 ppm, equivalent to doses of 0, 3750 or 7500 mg/kg bw per day for mice and 0, 1250 or 2500 mg/kg bw per day for rats, for 103 weeks *(6)*. The observed incidence of lesions and tumours was considered by the NCI to be comparable in frequency to the control

group or within the historical control range for mice and rats of this age and strain. The Committee concluded that, under the conditions of the bioassay, Unitane 0–220 was not toxic or carcinogenic by the oral route for both mice and rats. The Committee concluded that the NOAELs were 7500 mg/kg bw per day in mice and 2500 mg/kg bw per day in rats, the highest doses tested.

Genotoxicity

The Committee emphasized that the OECD guidelines for investigating genotoxicity have been developed and validated for chemicals, and that they may not be easily applicable without adaptations for testing poorly soluble particulate matter. Several papers provide some recommendations for assessing the genotoxicity of nanomaterials, for example, Doak et al. *(32)*. Several adaptations are still under debate, such as the top concentration and dose to be tested, precipitate consideration and the study design. Interference affecting the interpretation of the results can also occur, mostly for in vitro assays due to the high number of particles in contact. Additionally, the Committee did not consider bacterial reverse mutation studies in the assessment as they have been deemed unsuitable for assessing nanoparticles due to the inability of prokaryotes to internalize nanoparticles *(33,34)*.

E171 was tested in vitro using mammalian cells to investigate gene mutations *(35)* and chromosomal damage *(21,36–38)* according to OECD Test Guideline Nos 476 *(39)* and 487 *(40)* but with deviations noted by the Committee. Studies investigating E171 using assays for which there are no OECD test guidelines – for example, comet *(21,36,37,41–45)*, ToxTracker *(42)* and oxidative stress *(36,41,43)* – were also considered. The Committee found no convincing evidence demonstrating a genotoxic effect based on the in vitro data, but noted some equivocal findings and limitations of the different studies.

The Committee noted the difficulties in interpreting negative outcomes of oral in vivo genotoxicity studies that used particulate test materials with very low absorption (e.g. E171) in that exposure of target tissues, apart from immediate site-of-contact tissues, cannot currently be demonstrated.

There were no identified in vivo gene mutation studies testing E171. In vivo studies investigating systemic organs or tissues (e.g. liver, lung and bone marrow) using the micronucleus or chromosomal aberration assays *(46–48)* or in vivo comet assay *(46,49)* did not find a genotoxic effect. An in vivo comet study was negative for genotoxic effects in intestine (Peyer's patches), which is expected to be more largely exposed to the particles *(20)*. However, this study was not suitable for evaluating the genotoxic potential due to experimental limitations.

Overall, the Committee noted that the available data did not provide convincing evidence of genotoxicity for INS 171, but recognized the limitations of

the current methodology with respect to the testing of poorly soluble particulate materials.

Reproductive toxicity

An extended EOGRT study in rats *(18)* using E171 (anatase, mean 112–117 nm, recovered from the diet) was compliant with OECD Test Guideline No. 443 *(17)* and included the addition of the examination of aberrant crypt foci (ACF) (see "Special studies"). The study used doses ranging up to 1000 mg/kg bw per day and assessed all appropriate test guideline parameters in the parental, F1 and F2 generations, including neuropathology and immunology in the offspring. No treatment-related adverse effects were found on male or female sexual function, fertility, gestation, prenatal or postnatal development, sex hormone and thyroid hormone levels in serum, or neural development.

The Committee noted that the EOGRT study had not been able to establish whether there were effects on developmental immunotoxicity resulting from exposure to E171 due to a weak immune response against the administered keyhole limpet haemocyanin (KLH) antigen, and that the study authors stated that this part of the study will be repeated. The Committee concluded that, apart from the lack of conclusive results on developmental immunotoxicity, the NOAEL for the study was 1000 mg/kg bw per day, the highest dose tested.

Developmental toxicity

Developmental toxicity studies in rats were conducted in accordance with OECD Test Guideline No. 414 *(50)* using pg-TiO_2. Three different pg-TiO_2 were used (see "Explanation"), administered by gavage at doses ranging up to 1000 mg/kg bw per day. No treatment-related adverse effects were found for any of the pg-TiO_2 materials tested *(7)*. The Committee noted that the NOAELs for both maternal and developmental toxicity were 1000 mg/kg bw per day, the highest dose tested in all the studies.

Special studies

In a study in rats, animals were pretreated with the colon cancer initiator 1,2-dimethylhydrazine (DMH) then given E171 (anatase, 20–340 nm, 44.7% < 100 nm, ultrasonicated) at doses of 200 μg/kg bw per day or 10 mg/kg bw per day in the drinking-water for 100 days *(20)*. There were no effects from the dose of E171 at 200 μg/kg bw per day. At 10 mg/kg bw per day, E171 significantly increased the total number of aberrant crypts per colon from approximately 475 in the DMH control to 550 with DMH plus E171 exposure (based on the published bar chart). Additionally, the number of large ACF (considered to be early pre-cancerous lesions that may progress to cancer) per colon (defined as

> 3 aberrant crypts per ACF) was increased from approximately 35 in the DMH control to 45 with DMH plus E171 exposure (based on the published bar chart).

In a second experiment without DMH pretreatment, rats given a dose of E171 of 0 or 10 mg/kg bw per day in the drinking-water for 100 days demonstrated an increase in the occurrence of ACF from 0 in the controls to 1–3 ACF per colon in 4/11 treated animals *(20)*.

Blevins et al. *(29)* conducted a similar study using higher doses of E171 than Bettini et al. *(20)* and administering E171 in the diet, with or without pretreatment with DMH. Compared with respective controls, dietary exposure of rats to E171 (anatase, mean 110–115 nm, 36% < 100 nm) alone at daily doses up to 236 mg/kg bw per day for 100 days did not produce any significant effects on the number of ACF or aberrant crypts, the number of goblet cells per colonic gland or colonic gland length. There were also no histopathological changes observed in the small and large intestine, liver, spleen, lungs or testes. The authors noted that parts of the colon could not be examined because of technical difficulties; ACF counts per square centimetre were used to compare the groups. In rats exposed to the maximum E171 dose, the mean number of ACF/cm^2 was 0.9, similar to the control group (0.8 ACF/cm^2). E171 exposure after pretreatment of rats with DMH also had no statistically significant effect on the number of ACF or aberrant crypts, compared with the respective controls. The Committee noted that some histopathological effects, including the number of ACF, may have been missed because of the incomplete assessment of the whole colon.

An EOGRT was conducted according to OECD Test Guideline No. 443 *(17,18)*. E171 (anatase, median diameter 100 nm) was administered to rats in the diet at doses of up to 1000 mg/kg bw per day. A group of satellite animals from the F0 generation was used for evaluation of ACF, and killed after 122 days of exposure. Microscopic examination of the complete mucosal surface of the colons did not detect the presence of ACF. Mild distortion of the colon crypts, as displayed by a minimal increase in variability of crypt sizes, was observed in seven animals among all groups, but it was not treatment related. The Committee noted that additional studies with E171 dosing either via drinking-water or by gavage, involving sonification of the test material prior to dosing, have reported gastrointestinal tract effects, such as hyperplastic epithelial changes in the colon *(51)*, gut homeostasis disruption *(52,53)* and cytokine markers of colon inflammation *(14,52,54)*. However, the Committee considered these to be of questionable relevance to the safety assessment of INS 171 due to various limitations, including study design deficiencies, dosing methodology, small animal numbers and/or variability in the results. It was considered that adverse effects associated with oral exposure to E171 are largely derived from studies that administered homogenized suspensions of ultrasonically dispersed test material, which would not be representative of dietary exposure.

Observations in humans

A few epidemiological studies *(55–57)* address health effects related to dietary exposure to TiO_2 (form and size not specified). Potential associations with inflammatory bowel disease are discussed without allowing any conclusions to be made.

Assessment of dietary exposure

The Committee has not previously evaluated the dietary exposure to TiO_2 as a food additive. TiO_2 is permitted for use in a broad range of specified foods (including beverages) under the conditions of GMP as specified in table 3 of the GSFA *(1)*. At the current meeting, the Committee evaluated estimates of dietary exposure to TiO_2 submitted by the sponsor and calculated by the Committee for Europe based on mean use levels of TiO_2 in 11 food categories, including food supplements. In addition, dietary exposure estimates were evaluated from the literature for China *(58)*, the Netherlands (Kingdom of the) *(59,60)* and the United States of America (USA) *(61)*, and for Europe *(62)*. Table 2.1 provides an overview of the dietary exposure estimates.

EFSA *(62)* calculated the exposure for the European population according to both brand-loyal and non-brand-loyal scenarios. Because brand loyalty to certain foods (e.g. chewing gum, fine bakery wares or confectionery) could not be excluded, in Table 2.1 the Committee list the brand-loyal estimates of dietary exposure to TiO_2 as being relevant. These estimates are based on mean and maximum use levels, which account for brand loyalty by mapping the consumption of such foods at a maximum reported use level and that of other foods that may contain TiO_2 at a mean reported use level. These estimates of exposure covered 15 of the 48 food categories for which the use of TiO_2 was authorized in 2021 in the EU according to annex II of Regulation (EC) No. 1333/2008. The Committee noted that use of TiO_2 as a food additive was, from 14 January 2022, no longer approved in the EU *(63)*, and that the estimated exposure for 2021 is not representative of the current exposure to TiO_2 in the EU.

Ti as TiO_2 may also be present in food due to natural occurrence. These foods contain lower levels of TiO_2 than foods to which TiO_2 may be added as a food additive *(5,58,60)*. Considering the conservative assumptions underlying the exposure estimates in Table 2.1, the Committee considered it likely that the exposure to TiO_2 is not underestimated when these background concentrations are not included in the assessment. Furthermore, oral exposure to TiO_2 can also occur through the ingestion of toothpaste. This may be relevant for young children that are known to ingest this product *(60)*. However, the contribution of toothpaste to lifelong exposure to TiO_2 is expected to be limited, considering that toothpaste is not likely to be ingested by children older than 6 years or by adults.

Table 2.1
Overview of estimated dietary exposure of the total population to TiO_2 from its use as a food additive

Country	Source concentrations	Consumption	Age groups	Dietary exposure (mg/kg bw per day)	
				Mean	P95
China *(58)*	Analytical levels, median	3 × 24-hour dietary recall (24HDR)	Young children (2–5 years)	0.337	NR
			Adults (30–39 years)	0.0445	NR
			Total population (2 to ≥ 70 years)	0.071	NR
Netherlands (Kingdom of the) *(59,60)*	Analytical levels, mean	2 × food diary; 2 × 24HDR	2–6 years[a]	0.67	1.29
			7–69 years	0.17	0.50
			≥ 70 years	0.06	0.23
	Use levels and analytical levels, mean	2 × food diary; 2 × 24HDR	2–6 years[a]	1.4[b]	4.9
			7–69 years	0.7[b]	2.8
			≥ 70 years	0.5[b]	1.8
USA *(61)*	Analytical levels, mean	3 × 24HDR	Adults (18–30 years)	0.19	NR
Europe[c]	Use levels, mean[d]	2–7 days; dietary/food record; 24HDR	Infants (0–1 years)	0.01–0.59	0.07–2.6
			Toddlers (1–2 years)	0.23–0.63	1.0–8.9
			Other children (3–9 years)	1.0–3.3	2.5–7.5
			Adolescents (10–17 years)	0.59–2.3	1.6–7.1
			Adults (18 to ≥ 65 years)	0.05–2.0	0.18–5.2
	Use levels, mean[e]	2–7 days; dietary/food record; 24HDR	Infants (0–1 years)	0.00–2.7	0.11–9.4
			Toddlers (1–2 years)	0.35–3.9	1.5–8.0
			Other children (3–9 years)	1.1–3.7	3.4–8.1
			Adolescents (10–17 years)	0.62–2.4	1.7–7.3
			Adults (18 to ≥ 65 years)	0.05–2.1	0.18–5.3
	Use levels, maximum and mean[f]	2–7 days; dietary/food record; 24HDR	Infants (0–1 years)	0.05–3.5	0.1–14.3
			Toddlers (1–2 years)	0.8–10.0	2.6–28.0
			Other children (3–9 years)	1.7–9.7	5.2–25.4
			Adolescents (10–17 years)	1.1–5.0	3.3–14.9
			Adults (18 to ≥ 65 years)	0.4–5.5	1.7–13.1

24HDR: 24-hour dietary recall; bw: body weight; EFSA: European Food Safety Authority; FAIM: Food Additive Intake Model; NR: not reported; P95: 95th percentile; USA: United States of America.

[a] Estimates for children aged 2–6 years included the exposure via toothpaste, which accounted for 57% of the mean exposure to TiO_2.

[b] Median estimates (50th percentile).

[c] The European countries were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands (Kingdom of the), Portugal, Romania, Slovenia, Spain and Sweden. In the estimates of EFSA for Europe *(62)*, food consumption data from the United Kingdom were also included.

[d] Estimates obtained using FAIM v2.1 by the sponsor.

[e] Estimates obtained using FAIM v2.1 by the current Committee.

[f] Estimates based on the brand-loyal exposure scenario by EFSA *(62)*.

The Committee considered the assessment of dietary exposure to TiO_2 from its use as a food additive for the European population as most comprehensive with P95 estimates of exposure that could be as high as 28 mg/kg bw per day for children aged 1–2 years (see Table 2.1). However, the Committee noted that two studies based on analytical concentrations of TiO_2 in food resulted in much lower estimates of exposure to TiO_2 (see Table 2.1). Combined with the conservative

assumption of the exposure assessment for the European population – that all foods in a food category that could contain TiO_2 did in fact contain TiO_2 at the maximum or average use level (whereas in practice only a fraction of the foods will contain the additive) – the Committee selected a high P95 estimate of exposure to INS 171 of 10 mg/kg bw per day for the evaluation. The Committee considered that this estimate of dietary exposure to TiO_2 was still conservative considering the exposure estimates to TiO_2 evaluated by the Committee (see Table 2.1).

Evaluation

The Committee evaluated TiO_2 (INS 171) at its Thirteenth meeting *(2)* and assigned an ADI "not specified"[3] based on an absence of significant absorption and a lack of toxicological effects in the available experimental animal and human studies at the time.

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

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

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

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

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

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

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

A toxicological and dietary exposure monograph addendum was prepared.

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

The chemical and technical assessment was revised.

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3. Flavouring agents

3.1 Safety evaluations

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

Introduction

At the request of the CCFA at its Fifty-second session *(1)*, the Committee evaluated an additional five flavouring agents in the group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups. These five flavouring agents included succinic acid (No. 2307), an aldehyde (No. 2308), mixture of ricinoleic acid, linoleic acid and oleic acid (No. 2310) and two esters (Nos 2309 and 2311).

The Committee decided not to review succinic acid (No. 2307) because it had previously been evaluated as a food additive at the Twenty-ninth meeting *(2)*. At that meeting, the Committee concluded that "Succinic acid is a natural constituent of plants and animals that are commonly used as food. Experimental animals can tolerate high dietary concentrations of succinic acid. Succinic acid does not represent a hazard at the levels at which it is likely to be used as a food additive due to its normal role in metabolism. An ADI 'not specified' was established for the succinate moiety" *(2)*. None of the other four flavouring agents has previously been evaluated by the Committee. These four additional members of this group were evaluated according to the revised Procedure for the Safety Evaluation of Flavouring Agents *(3)*.

The Committee had previously evaluated 47 flavouring agents from this group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups at its Fifty-third meeting *(4)*. At its Seventy-third meeting *(5)*, the Committee evaluated another 44 flavouring agents from this group. These additional flavouring agents included 23 esters, 11 diesters, 5 acids, 2 primary alcohols, 2 ketals and 1 acetal. The Seventy-third Committee concluded that no safety concerns were raised at the estimated dietary exposures for most of these flavouring agents, but that additional toxicological data would be necessary to complete the safety evaluation for two structural class III flavouring agents, namely ethyl levulinate propyleneglycol ketal (No. 1973) and the mixture of isopropylideneglyceryl 5-hydroxydecanoate and δ-decalactone (No. 1988) *(5)*. Specifically, information on the rate and extent of hydrolysis as well as relevant short-term studies for these flavouring agents or structurally related substances were required.

The additional four flavouring agents in this group evaluated at the present meeting are (±)-6-methoxy-2,6-dimethylheptanal (No. 2308), ethyl

5-formyloxydecanoate (No. 2309), mixture of ricinoleic acid, linoleic acid and oleic acid (No. 2310) and ethyl 3-methyl-2-oxopentanoate (No. 2311). None of the four flavouring agents in this group has been reported to occur naturally in foods. All four additional members of this group were evaluated according to the revised Procedure for the Safety Evaluation of Flavouring Agents *(3)*.

A literature search for toxicological data was conducted in Scopus and PubMed using the names and CAS numbers of the flavouring agents under evaluation in this group.

The call for data included the previously evaluated flavouring agents No. 1973 and No. 1988. For flavouring agent No. 1973, the data submitted to the Committee for evaluation consisted only of study summaries from the database of the European Chemicals Agency (ECHA). These studies could not be assessed by the Committee in the absence of full study reports. For flavouring agent No. 1988, no data were submitted. The Committee was therefore unable to evaluate these two flavourings agents.

Assessment of dietary exposure

The total annual production volume of the four additional flavouring agents in the group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups is 152 kg in Japan, 54 kg in the USA and 0.1 kg in Latin America (Table 3.1) *(6–9)*. No production volume was reported for the EU. More than 99% of the annual production volume for Japan is accounted for by a mixture of ricinoleic acid, linoleic acid and oleic acid (No. 2310).

Dietary exposures were estimated by both the single portion exposure technique (SPET) and the maximized survey-derived intake (MSDI) method, with the highest values reported in Table 3.1 *(6–8)*. The SPET and MSDI method exposure values are in the range of 100–1880 µg/day and 0.005–43 µg/day, respectively. The estimated daily dietary exposure was highest for ethyl 5-formyloxydecanote (No. 2309) at 1880 µg/day, the SPET value obtained for processed vegetables and nuts and seeds.

Absorption, distribution, metabolism and elimination

Information on the absorption, distribution, metabolism and elimination (ADME) of the flavouring agents belonging to the group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups is provided in the monographs of the Forty-ninth and Seventy-third meetings *(10,11)*.

As most of the substances in this group are esters, diesters, acetals or ketals, they are anticipated to readily undergo hydrolysis to their corresponding

Table 3.1

Annual volumes of production and daily dietary exposures for aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups used as flavouring agents in Japan and the USA, and in Europe and Latin America

Flavouring agent (No.)	Most recent annual volume of production (kg)[a]	Dietary exposure				Annual volume of consumption via natural occurrence in foods (kg)[d]
		MSDI[b]		SPET[c]		
		µg/day	µg/kg bw per day	µg/day	µg/kg bw per day	
(±)-6-Methoxy-2,6-dimethylheptanal (2308)				**100**	**1.7**	–
Japan	NR	ND	ND			
USA	53	6	0.09			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
Ethyl 5-formyloxydecanoate (2309)				**1880**	**31**	–
Japan	2	0.6	0.01			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
Mixture of ricinoleic acid, linoleic acid and oleic acid (2310)				**1000**	**17**	–
Japan	150	43	0.7			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
Ethyl 3-methyl-2-oxopentanoate (2311)				**600**	**10**	–
Japan	NR	ND	ND			
USA	1	0.1	0.002			
Europe	NR	ND	ND			
Latin America	0.1	0.005	0.000 09			
Total						
Japan	152					
USA	54					
Europe	NR					
Latin America	0.1					

–: not reported to occur naturally in foods; MSDI: maximized survey-derived intake; ND: no intake data reported; NR: no volume data reported; SPET: single portion exposure technique; US FDA: United States Food and Drug Administration.

[a] From the International Organization for the Flavor Industry *(6,7)*. Values greater than 0 kg but less than 0.1 kg were reported as 0.1 kg.

[b] Exposure (µg/person per day) calculated as: [(annual volume, kg) × (1×10^9 µg/kg)]/(population × survey correction factor × 365 days), where population (10%, "eaters only") = 12×10^6 for Japan, 33×10^6 for the USA, 40×10^6 for Europe and 65×10^6 for Latin America, with correction factor = 0.8 from the IOFI Global Poundage Survey or private communication to FEMA representing the assumption that only 80% of the annual flavour volume was reported *(6,7)*. Intake (µg/kg bw per day) calculated as: (µg/person per day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[c] SPET (µg/person per day) calculated as: (US FDA standard food portion, g/day) × (highest usual use level) *(8)*. The dietary exposure from the single food category leading to the highest dietary exposure from one portion is taken as the SPET estimate. SPET (µg/kg bw per day) calculated as: (µg/day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[d] Quantitative data for the USA reported by Stofberg and Grundschober *(9)*.

alcohol (saturated linear or branched-chain aliphatic primary alcohols, or branched-chain hydroxyl- or keto-alcohols). The presence of a second oxygenated functional group is unlikely to have much impact on ester hydrolysis. The β-keto acids and derivatives readily undergo decarboxylation and, with α-keto and α-hydroxyacids, yield breakdown products that are incorporated into normal biochemical pathways. The γ-keto acids and related substances may undergo complete or partial β-oxidation to yield metabolites that are eliminated in the urine. The ω-substituted derivatives are predicted to be readily oxidized and/or excreted in the urine. The simple aliphatic dicarboxylic and tricarboxylic acids either occur endogenously in humans or are structurally related to endogenous substances. These substances are metabolized through the fatty acid β-oxidation pathway or the tricarboxylic acid cycle *(12)*.

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

Step 1. There are no structural alerts for genotoxicity for the four additional flavouring agents (Nos 2308–2311) in this group. Chemical-specific genotoxicity data on previously evaluated flavouring agents in this group and two of the four (Nos 2308 and 2309) new flavouring agents do not indicate that they are potentially genotoxic.

Step 2. In applying the revised Procedure for the Safety Evaluation of Flavouring Agents to the four flavouring agents, the Committee assigned the four flavouring agents (Nos 2308–2311) to structural class I *(13)*.

Step 3. Dietary exposures were estimated with both the MSDI method and the SPET and are presented in Table 3.1.

Step 4. The highest estimated dietary exposures for three flavouring agents (Nos 2308, 2310 and 2311) in structural class I are below the threshold of concern (i.e. 1800 µg/person per day for class I). The Committee therefore concluded that these three flavouring agents do not raise any safety concerns at current estimated dietary exposures.

The highest estimated dietary exposure, for ethyl 5-formyloxydecanoate (No. 2309), is above the threshold of concern (i.e. 1800 µg/person per day for class I), so its evaluation proceeded to Step 5 of the revised Procedure.

Step 5. Although chemical-specific toxicity studies for ethyl 5-formyloxydecanoate (No. 2309) are not available, the following NOAELs are available for structurally related lactones in 2-year bioassays in rats: 250 mg/kg bw per day for both γ-nonalactone and γ-undecalactone, and 110 mg/kg bw per day for γ-butyrolactone. In a 2-year study in mice with γ-butyrolactone, a NOAEL of 260 mg/kg bw per day was established. The studies with γ-nonalactone and γ-undecalactone in rats were considered previously by the Committee, and ADIs were established at the Eleventh meeting *(14)*. For ethyl 5-formyloxydecanoate

Table 3.2

Summary of the results of safety evaluations of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups used as flavouring agents[a,b,c]

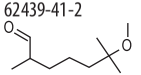
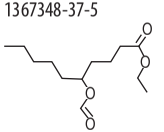
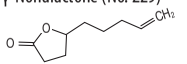
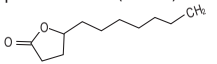
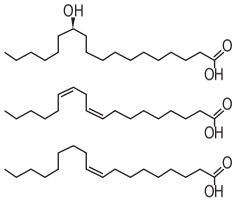
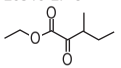
Flavouring agent	No.	CAS No. and structure	Step 4 Does the highest dietary exposure estimate exceed the threshold of toxicological concern?[d]	Step 5 Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate margin of exposure?[e]	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
Structural class I							
(±)-6-Methoxy-2,6-dimethylheptanal	2308	62439-41-2 	No	NR	–[f]	–	No safety concern
Ethyl 5-formyloxydecanoate	2309	1367348-37-5 	Yes, SPET: 1880 µg/day	Yes, NOAELs have been reported for structurally related lactones in 2-year studies in rats: 250 mg/kg bw per day for γ-nonalactone and γ-undecalactone. These NOAELs provide an adequate MOE (> 1000) for ethyl 5-formyloxydecanoate.	–[g]	γ-Nonalactone (No. 229)  γ-Undecalactone (No. 233) 	No safety concern
Mixture of 88–90% (w/w) ricinoleic acid, 7–8% linoleic acid (No. 116) and 5-6% oleic acid (No. 333), with around 2–3% each of stearic acid (No. 116) and palmitic acid (No. 115)	2310	61789-44-4 	No	NR	–[h]	Unknown	No safety concern
Ethyl 3-methyl-2-oxopentanoate	2311	26516-27-8 	No	NR	–[i]	Unknown	No safety concern

Table 3.2 (continued)

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

[a] In total, 47 flavouring agents from this group were previously evaluated by the Committee at its Fifty-third meeting *(4)* and 44 flavouring agents at its Seventy-third meeting *(5)*. The Committee concluded that 89 flavouring agents raised no safety concerns at the estimated dietary exposures. For ethyl levulinate propyleneglycol ketal (No. 1973) and the mixture of isopropylideneglyceryl 5-hydroxydecanoate and δ-decalactone (No. 1988), the Committee concluded that additional data would be necessary to complete the evaluation *(5)*.

[b] *Step 1*: The weight of evidence from the chemical-specific data on genotoxicity for two of the above four flavouring agents (Nos 2308 and 2309) indicates that neither are a potential DNA-reactive carcinogen.

[c] *Step 2*: The four flavouring agents are in structural class I.

[d] The thresholds of toxicological concern for structural class I, II and III are 1800, 540 and 90 µg/day, respectively. All 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 highest estimate for each flavouring agent. All dietary intake values are expressed in µg/day.

[e] The MOE was calculated based on the highest daily per capita intake calculated either by SPET or MSDI.

[f] It is anticipated that the compound will be metabolized mainly by oxidation to 6-methoxy-2,6-dimethylheptanoic acid followed by conjugation with glucuronic acid. Reduction to the corresponding alcohol and O-demethylation are also possible metabolic routes. Metabolites would be mainly excreted in the urine.

[g] It is anticipated that ethyl 5-formyloxydecanoate will be metabolized mainly by hydrolysis to liberate 5-formyloxydecanoic acid, 5-hydroxydecanoic acid, and ethanol and formic acid. Hydrolysis will be followed by β-oxidation of the acid and cleavage to yield acetyl CoA fragments that will enter the citric acid cycle and be converted to carbon dioxide and water.

[h] The mixture of ricinoleic, linoleic and oleic acids are anticipated to be absorbed and to undergo oxidation and β-cleavage in the fatty acid pathway.

[i] It is anticipated that ethyl 3-methyl-2-oxopentanoate, as for other aliphatic esters, will be hydrolysed to its corresponding alcohol and acid. The liberated ethanol would be excreted via exhalation or further metabolized by the body. The 2-oxopentanoic acid that is formed would likely undergo additional metabolism via β-oxidation.

(No. 2309), a NOAEL of 250 mg/kg bw per day for the two structurally related substances – γ-nonalactone (No. 229) and γ-undecalactone (No. 233) – in a 2-year dietary study in rats *(15)* provides an adequate margin of exposure (MOE) (> 1000) relative to the SPET estimate of 1880 µg/day (31 µg/kg bw per day for a 60-kg person) (Table 3.2). On this basis, ethyl 5-formyloxydecanoate does not raise a safety concern at the current levels of intake.

Consideration of combined intakes from use as flavouring agents

The Committee previously considered the potential combined intake of this group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups, and no safety concerns were raised. As the MSDI values for four of the additional flavouring agents in this group (Nos 2308–2311) are low (0.005–43 µg/day), these flavouring agents would make a negligible contribution to the combined intake of this group.

Consideration of secondary components

Two flavouring agents in this group (Nos 2309 and 2310) have minimum assay values of less than 95% (Annex 4). The major secondary components of No. 2309 are δ-decalactone (No. 232; structural class I) present at 4%, and ethyl-5-acetoxydecanoate present at 2%. The Committee previously evaluated δ-decalactone (No. 232) and concluded that it did not raise a safety concern at estimated dietary exposures when used as a flavouring agent *(16)*. The SPET value for No. 2309 is 1880 µg/day; 2% of this value (concentration of ethyl-5-acetoxydecanoate) is 38 µg/day, which is below the class III threshold of

toxicological concern. The secondary components of No. 2310, including 7–8% linoleic acid (No. 332), 5–6% oleic acid (No. 333), 2–3% stearic acid (No. 116) and 2–3% palmitic acid (No. 115), were previously considered by the Committee to raise no safety concerns at estimated dietary exposures when used as a flavouring agent *(16)*.

Consideration of additional data on previously evaluated flavouring agents

The Committee considered additional data submitted by the sponsor on seven previously evaluated flavouring agents in this group. The additional studies on toxicokinetics and metabolism, and reproductive and developmental toxicity of hydroxycitronellal (No. 611), as well as on genotoxicity for several flavouring agents (Nos 592, 605, 606, 611, 614, 622 and 629) all support the conclusions from previous evaluations.

Conclusions

Additional studies on toxicokinetics and metabolism, reproductive and developmental toxicity, and genotoxicity were available for some previously evaluated substances in this group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups *(4,5)*. None of the previously evaluated flavouring agents in this group was considered to raise a safety concern.

For the evaluation of the four additional flavouring agents, studies of acute toxicity (Nos 2308 and 2311) and genotoxicity (Nos 2308 and 2309) were available. The Committee concluded that the four additional flavouring agents (Nos 2308–2311) would not raise any safety concerns at the current estimated dietary exposures.

For flavouring agent No. 1973, only study summaries without the original full study reports had been submitted for evaluation. For flavouring agent No. 1988, no data were submitted. The Committee could therefore not evaluate these two flavouring agents.

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 citronelloxyacetaldehyde (No. 592), 1,3-nonanediol acetate (No. 605), levulinic acid (No. 606), hydroxycitronellal diethyl acetal (No. 613), diethyl malonate (No. 614), diethyl tartrate (No. 622) and triethyl citrate (No. 629) within 2 years (i.e. by December 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

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

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

Introduction

At the request of the CCFA at its Fifty-second session *(1)*, the Committee evaluated an additional 13 flavouring agents belonging to the group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters for the first time. The group included nine aldehydes (Nos 2286, 2288–2290, 2292, 2293, 2296–2298), two acids (Nos 2291 and 2295) and two esters (Nos 2287 and 2294). The evaluations were conducted according to the revised Procedure for the Safety Evaluation of Flavouring Agents *(3)*.

The Committee previously evaluated 42 members of this group of flavouring agents at its Fifty-first meeting *(17)* and concluded 41 of these flavouring agents did not raise any safety concerns at the estimated dietary exposures. The evaluation of the remaining flavour, ethyl-2-methyl-3,4-pentadienoate (No. 353), was deferred to the Sixty-eighth meeting *(18)* where it was evaluated alongside 27 additional flavouring agents from this group. The Committee concluded no safety concerns were raised with these 28 flavouring agents at the estimated dietary exposures. The Committee also evaluated 20 members of this group of flavouring agents at its Sixty-first meeting *(19)*, nine members of the group at its Seventy-sixth meeting *(20)* and two members of the group at its Eighty-sixth meeting *(21)*, and concluded none would raise a safety concern at their estimated dietary exposures. The safety of *trans*-5-dodecenal (No. 2288) as a constituent of lemongrass oil was also evaluated by the Committee at its Sixty-first meeting *(22)*. The Committee concluded that lemongrass oil was not expected to raise a safety concern based on the estimated dietary exposure.

The 13 additional flavouring agents evaluated at the present meeting are (4*Z*,7*Z*)-trideca-4,7-dienal (No. 2286), *cis*-5-dodecenyl acetate (No. 2287), *trans*-5-dodecenal (No. 2288), *cis*-6-dodecenal (No. 2289), *cis*-9-dodecenal (No. 2290), (*E*)-3-methyl-4-dodecenoic acid (No. 2291), *trans*-5-octenal (No. 2292), *trans*-tetradec-4-enal (No. 2293), 2,6-dimethylheptenyl formate (No. 2294), (*Z*)-9-dodecenoic acid (No. 2295), *cis*-tridec-5-enal (No. 2296), (*Z*)-8-pentadecenal (No. 2297) and 4,7-decadienal (mixture of isomers) (No. 2298).

Several of the flavouring agents in this group are reported to occur naturally in ambrette seed essential oil (No. 2287), cardamom and *Echinacea angustifolia* root (No. 2288), clementines (No. 2289) and cucumber (No. 2297) *(23–28)*.

A literature search for toxicological data was conducted in Google Scholar and PubMed using the names and CAS numbers of the flavouring agents under evaluation in this group. Two fragrance safety assessments *(29,30)* conducted by the Research Institute for Fragrance Materials were identified in the literature search. These assessments summarized an in vitro micronucleus assay *(31)* and an in vivo oral micronucleus assay *(32)* with 4,7-decadienal (mixture of isomers) (No. 2298), described in the present monograph, that provided no additional toxicological information considered relevant to this evaluation. Summaries of studies submitted from an ECHA database (https://echa.europa.eu/nl/information-on-chemicals/registered-substances) could not be assessed by the Committee in the absence of full study reports. Further, the results of study reports not published in full in English, and that could not be translated by a member of the Committee, could not be assessed by the Committee. No additional relevant references were identified.

Assessment of dietary exposure

Annual volumes of production of the group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters of flavouring agents, and the daily dietary exposures calculated using both the MSDI method and the SPET, are summarized in Table 3.3 *(6–9)*. The total annual production volume of the 12 additional flavouring agents (excluding No. 2298, for which a safety evaluation could not be completed) belonging to this group is 6.3 kg in Japan and 16 kg in the USA, and zero in Europe and Latin America *(6,7)*. (*Z*)-9-dodecenoic acid (No. 2295) accounts for more than 95% of the total annual production volume in Japan.

Dietary exposures were estimated by both the SPET and the MSDI method, with the highest exposure values reported in Table 3.3 *(6–8)*. The SPET and MSDI method exposure values are in the range of 0.04–1000 μg/day and 0.03–3 μg/day, respectively. The estimated daily dietary exposure was highest for (*Z*)-9-dodecenoic acid (No. 2295) at 1000 μg/day, the SPET value for milk and dairy-based drinks.

Absorption, distribution, metabolism and elimination

The ADME of the flavouring agents in this group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters were described in the reports of the Fifty-first, Sixty-first, Sixty-eighth,

Table 3.3

Annual volumes of production and daily dietary exposures for linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters used as flavouring agents in Japan and the USA, and in Europe and Latin America

Flavouring agent (No.)	Most recent annual volume of production (kg)[a]	Dietary exposure				Annual volume of consumption via natural occurrence in foods (kg)[d]
		MSDI[b]		SPET[c]		
		µg/day	µg/kg bw per day	µg/day	µg/kg bw per day	
(4*Z*,7*Z*)-Trideca-4,7-dienal (2286)				**0.2**	**0.003**	–
Japan	0.1	0.03	0.000 5			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***cis*-5-Dodecenyl acetate (2287)**				**13**	**0.2**	–
Japan	NR	ND	ND			
USA	3	0.3	0.005			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***trans*-5-Dodecenal (2288)**				**22.5**	**0.4**	–
Japan	150	43	0.7			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***cis*-6-Dodecenal (2289)**				**15**	**0.3**	–
Japan	NR	ND	ND			
USA	2	0.2	0.003			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***cis*-9-Dodecenal (2290)**				**9**	**0.2**	–
Japan	NR	ND	ND			
USA	2	0.2	0.003			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
(*E*)-3-Methyl-4-dodecenoic acid (2291)				**0.8**	**0.01**	–
Japan	0.1	0.03	0.000 5			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***trans*-5-Octenal (2292)**				**75**	**1.3**	–
Japan	NR	ND	ND			
USA	1	0.1	0.002			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			

Flavouring agent (No.)	Most recent annual volume of production (kg)[a]	Dietary exposure				Annual volume of consumption via natural occurrence in foods (kg)[d]
		MSDI[b]		SPET[c]		
		µg/day	µg/kg bw per day	µg/day	µg/kg bw per day	
***trans*-Tetradec-4-enal (2293)**				**90**	**1.5**	–
Japan	NR	ND	ND			
USA	2	0.2	0.003			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
2,6-Dimethylheptenyl formate (2294)				**90**	**1.5**	–
Japan	NR	ND	ND			
USA	2	0.2	0.003			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
(*Z*)-9-Dodecenoic acid (2295)				**1000**	**17**	–
Japan	6	2	0.03			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
***cis*-Tridec-5-enal (2296)**				**90**	**1.5**	–
Japan	NR	ND	ND			
USA	2	0.2	0.003			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
(*Z*)-8-Pentadecenal (2297)				**0.04**	**0.000 7**	–
Japan	0.1	0.03	0.000 5			
USA	NR	ND	ND			
Europe	NR	ND	ND			
Latin America	NR	ND	ND			
Total						
Japan	6.3					
USA	16					
Europe	NR					
Latin America	NR					

–: not reported to occur naturally in foods; MSDI: maximized survey-derived intake; ND: no intake data reported; NR: no volume data reported; SPET: single portion exposure technique; US FDA: United States Food and Drug Administration; USA: United States of America.

[a] From the International Organization for the Flavor Industry *(6,7)*. Values greater than 0 kg but less than 0.1 kg were reported as 0.1 kg.

[b] MSDI (µg/day) calculated as: [(annual volume, kg) × (1×10^9 µg/kg)]/(population × survey correction factor × 365 days), where population (10%, "eaters only") = 12×10^6 for Japan, 33×10^6 for the USA, 40×10^6 for Europe and 65×10^6 for Latin America, with correction factor = 0.8 from the IOFI Global Poundage Survey or private communication to FEMA representing the assumption that only 80% of the annual flavour volume was reported, respectively *(6,7)*. MSDI (µg/kg bw per day) calculated as: (µg/day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[c] SPET (µg/day) calculated as: (US FDA standard food portion, g/day) × (highest usual use level) *(8)*. The dietary exposure from the single food category leading to the highest dietary exposure from one portion is taken as the SPET estimate. SPET (µg/kg bw per day) calculated as: (µg/day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[d] Quantitative data for the USA reported by Stofberg and Grundschober *(9)*.

Seventy-sixth and Eighty-sixth meetings *(17–21)*. No additional information was available for this meeting.

The aliphatic esters (Nos 2287 and 2294) are expected to be hydrolysed by esterases to their corresponding unsaturated aliphatic alcohols and carboxylic acids in the gastrointestinal tract *(20,21)*. The resulting linear and branched-chain unsaturated primary alcohols are expected to be rapidly absorbed and further oxidized into their corresponding aldehydes and acids. Aliphatic aldehydes and acids are also expected to be readily absorbed *(33)*. Once absorbed, aldehydes are oxidized to their corresponding unsaturated carboxylic acids. These unsaturated carboxylic acids then undergo further enzymatic conversion prior to entry into the β-oxidation pathway, where they are fully metabolized to carbon dioxide and water via the citric acid cycle *(20,21)*.

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

Step 1. Data on previously evaluated flavouring agents in this group did not raise any concerns for genotoxic potential, and there were no structural alerts for any of the 13 additional flavouring agents in this group (Nos 2286–2298). Genotoxicity data were available for four of the 13 newly evaluated flavouring agents (Nos 2291, 2295, 2297 and 2298). Data for three of these flavouring agents (Nos 2291, 2295 and 2297) did not indicate that they were genotoxic. For the flavouring agent 4,7-decadienal (mixture of isomers) (No. 2298), a positive finding was reported in an in vitro micronucleus assay in the presence of metabolic activation. The results of an in vivo bone marrow micronucleus assay in mice were negative, but the test material was not detected in the plasma and target organ exposure was therefore not confirmed. The Committee concluded that it was unable to complete the safety evaluation for this flavouring agent (No. 2298) without additional data demonstrating the absence of clastogenicity. Flavouring agent No. 2298 was therefore not considered further using the revised Procedure for the Safety Evaluation of Flavouring Agents. The Committee also noted that, although genotoxicity data were available for only three of the 12 remaining flavouring agents, these data were representative of the expected genotoxicity of the structurally related nine additional flavouring agents.

Step 2. In applying the revised Procedure for the Safety Evaluation of Flavouring Agents to the remaining 12 additional flavouring agents (Nos 2286–2297), the Committee assigned all 12 agents to structural class I *(13)*. Structural class was assigned using the quantitative structure-activity relationship (QSAR) tool Toxtree (version 3.1.0).

Step 3. Dietary exposures were estimated with both the MSDI method and the SPET and are presented in Table 3.3.

Step 4. The highest estimated dietary exposures for all 12 flavouring agents in structural class I (Nos 2286–2297) are below the threshold of toxicological

concern (i.e. 1800 µg/person per day). The Committee therefore concluded that these 12 flavouring agents did not raise any safety concerns at current estimated dietary exposures.

Table 3.4 summarizes the evaluations of the 12 flavouring agents belonging to the group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters that were considered at the present meeting (Nos 2286–2297).

Consideration of the combined intakes from use as flavouring agents

The Committee previously considered the potential combined intake of this group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters, and no safety concerns were raised. As the MSDI values for the 12 additional flavouring agents in this group (Nos 2286–2297) are low (0.03–3 µg/day), they would make a negligible contribution to the combined intake of this group.

Consideration of secondary components

One flavouring agent in this group, *cis*-tridec-5-enal (No. 2296), has a minimum assay value of less than 95% (> 90% for the *cis*-isomer) (Annex 4). The major secondary component is *trans*-tridec-5-enal, which is present at more than 5%. The SPET value for *cis*-tridec-5-enal (No. 2296) is 90 µg/day, and 5% of this value is 5 µg/day (rounded from 4.5 µg/day). *trans*-Tridec-5-enal is structurally related to *cis*-tridec-5-enal, and both isomers are expected to be completely metabolized via the fatty acid pathway and the citric acid cycle to carbon dioxide and water. On this basis, *trans*-tridec-5-enal is not considered to raise a safety concern when consumed as a component of No. 2296 used as a flavouring agent at its current estimated dietary exposure.

Consideration of additional data on previously evaluated flavouring agents

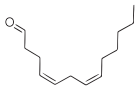
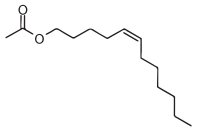
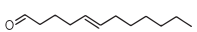
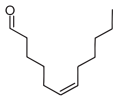
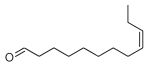
Summaries of unpublished study reports on acute toxicity from the ECHA database (Nos 330, 331, 336, 1623), genotoxicity (Nos 315, 336, 1639), and reproductive and developmental toxicity (Nos 315, 331) were submitted to the Committee by the sponsor for six previously evaluated flavouring agents. The Committee could not assess these studies in the absence of the original full study reports, and therefore did not include these studies in the present monograph.

Conclusions

Studies of hydrolysis, ADME, acute, short- and long-term toxicity, genotoxicity and developmental toxicity were available for the previous evaluations of 100 substances in this group of linear and branched-chain aliphatic, unsaturated and

Table 3.4

Summary of the results of safety evaluations of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters used as flavouring agents[a,b,c]

Flavouring agent	No.	CAS No. and structure	Step 4 Does the highest dietary exposure estimate exceed the threshold of toxicological concern?[d]	Step 5 Does a NOAEL exist for the flavouring agent or structural relative that provides an adequate margin of exposure?	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
Structural class I							
(4*Z*,7*Z*)-Trideca-4,7-dienal	2286	13552-95-9 	No	NR	–[e]	–	No safety concern
cis-5-Dodecenyl acetate	2287	16676-96-3 	No	NR	–[f]	–	No safety concern
trans-5-Dodecenal	2288	68820-34-8 	No	NR	–[e]	–	No safety concern
cis-6-Dodecenal	2289	126745-61-7 	No	NR	–[e]	–	No safety concern
cis-9-Dodecenal	2290	56219-03-5 	No	NR	–[e]	–	No safety concern

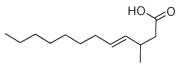
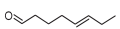
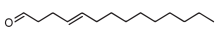
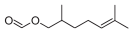
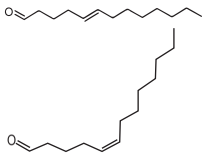
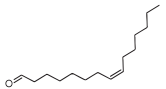
Flavouring agent	No.	CAS No. and structure	Step 4 Does the highest dietary exposure estimate exceed the threshold of toxicological concern?[d]	Step 5 Does a NOAEL exist for the flavouring agent or structural relative that provides an adequate margin of exposure?	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
(*E*)-3-Methyl-4-dodecenoic acid	2291	2088117-65-9 	No	NR	–[g]	–	No safety concern
trans-5-Octenal	2292	41547-29-9 	No	NR	–[e]	–	No safety concern
trans-Tetradec-4-enal	2293	115018-39-8 	No	NR	–[e]	–	No safety concern
2,6-Dimethylheptenyl formate	2294	2119671-25-7 	No	NR	–[f]	–	No safety concern
(*Z*)-9-Dodecenoic acid	2295	22032-47-9 	No	NR	–[g]	–	No safety concern
cis-Tridec-5-enal	2296	68820-38-2; 2112754-74-0 	No	NR	–[e]	–	No safety concern

Table 3.4 (continued)

Flavouring agent	No.	CAS No. and structure	Step 4 Does the highest dietary exposure estimate exceed the threshold of toxicological concern?[d]	Step 5 Does a NOAEL exist for the flavouring agent or structural relative that provides an adequate margin of exposure?	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
(*Z*)-8-Pentadecenal	2297	65398-36-9 	No	NR	–[e]	–	No safety concern

CAS: Chemical Abstracts Service; NOAEL: no-observed-adverse-effect level; NR: not relevant because the highest estimated dietary exposure does not exceed the threshold of concern for the relevant structural class.

[a] A total of 100 flavouring agents in this group were previously evaluated by the Committee at the Fifty-first, Sixty-first, Sixty-eighth, Seventy-sixth and Eighty-sixth meetings *(17–21)*.

[b] *Step 1*: Genotoxicity data on the flavouring agents in this group do not raise concerns for genotoxicity.

[c] *Step 2*: All 12 newly evaluated flavouring agents (Nos 2286–2297) belong to structural class I.

[d] The threshold for human dietary exposure for structural class I is 1800 µg/day. The dietary exposure values listed represent the highest estimated dietary exposures calculated using either the SPET or the MSDI method. The SPET gave the highest estimated dietary exposure in each case.

[e] Aldehydes are expected to be oxidized to their corresponding carboxylic acids, which are completely metabolized via the fatty acid pathway and the tricarboxylic acid cycle to carbon dioxide and water.

[f] Esters are expected to undergo hydrolysis to their corresponding primary alcohols and carboxylic acids. The resulting alcohols are oxidized to their corresponding aldehydes and carboxylic acids, which are completely metabolized via the fatty acid pathway and the tricarboxylic acid cycle to carbon dioxide and water.

[g] Carboxylic acids are completely metabolized via the fatty acid pathway and the tricarboxylic acid cycle to carbon dioxide and water.

unconjugated alcohols, aldehydes, acids and related esters. None of the agents in this group raised a safety concern.

For the evaluation of the 13 additional flavouring agents in this group, studies of genotoxicity were available for four of the agents (Nos 2291, 2295, 2297 and 2298). The Committee concluded that 12 of the 13 flavouring agents (Nos 2286–2297) would not raise any safety concerns at the current estimated dietary exposures. The studies of genotoxicity available for 4,7-decadienal (mixture of isomers) (No. 2298) indicated positive results in vitro, which did not allow the evaluation to be completed at this meeting. The Committee concluded that further investigation is required to demonstrate the absence of clastogenicity.

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 *cis*-3-hexen-1-ol (No. 315), 10-undecenal (No. 330), 10-undecenoic acid (No. 331), *cis*-3-hexenyl cis-3-hexenoate (No. 336), 5-hexenol (No. 1623) and methyl 10-undecenoate (No. 1639) within 2 years (i.e. by December 2025) so that a re-evaluation of these previously evaluated compounds can be completed.

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

3.1.3 Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids

Introduction

At the request of the CCFA at its Fifty-second session *(1)*, the Committee evaluated an additional eight flavouring agents in the group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids. The additional agents included six aldehydes (Nos 2299, 2301, 2303–2306) and two acids (Nos 2300 and 2302). None of these eight flavouring agents has previously been evaluated by the Committee. All eight flavouring agents have been reported to occur naturally in many foodstuffs and drinks.

At its Forty-ninth meeting, the Committee evaluated 38 flavouring agents from the group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids *(16)*. The Committee concluded that none of the 38 flavouring agents would raise a safety concern at their respective estimated per capita dietary exposure.

Because the Committee considered that the use of acetaldehyde (No. 80) as a structural analogue in the safety assessment of flavouring substances would require further evaluation, the Committee was unable to complete the evaluation of Nos 2299, 2303 and 2306. The additional five members of this group evaluated at the present meeting, according to the revised Procedure for the Safety Evaluation of Flavouring Agents *(3)*, were therefore pentadecanoic acid (No. 2300), tridecanal (No. 2301), tridecanoic acid (No. 2302), acetaldehyde di-isobutyl acetal (No. 2304) and acetaldehyde ethyl isobutyl acetal (No. 2305).

A literature search of toxicological data was conducted in Scopus, PubMed, ADRIS and PubChem using the names and CAS numbers of the flavouring agents under evaluation in this group. This search did not identify any publications that provided data relevant to this evaluation.

The Committee also considered additional submitted data for five previously evaluated flavouring agents (Nos 80, 85, 86, 93 and 110) in this group.

Assessment of dietary exposure

Annual volumes of production of this group of flavouring agents and the daily dietary exposures calculated using both the MSDI method and the SPET are summarized in Table 3.5 *(6–9, 34)*.

The total annual production volume of the five additional flavouring agents belonging to the group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids is 1.3 kg in Japan, 202 kg in the USA and 200 kg in Europe *(6,7)*. More than 99% of annual production volumes in the USA and in Europe are accounted for by acetaldehyde di-isobutyl acetal (No. 2304) and acetaldehyde ethyl isobutyl acetal (No. 2305). More than 60% of the total annual production volume in Japan is accounted for by pentadecanoic acid (No. 2300).

Dietary exposures were estimated by both the SPET and the MSDI method, with the highest exposure values reported in Table 3.5 *(6–9,34)*. The SPET and MSDI method exposure values are in the range of 1.6–7500 µg/day and 0.03–10 µg/day, respectively. The estimated daily dietary exposure was highest for acetaldehyde di-isobutyl acetal (No. 2304) at 7500 µg/day, the SPET value for non-alcoholic soft beverages.

Absorption, distribution, metabolism and elimination

Information on the ADME of the flavouring agents belonging to the group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids is described in the monograph of the Forty-ninth meeting *(10)*. Briefly, linear aliphatic acyclic alcohols, aldehydes and carboxylic acids are readily absorbed from the gastrointestinal tract. Their half-lives in plasma are difficult to measure

Table 3.5

Annual volumes of production and daily dietary exposures of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids used as flavouring agents in Japan, the USA and Europe

Flavouring agent (No.)	Most recent annual volume of production (kg)[a]	Dietary exposure				Annual volume of consumption via natural occurrence in foods (kg)[d]	Consumption ratio[e]
		MSDI[b]		SPET[c]			
		µg/day	µg/kg bw per day	µg/day	µg/kg bw per day		
Pentadecanoic acid (2300)				**40**	**0.7**	**300 960[f]**	**NR**
Japan	0.8	0.2	0.004				
USA	NR	ND	ND				
Europe	NR	ND	ND				
Tridecanal (2301)				**300**	**5**	**1290[f]**	**645**
Japan	0.4	0.1	0.002				
USA	2	0.2	0.003				
Europe	NR	ND	ND				
Tridecanoic acid (2302)				**1.6**	**0.03**	**37 640[f]**	**NR**
Japan	0.1	0.03	0.000 5				
USA	NR	ND	ND				
Europe	NR	ND	ND				
Acetaldehyde di-isobutyl acetal (2304)				**7500**	**125**	**203[f]**	**2**
Japan	NR	ND	ND				
USA	100	10	0.2				
Europe	100	9	0.1				
Acetaldehyde ethyl isobutyl acetal (2305)				**6000**	**100**	**203[f]**	**2**
Japan	NR	ND	ND				
USA	100	10	0.2				
Europe	100	9	0.1				
Total							
Japan	1.3						
USA	202						
Europe	200						

MSDI: maximized survey-derived intake; ND: no intake data reported; NR: no volume data reported; SPET: single portion exposure technique; US FDA: United States Food and Drug Administration.

[a] From the International Organization for the Flavor Industry *(6,7)*. Values greater than 0 kg but less than 0.1 kg were reported as 0.1 kg.

[b] Exposure (µg/person per day) calculated as: [(annual volume, kg) × (1×10^9 µg/kg)]/(population × survey correction factor × 365 days), where population (10%, "eaters only") = 12×10^6 for Japan, 33×10^6 for the USA and 40×10^6 for Europe, with correction factor = 0.8 from the IOFI Global Poundage Survey or private communication to FEMA representing the assumption that only 80% of the annual flavour volume was reported *(6,7)*. Intake (µg/kg bw per day) calculated as: (µg/person per day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[c] SPET (µg/person per day) calculated as: (US FDA standard food portion, g/day) × highest usual use level *(8)*. The dietary exposure from the single food category leading to the highest dietary exposure from one portion is taken as the SPET estimate. SPET (µg/kg bw per day) calculated as: (µg/day)/body weight, where body weight = 60 kg. Slight variations may occur from rounding.

[d] Quantitative data for the USA reported by Stofberg and Grundschober *(9)*.

[e] The consumption ratio is calculated as: (annual volume of consumption via natural occurrence in foods, kg)/(most recent annual volume of production as a flavouring agent, kg).

[f] Van Dongen & Donders *(34)*.

since many low-molecular-weight alcohols (e.g. ethanol), aldehydes and carboxylic acids (e.g. acetate and propionate) are endogenous in humans.

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

Step 1. There are no structural alerts for genotoxicity for the five additional flavouring agents (Nos 2300–2302, 2304 and 2305) in this group. Experimental specific genotoxicity data on the new flavouring agents and on previously evaluated flavouring agents in this group do not indicate a genotoxic potential.

Step 2. In applying the revised Procedure for the Safety Evaluation of Flavouring Agents to the five flavouring agents, the Committee assigned all five flavouring agents (Nos 2300–2302, 2304 and 2305) to structural class I *(13)*.

Step 3. Dietary exposures were estimated with both the MSDI method and the SPET and are presented in Table 3.5 *(16,35)*.

Step 4. The highest estimated dietary exposures for three flavouring agents (Nos 2300–2302) in structural class I are below the threshold of concern (i.e. 1800 µg/person per day for class I). The Committee concluded that these three flavouring agents would not raise any safety concerns at current estimated dietary exposures.

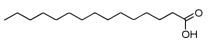
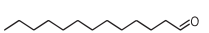
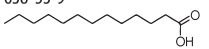
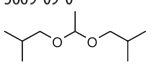
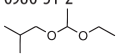
The highest estimated dietary exposures for the remaining two flavouring agents in structural class I (Nos 2304 and 2305) are above the threshold of concern (i.e. 1800 µg/person per day for class I). Their evaluation proceeded to Step 5 of the revised Procedure.

Step 5. For acetaldehyde di-isobutyl acetal (No. 2304), the NOAEL of 1251 mg/kg bw per day for the structurally related substance isobutyl alcohol (No. 251) in a 90-day study in rats *(35)* provides an adequate MOE (10 008) relative to the SPET estimate of 7500 µg/day. The same NOAEL of 1251 mg/kg bw per day for isobutyl alcohol (No. 251) is appropriate for assessing the structurally related flavouring agent acetaldehyde ethyl isobutyl acetal (No. 2305); it provides an adequate MOE (12 510) relative to the SPET estimate of 6000 µg/day for this substance when used as a flavouring agent (Table 3.6).

Flavouring agents Nos 2303 and 2306 are of structural class I, and flavouring agent No. 2299 is of structural class III. All three flavouring agents exceed their respective threshold of toxicological concern (TTC) (i.e. 1800 µg/kg bw per day for Nos 2303 and 2306; 90 µg/kg bw per day for No. 2299). The structural analogue proposed to complete the evaluation of those three flavouring agents that exceed the TTC was acetaldehyde (No. 80) *(16)*. However, the Committee was aware of the concerns with regards to acetaldehyde arising from the International Agency for Research on Cancer (IARC) evaluation of the consumption of alcoholic beverages *(36)*. IARC concluded that acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans

Table 3.6

Summary of the results of safety evaluations of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids used as flavouring agents[a,b,c]

Flavouring agent	No.	CAS No. and structure	Step 4 Does the highest dietary exposure estimate exceed the threshold of toxicological concern?[d]	Step 5 Does a NOAEL exist for the flavouring agent or a structural relative that provides an adequate margin of exposure?[e]	Comments on predicted metabolism	Structural relative name (No.) and structure	Conclusion based on current estimated dietary exposure
Structural class I							
Pentadecanoic acid	2300	1002-84-2 	No	NR	–[f]	–	No safety concern
Tridecanal	2301	10486-19-8 	No	NR	–[f]	–	No safety concern
Tridecanoic acid	2302	638-53-9 	No	NR	–[f]	–	No safety concern
Acetaldehyde di-isobutyl acetal	2304	5669-09-0 	Yes, SPET: 7500 µg/day	Yes, the NOAEL of 1251 mg/kg bw per day for structural related isobutyl alcohol (No. 251) in a 90-day study in rats *(35)* is 10 008 times the estimated dietary exposure of No. 2304 when used as a flavouring agent	–[g]	Isobutyl alcohol (No. 251) 	No safety concern
Acetaldehyde ethyl isobutyl acetal	2305	6986-51-2 	Yes, SPET: 6000 µg/day	Yes, the NOAEL of 1251 mg/kg bw per day for structural related isobutyl alcohol (No. 251) in a 90-day study in rats *(35)* is 12 510 times the estimated dietary exposure of No. 2305 when used as a flavouring agent	–[g]	Isobutyl alcohol (No. 251) 	No safety concern

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

[a] In total, 38 flavouring agents in this group were previously evaluated by the Committee at its Forty-ninth meeting *(16)*.

[b] *Step 1*: The weight of evidence from the chemical-specific data on genotoxicity for one (No. 2301) of the above five flavouring agents indicates that it is not a potential DNA-reactive carcinogen.

[c] *Step 2*: All five flavouring agents are in structural class I.

[d] The thresholds of toxicological concern for structural class I, II and III are 1800, 540 and 90 µg/day, respectively. All 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 highest estimate for each flavouring agent. All dietary intake values are expressed in µg/day.

[e] The margin of exposure was calculated based on the highest daily per capita intake calculated either by SPET or MSDI.

Table 3.6 (continued)

[f] In general, saturated linear primary alcohols are rapidly oxidized in vivo to the corresponding aldehyde in the presence of alcohol dehydrogenase (ADH). The resulting aldehyde undergoes rapid in vivo oxidation to the corresponding carboxylic acid, which participates in normal fatty acid metabolism. Even-numbered carbon acids (e.g. hexanoic acid) continue to be cleaved to acetyl CoA while odd-numbered carbon acids (e.g. pentanoic acid) yield acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly, while propionyl CoA is methylated to R-methylmalonyl CoA, epimerized to the S-isomer and finally isomerized to succinyl CoA via the action of methylmalonyl CoA mutase. Succinyl CoA then enters the tricarboxylic acid cycle.

[g] Acetals are readily hydrolysed in the acidic environment of the stomach, intestinal fluid or in the liver to yield the component alcohol and aldehyde. The resulting alcohol can be readily oxidized to corresponding acid and can undergo β-oxidative cleavage.

(Group 1). The Committee therefore considered that the use of acetaldehyde (No. 80) as a structural analogue in the safety assessment of flavouring substances would require further evaluation. Furthermore, the Committee concluded that the use of acetaldehyde (No. 80) as a flavouring agent requires re-evaluation.

Consideration of combined intakes from use as flavouring agents

The Committee previously considered the potential combined intake of this group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids, and no safety concerns were raised. As the MSDI values for the five additional flavouring agents in this group (Nos 2300–2302, 2304 and 2305) are low (0.03–10 μg/day), they would make a negligible contribution to the combined intake of this group. In the USA, the available quantitative data indicate that the dietary consumption of the saturated linear aliphatic alcohols, aldehydes and acids considered here from naturally occurring sources exceeds consumption from their use as flavouring agents *(9,34)*.

Consideration of additional data on previously evaluated flavouring agents

The Committee considered additional data on five of the 38 previously evaluated flavouring agents in this group. Studies of short-term toxicity (No. 110), long-term toxicity and carcinogenicity (No. 80), genotoxicity (Nos 86, 93, 110), and reproductive and developmental toxicity (No. 85) were available. The results of these studies support the conclusions of the previous evaluations of the absence of any safety concerns at the estimated dietary exposures.

Conclusions

Studies of genotoxicity were available for three substances (Nos 86, 93, 110) in this group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids evaluated previously *(16)*. The Committee concluded that none of the previously evaluated flavouring agents in this group raised a safety concern.

For the evaluation of five new flavouring agents, two studies of genotoxicity (No. 2301) were available. The Committee concluded that the five flavouring agents (Nos 2300–2302, 2304 and 2305) would not raise any safety concerns at the current estimated dietary exposures.

The Committee considered that the use of acetaldehyde (No. 80) as a structural analogue in the safety assessment of flavouring substances would require further evaluation. The Committee was therefore unable to complete the evaluation of Nos 2299, 2303 and 2306. The Committee also concluded that the use of acetaldehyde (No. 80) as a flavouring agent requires re-evaluation.

An addendum to the monograph was prepared.

Recommendations

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

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

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

3.2 Specifications of identity and purity

3.2.1 New specifications (from Sections 3.1.1–3.1.3)

The Committee received information in support of the establishment of full specifications for 26 flavourings: five flavourings of the group of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (Nos 2307–2311); 13 flavouring agents of the group of linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters (Nos 2286–2298); and eight flavouring agents of the group of saturated aliphatic acyclic linear primary alcohols, aldehydes and acids (Nos 2299–2306). No. 2307, succinic acid, had previously been evaluated as a food additive, and was therefore not included in this evaluation.

Full specifications were prepared for 21 flavouring agents. Tentative specifications were prepared for four flavouring agents – No. 2298 in linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters; and Nos 2299, 2303 and 2306 in saturated aliphatic

acyclic linear primary alcohols, aldehydes and acids – as the safety evaluations for these flavouring agents were not completed.

Recommendations

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

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4. Corrigenda

The requests for corrections in Table 4.1, reported to the JECFA Secretariat, were evaluated at the Ninety-seventh JECFA meeting and found to be necessary. Corrections will be made only in the online database for specifications.

Table 4.1
Requests for corrections submitted to the JECFA Secretariat

Substance	Original text	Revised text	Additional information
Modified starches	Table on page 3 of specifications *(1)* Page 13 CAS numbers 601464-73-0 (Amylopectin, acetate) Page 22 Increase temperature to 250 °C at a rate of 14.5 °C/s. Hold at 250 °C for 1 min Page 22 Split/splitless injector settings Injector temperature: 250 °C Injection mode: splitless for 0.8 min	See revised table (Table 4.2) below CAS numbers 60164-73-0 (Amylopectin, acetate) Increase temperature to 250 °C at a rate of 14.5 °C/min, hold at 250 °C for 1 min Split/splitless injector settings Injector temperature: 250 °C Injection mode: splitless for 0.8 min Recommended liner of at least: 870 µL	Revised table (Table 4.2) is in alignment with specifications
Pullulan	Chemical formula: $(C_6H_{10}O_5)_x$ Characteristics: Mono-, di- and oligosaccharides Not more than 10% (expressed as glucose) Purity tests: Mono-, di- and oligosaccharides Procedure – Weigh accurately 0.8 g sample and dissolve in water to make 100 ml (stock solution). Method of assay: P(%) = 100 – (L+C) where L is loss on drying; and C is taken from the calculation for mono-, di- and oligosaccharides.	Chemical formula: $(C_{36}H_{60}O_{30})_n$ Characteristics: Mono-, di- and oligosaccharides Not more than 10% (expressed as glucose), on the dried basis Purity tests: Mono-, di- and oligosaccharides Procedure – Weigh accurately 0.8 g sample previously dried and dissolve in water to make 100 ml (stock solution). Method of assay: P(%) = [100 – C] where C is taken from the calculation for mono-, di- and oligosaccharides.	
Spirulina extract (INS 134)	Method of assay: Calculate the allophycocyanin content (percent, w/w) as follows: TaPC = [(0.180 x A620) – (0.042 x A650) x V1 x 100] / W1	Method of assay: Calculate the allophycocyanin content (percent, w/w) as follows: TaPC = [(0.180 x A650) – (0.042 x A620) x V1 x 100] / W1	

Table 4.2
Modified starches *(1)*; revised table

Summary table							
GENERAL REQUIREMENTS							
	IDENTIFICATION			**PURITY**			
Solubility	**Microscopy**	**Iodine Stain**	**Copper Reduction**	**Loss on Drying**	**Lead**	**Microbiological Criteria**	**Sulfur dioxide**
Insoluble in cold water, **if not pre-gelatinised.**	Granular structure typical of the starch source	Colour from dark blue to orange-red after addition of iodine TS	Red precipitate after addition of hot alkaline cupric tartrate to a test sample refluxed under acidic condition	Cereal starch ≤15.0%; Potato starch: ≤21.0%; Other starches: ≤18.0%	≤0.2mg/kg d.w. Pb (≤0.1 mg/kg) for starch sodium octenylsuccinate for infant formula	Aerobic Plate Count: ≤100,000 CFU/g; Yeasts and molds: ≤1,000 CFU/g; Total Coliforms: ≤100 CFU/g;	Modified cereal starches: ≤50 mg/kg d.w.; Other modified starches ≤10 mg/kg d.w.
SPECIFIC REQUIREMENTS							
Modified Starch	**Annex**	**IDENTIFICATION**		**PURITY**			
Dextrin roasted starch (INS 1400)	1	Dispersion test		No additional			
Acid treated starch (INS 1401)	1	Dispersion test		No additional			
Alkaline treated starch (INS 1402)	1	Dispersion test		No additional			
Bleached starch (INS 1403)	2	No additional		Carboxyl groups (≤0.1% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2			
Oxidized starch (INS 1404)	5	Hypochlorite oxidized starch		Carboxyl groups (≤1.3% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2			
Enzyme-treated starch (INS 1405)	1	Dispersion index ~~(Information Required); Reducing sugars (Information Required~~) test		No additional			
Monostarch phosphate (INS 1410)	3	Phosphate groups		Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w for other starches)			
Distarch phosphate (INS 1412)	3	Crosslinking		Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w. for other starches)			
Phosphated distarch phosphate (INS 1413)	3	Crosslinking		Phosphate (≤0.5% d.w. for potato or wheat starches; ≤0.4% d.w. for other starches)			
Acetylated distarch phosphate (INS 1414)	3, 4	Acetyl group; Ester group; Crosslinking		Phosphate (≤0.14% d.w. for potato or wheat starches; ≤0.04% d.w. for other starches) Acetyl groups (≤2.5% d.w.); ~~Ester groups (≤0.5% d.w.)~~			
Starch acetate (INS 1420)	4	Acetyl group; Ester group		Acetyl groups (≤2.5% d.w.); ~~Ester groups (≤0.5% d.w.)~~			
Acetylated distarch adipate (INS 1422)	4, 8	Acetyl group; Ester group; Crosslinking		Acetyl groups (≤2.5% d.w.); Vinyl acetate (≤0.1 mg/kg); ~~Ester groups (≤0.5%d.w.)~~ Adipate groups (≤0.135% d.w.); Residual free adipic acid (≤0.025% d.w.)			
Hydroxypropyl starch (INS 1440)	7	Hydroxypropyl ether groups		Hydroxypropyl groups (≤7.0% d.w.); Propylene chlorohydrins (≤1 mg/kg d.w.)			

Modified Starch	Annex	IDENTIFICATION	PURITY
Hydroxypropyl distarch phosphate (INS 1442)	3, 7	Hydroxypropyl ether groups; Crosslinking	Phosphate (≤0.14% d.w. for potato or wheat starches; ≤0.04% d.w. for other starches) Hydroxypropyl groups (≤7.0% d.w.); Propylene chlorohydrins (≤1 mg/kg d.w.)
Starch sodium octenylsuccinate (INS 1450)	6	No additional	Octenylsuccinyl groups (≤3% d.w.); Residual free octenylsuccinic acid (≤0.3% d.w.);
Acetylated oxidized starch (INS 1451)	4, 5	Acetyl group	Acetyl groups (≤2.5% d.w.); Vinyl acetate (≤0.1 mg/kg); ~~Ester groups (≤ 0.5% d.w.)~~ Carboxyl groups (≤1.3% d.w.); Residual oxidizing substances < 180 mg/kg calculated as H_2O_2

Reference

1. Online edition. Steviol glycosides (Framework) specification. Monograph 26; 2021 (https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/, accessed 15 November 2023).

Annex 1

Meeting agenda

Food and Agriculture Organization of the United Nations

World Health Organization

97th JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
Rome, 31 October–9 November 2023

1. Opening (Dr Divine Njie, FAO and Dr Moez Sanaa, WHO)

2. Declarations of interest (information by the Secretariat on any declared interests and discussion)

3. Election of Chairperson and Vice-Chairperson, appointment of Rapporteurs

4. Adoption of the agenda

5. Matters of interest arising from the Fifty-third session of the Codex Committee on Food Additives (Ms Lingping Zhang)

6. Critical issues and questions from Working Papers (first brief round of discussion on all subjects to inform the full committee)

7. Evaluations
   - 7.1. Food additives (full evaluation)
     - a. Titanium dioxide (INS 171)
   - 7.2. Flavours (full evaluation)
     - a. Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (5 substances)
     - b. Linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters (13 substances)
     - c. Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids (8 substances)

8. Other matters as may be brought forth by the Committee during discussions at the meeting

9. Errata/corrigenda

10. Report adoption

Annex 2

Toxicological information and information on specifications

Table A2.1

Flavouring agents evaluated by the revised Procedure for the Safety Evaluation of Flavouring Agents: aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups

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

N: new specifications.

Table A2.2

Flavouring agents evaluated by the revised Procedure for the Safety Evaluation of Flavouring Agents: linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters

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

N: new specifications.

Table A2.3

Flavouring agents evaluated by the revised Procedure for the Safety Evaluation of Flavouring Agents: saturated aliphatic acyclic linear primary alcohols, aldehydes and acids

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

N: new specifications.

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.

25. A review of the technological efficacy of some antimicrobial agents. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.

26. Evaluation of food additives: some enzymes, modified starches, and certain other substances: Toxicological evaluations and specifications and a review of the technological efficacy of some

antioxidants (Fifteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. Toxicological evaluation of some enzymes, modified starches, and certain other substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.

28. Specifications for the identity and purity of some enzymes and certain other substances. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.

29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.

30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.

31. Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbamate, and octyl gallate. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.

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33. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents. FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.

34. Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers. FAO Food and Nutrition Paper, No. 4, 1978.

35. Evaluation of certain food additives (Eighteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.

36. Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.

37. Specifications for the identity and purity of some food colours, enhancers, thickening agents, and certain food additives. FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.

38. Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances (Nineteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.

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41. Evaluation of certain food additives (Twentieth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Food and Nutrition Meetings Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.

42. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 10, 1976.

43. Specifications for the identity and purity of some food additives. FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additives Series, No. 11, 1977.

44. Evaluation of certain food additives (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.

45. Summary of toxicological data of certain food additives. WHO Food Additives Series, No. 12, 1977.

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48. Summary of toxicological data of certain food additives and contaminants. WHO Food Additives Series, No. 13, 1978.

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63. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.

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113. Evaluation of certain veterinary drug residues in food (Forty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 855, 1995, and corrigendum.

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119. Evaluation of certain veterinary drug residues in food (Forty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 864, 1996.

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Annex 4

Summary of the safety evaluation of the secondary components for flavouring agents 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
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups				
2309	Ethyl 5-formyloxydecanoate	> 91%	4% δ-decalactone (No. 232); 2% ethyl-5-acetoxydecanoate	δ-Decalactone (No. 232) was previously evaluated by the Committee as not raising a safety concern at estimated dietary exposure when used as a flavouring agent. The SPET value for No. 2309 is 1880 µg/day and 2% of this value (concentration of ethyl-5-acetoxydecanoate) is 38 µg/day, which is below the class III threshold of toxicological concern.
2310	Mixture of ricinoleic acid, linoleic acid and oleic acid	> 92%	2–3% stearic acid (No. 116); and 2–3% palmitic acid (No. 115)	All secondary components of No. 2310 were previously evaluated by the Committee as not raising any safety concerns at estimated dietary exposure when used as a flavouring agent.
Linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters				
2296	*cis*-Tridec-5-enal	> 90% *cis*-tridec-5-enal	Secondary constituent: 5% *trans*-tridec-5-enal	The SPET value for No. 2296 is 90 µg/day and 5% of this value (concentration of *trans*-tridec-5-enal) is 5 µg/day. *Trans*-tridec-5-enal is structurally related to *cis*-tridec-5-enal and both isomers are expected to be completely metabolized via the fatty acid pathway and the citric acid cycle to carbon dioxide and water. On this basis, *trans*-tridec-5-enal does not raise a safety concern when consumed as a component of No. 2296 used as a flavouring agent at its current estimated dietary exposure.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

Evaluation of certain veterinary drug residues in food
Ninety-fourth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1041, 2022 (107 pages)

Evaluation of certain food additives
Ninety-second report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1037, 2022 (76 pages)

Safety evaluation of certain food additives
Ninety-second meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 83, 2022 (152 pages)

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Ninety-first report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1036, 2022 (126 pages)

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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 titanium dioxide (TiO_2 or INS 171), including the identification of TiO_2 test materials that were considered representative of INS 171.

Summaries are also provided of the safety evaluations of three groups of flavouring agents: aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups; linear and branched-chain aliphatic, unsaturated and unconjugated alcohols, aldehydes, acids and related esters; and saturated aliphatic acyclic linear primary alcohols, aldehydes and acids. New specifications were prepared for 4, 12 and 5 flavouring agents from these groups, respectively.

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.

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