WHO Technical Report Series

983

Evaluation of certain food additives and contaminants

Seventy-seventh report of the
Joint FAO/WHO Expert Committee on
Food Additives

Food and Agriculture Organization of the United Nations

World Health Organization

World Health Organization

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WHO Library Cataloguing-in-Publication Data:

Evaluation of certain food additives and contaminants: seventy-seventh report of the Joint FAO/WHO Expert Committee on Food Additives.

(WHO technical report series ; no. 983)

1.Food additives - analysis. 2.Food additives - toxicity. 3.Food contaminants - analysis. 4.Food contaminants - toxicity. 5.Diet - adverse effects. 6.Risk assessment. I.World Health Organization. II.Food and Agriculture Organization of the United Nations. III.Joint FAO/WHO Expert Committee on Food Additives. Meeting (77th: 2013, Rome, Italy). IV.Series.

ISBN 978 92 4 120983 0 (NLM classification: WA 712)

ISSN 0512-3054

Typeset in India

Printed in Malta

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Rome, 4–13 June 2013

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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Safety evaluation of certain food additives and contaminants.

WHO Food Additives Series, No. 68, 2013.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications. FAO JECFA Monographs 14, 2013.

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met in Rome, Italy, from 4 to 13 June 2013. The meeting was opened by Dr Ren Wang, the Assistant Director-General for the Agriculture and Consumer Protection Department of the Food and Agriculture Organization of the United Nations (FAO), on behalf of the Directors-General of FAO and the World Health Organization (WHO).

Dr Wang informed the meeting of the future strategic direction of FAO following a review guided by the Director-General upon taking office in January 2012. He also referred to the forthcoming FAO Conference at which Member countries will be asked to endorse the new direction and future priorities. Dr Wang emphasized that the scientific advice provided by JECFA contributes to food safety and underpins international standards of the Codex Alimentarius Commission, which is celebrating its fiftieth year. He expressed his sincere appreciation to the experts for putting their time and expertise at the service of FAO and WHO.

1.1 Declarations of interests

The Secretariat informed the Committee that all experts participating in the seventy-seventh meeting had completed declaration of interests forms. A potential conflict was identified for Dr Yusai Ito. Data submitted for the revision of specifications on annatto extracts were conducted in his laboratory. Dr Ito did not participate in the discussion on this matter.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been 76 previous meetings of the Committee (Annex 1). The present meeting was convened on the basis of a recommendation made at the seventy-sixth meeting (Annex 1, reference *211*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives (section 2);

— to review and prepare specifications for certain food additives (section 3 and Annex 2);

— to undertake toxicological evaluations of certain food additives (section 3 and Annex 2);

— to undertake a dietary exposure assessment of one food contaminant (section 4 and Annex 2).

2.1 Modification of the agenda

The agenda was modified to include 3-phytase from *Aspergillus niger* expressed in *Aspergillus niger* for modification of the method that is listed in the specifications, following a request from the Forty-fifth Session of the Codex Committee on Food Additives (CCFA) (*2*).

2.2 Report from the Forty-fifth Session of the Codex Committee on Food Additives (CCFA)

The Codex Secretariat provided the Committee with an update of the work of CCFA since the seventy-sixth meeting of JECFA (Annex 1, reference *211*), including the main achievements and outputs of the Forty-fifth Session of CCFA (*2*).

Following the outcome of the seventy-sixth meeting of JECFA, the Forty-fifth Session of CCFA invited Member countries to submit to JECFA (i) data on actual use levels for magnesium-containing food additives and for phosphate-containing

food additives; and (ii) new information on the toxicological effects of phosphate salts, expressed as phosphorus. It also recommended the inclusion of the three enzymes evaluated by the seventy-sixth meeting of JECFA in the database on processing aids, prepared by China; and agreed to revoke the specifications of mineral oil (medium and low viscosity) classes II and III (International Numbering System [INS] 905 e,f,g) and to revise the name and adopt the new specifications of INS 905e mineral oil, medium viscosity.

The Forty-fifth Session of CCFA finalized work on more than 600 provisions of the *Codex General Standard for Food Additives* (GSFA) (*3*) and concluded the revision of the provisions of aluminium-containing food additives, as recommended by the seventy-fourth meeting of JECFA (Annex 1, reference *205*). In addition, CCFA recommended the adoption of new and revised specifications for the identity and purity of 8 food additives and 93 flavourings, prepared by the seventy-sixth meeting of JECFA; and amendments to the INS. With regard to ammonium aluminium silicate, pearlescent pigment, CCFA agreed to consider its inclusion in the INS in light of the outcome of the current meeting of JECFA.

The Forty-fifth Session of CCFA agreed on a revised priority list of compounds for evaluation (or re-evaluation) by JECFA, which includes 19 food additives and 124 flavourings. Because of the large number of substances on the priority list, CCFA assigned high priority to 10 of them. CCFA continued its discussion on the prioritized list of 107 food colours evaluated by JECFA and agreed to consider at its next session a document identifying different options for the use of the outcomes of the prioritization exercise and other feasible steps to identify compounds for re-evaluation by JECFA.

The Forty-fifth Session of CCFA further agreed to consider at its next session a document regarding the inclusion of secondary additives in specifications and the need to develop guidance on how to address their use and to start work on the revision of the Codex *Guidelines for Simple Evaluation of Food Additive Intake* (*4*), which aims to assist Member countries, especially developing countries, in their assessment of dietary exposure to food additives by reflecting current procedures in place to carry out such work in a simple way.

2.3 Report from the Seventh Session of the Codex Committee on Contaminants in Foods (CCCF)

The Codex Secretariat informed the Committee about the status of work on cadmium contamination in foods in CCCF since the last re-evaluation of cadmium by JECFA at its seventy-third meeting (Annex 1, reference *202*).

Based on the outcome of this evaluation, the Fifth Session of CCCF (*5*) agreed that there was no need to revise the maximum levels (MLs) for cadmium in the *Codex General Standard for Contaminants and Toxins in Food and*

Feed (*6*) or the provisions in the *Code of Practice Concerning Source Directed Measures to Reduce Contamination of Food with Chemicals* (*7*).

The Sixth Session of CCCF (*8*) considered a request for the establishment of MLs for cadmium in cocoa and cocoa products and decided to include cadmium on the priority list for evaluation by JECFA for an assessment of exposure from cocoa and cocoa products. The outcome of the assessment will be considered by the Eighth Session of CCCF (in 2014) to decide upon new work on the establishment of MLs for cadmium in cocoa and cocoa products or any other appropriate risk management options available.

2.4 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives, the Committee took into consideration the principles established and contained in the publication, Environmental Health Criteria, No. 240, *Principles and Methods for the Risk Assessment of Chemicals in Food*, published in 2009 (*9*).

2.5 Food additive specifications

2.5.1 *Requirements for submission of analytical methods*

The Committee, while encouraging the use of analytical methods published in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*), noted that reference to specific methods of analysis should not be taken as precluding the use of other methods, provided these methods give results of equivalent accuracy and specificity to those quoted. In order to assess and ensure the accuracy and reliability of the data submitted, the Committee recommends the use of methods that are appropriately validated. It also recommends that in relevant cases, the detailed analytical method be provided, together with validation data, in response to specific JECFA calls for data.

2.5.2 *Analytical method for the determination of residual solvents by headspace gas chromatography*

The Committee at its current meeting noted that the specifications for paprika extract and annatto extracts (solvent-extracted bixin and norbixin) contained the requirement for the determination of residual solvents. The use of the general method for residual solvent by headspace gas chromatography published in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*) was not suitable for the analysis of these substances because of their low solubility in water or methanol, listed as the solvents in the general method. The Committee agreed that alternative solvents were appropriate for the assay of these substances. The

Committee noted that there may be many substances that are insufficiently soluble in water or methanol or may contain methanol as a residual solvent from the manufacturing process. Therefore, the Committee recommended that the issue of the suitability of dissolution solvents for the determination of residual solvents in food additives be investigated at a future meeting.

2.5.3 *Analytical method for the determination of carbon number at 5% distillation point*

The Committee at its current meeting noted that the specifications for mineral oil (medium viscosity) contained a gas chromatographic method for the determination of carbon number at 5% distillation point that uses a packed column. The Committee noted that there was a general requirement to replace these methods with methods using capillary columns. A method using a wide-bore column was included in the revised specifications. The Committee also noted that the original method was included in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*) and recommended that a note be included in Volume 4 to indicate the availability of a newer method. The Committee further recommended that the suitability of this method for use in the analysis of similar substances be evaluated at a future meeting.

2.6 GEMS/Food consumption data

A WHO representative gave a presentation on the new Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) Cluster Diets to the Committee for consideration and discussion.

GEMS/Food diets have always reported per capita amounts of food (grams per person per day) available for consumption, derived from FAO Food Balance Sheet data, to give the best coverage for all countries in the world, as dietary information at the individual level from national nutrition surveys is not available for many countries. Cluster Diets were first developed in 1997 by grouping together countries that had geographical proximity as well as similar per capita data for 20 key foods. This resulted in 13 clusters of countries. The 13 Cluster Diets were revised in 2006 using updated FAO Food Balance Sheet data.

In 2012, a more sophisticated statistical approach was taken, whereby an expanded set of FAO Food Balance Sheet data for 415 primary or semi-processed food products for 179 countries for the period from 2002 to 2007 (data available on the FAO web site[1]) was used to make a substructure of 30

[1] http://faostat3.fao.org/home/index.html

consumption systems. Clusters of countries were then derived according to their consumption profiles, which could include one or more consumption systems (these could be a single food, such as cassava, cows' milk or rice, or groups of foods consumed together, such as yams and taro). As a consequence, the new Cluster Diets published by WHO in 2012 report on per capita food data for 17 clusters and replace the 13 Cluster Diets previously used (refer to Annex 3 for the grouping of countries in the 17 clusters). Data in these new Cluster Diets are available at three levels of detail: Level 1 for 17 major food groups (e.g. cereals and cereal products); Level 2 for 62 major food subgroups (e.g. cereal grains and flours); and Level 3 for 415 precise food subgroups (e.g. rice). Level 1 and Level 2 data are available on the WHO web site[2].

The Cluster Diets were considered to be most useful for application in international dietary exposure assessments where the chemical use or contamination level was likely to be similar worldwide—for example, for an additive used in beer. In that case, the type and amount of beverages available for consumption would be the main driver of differences in estimated mean population chronic dietary exposure to the food chemical across different clusters. For contaminants, if sufficient concentration data were available for foods at the individual country level, it would be preferable in most cases to derive summary concentration data for different foods for each cluster of countries, which could then be combined with the per capita consumption data to better estimate mean population chronic dietary exposure to the contaminant for each cluster.

In addition to Cluster Diets, which represent per capita food data, FAO and WHO have recently developed a database that collates food consumption data derived from individual records for 26 countries for use in chronic and acute dietary exposure assessments. The database was presented to the Committee, which noted that the data could be filtered by age class, country, food group (Level 2) and food item (Level 3), allowing users to focus on a specific data set, depending on the food chemical under consideration.

WHO also presented a study that aimed to determine the validity of the assumption that per capita food amounts (food available for consumption) would always be higher than the population mean amount of these foods derived from individual records from national nutrition surveys. The study compared information for four food groups from individual chronic food consumption data for 20 countries (for which data derived from individual records from surveys of 2 days' duration or more were available for adults or the general population) and per capita food data from the seven related

[2] http://www.who.int/entity/foodsafety/chem/Cluster_diets_2012_consumption.xls

Cluster Diets. Results from the study indicate that Cluster Diets do not systematically overestimate mean population food consumption amounts, as had been previously assumed (*9*). For example, for some processed or semi-processed foods (e.g. cereal products), the mean population food consumption amounts derived from national survey data were higher than the corresponding per capita amount from the relevant Cluster Diet. It was noted that direct comparisons between the two different types of data sets should be made with caution. In general, the overall sum of raw, semi-processed and processed food amounts for each food category at Level 2 tended to be similar in the relevant Cluster Diet and national food consumption data sets, indicating that there may be some discrepancies in the way in which raw versus processed foods had been classified in the different types of data sets.

The Committee welcomed the update of the WHO GEMS/Food Cluster Diets and the establishment of the food consumption database based on individual records from national surveys. The Committee applied the new Cluster Diets to evaluations at the present meeting, where relevant. The Committee noted that both the Cluster Diets and the available individual food consumption data for individual countries should be considered in international food chemical dietary exposure assessments, with expert judgement required to determine their appropriate use.

2.7 FOSCOLLAB

The WHO Secretariat presented to the Committee a global platform for food safety data and information called FOSCOLLAB (Food Safety Collaboration), which was recently launched on the WHO web site[3]. FOSCOLLAB enables users to access integrated data and information from the agriculture, food and human health areas to support decision-making in food safety.

FOSCOLLAB integrates data and information from various existing WHO databases, such as JECFA evaluations, GEMS/Food contaminant occurrence data (including level of detection and average concentration by commodity), GEMS/Food consumption data and WHO Collaborating Centres (including institutions working in the area of food contaminants), as well as the *Codex General Standard for Contaminants and Toxins in Food and Feed* (*6*). FOSCOLLAB has the capability to generate reports, which the user can export into specific formats, such as PDFs or slide presentations. FOSCOLLAB is built on a modular basis; it currently contains data on food contaminants and can be expanded in the future with information on other food chemicals, such as food additives and residues of pesticides and veterinary drugs. Common denominators between databases are the food category, hazard, country and year.

[3] http://www.who.int/foodsafety/foscollab/en/index.html

The WHO Secretariat invited the meeting participants to test FOSCOLLAB and provide comments for further improvements and to shape its scope and functionalities, including recommending possible data sets for future inclusion. The Committee appreciated this new tool and is looking forward to further developments.

3. Specific food additives

The Committee evaluated two food additives for the first time and re-evaluated five others. Seventeen food additives were considered for revision of specifications only. Information on the safety evaluations and specifications is summarized in Annex 2. Details on further toxicological studies and other information required for certain substances are summarized in section 5.

3.1 Safety evaluations

3.1.1 *Advantame*

Explanation

Advantame (*N*-[*N*-[3-(3-hydroxy-4-methoxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine-1-methyl ester, monohydrate, Chemical Abstracts Service No. 714229-20-6) is an *N*-substituted (aspartic acid portion) derivative of aspartame that is structurally similar to another *N*-substituted aspartame derivative, neotame.

Advantame has not previously been evaluated by the Committee. Although it was submitted at the seventy-sixth meeting (Annex 1, reference *211*) for consideration as a flavouring agent, the Committee decided that it would be inappropriate to evaluate this substance as a flavouring agent because it is a high-intensity sweetener, and evaluation as a food additive had been requested by the Forty-fourth Session of CCFA (*10*).

Chemical and technical considerations

Advantame appears as a white to yellow powder that is very slightly soluble in water and sparingly soluble in ethanol. It is used as a high-intensity, non-nutritive sweetener in tabletop sweeteners and in a wide variety of foods, and it has been demonstrated to be approximately 100 times sweeter than aspartame and approximately 20 000–37 000 times sweeter than sucrose.

Advantame is manufactured by *N*-alkylation of the aspartic acid portion of aspartame (L-α-aspartyl-L-phenylalanine methylester), with 3-(3-hydroxy-4-methoxyphenyl) propionaldehyde produced by selective catalytic

hydrogenation from 3-hydroxy-4-methoxycinnamaldehyde. Methanol and ethyl acetate are used as reaction solvents and recrystallization solvents in the preparation of advantame.

The final advantame product has a purity of not less than 97.0% on an anhydrous basis. Specifications of not more than 1.0% and 1.5% were set for the advantame acid (*N*-[*N*-[3-(3-hydroxy-4-methoxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine) and other related substances, respectively. In addition, the limits for residual solvents, residues on ignition and lead were specified.

Advantame slowly degrades under acidic conditions and at high temperature under baking conditions. The main degradation product is the advantame acid. In contrast to aspartame, advantame does not form the diketopiperazine derivative, as there is no free amino group to start the internal reaction of cyclization.

Toxicological data

A comprehensive range of studies on pharmacokinetics and toxicokinetics, acute toxicity, short-term and long-term toxicity, carcinogenicity, genotoxicity, and developmental and reproductive toxicity undertaken with appropriate standards for study protocol and conduct were taken into consideration in the safety assessment of advantame.

In all species studied (mice, rats, rabbits, dogs and humans), advantame is rapidly converted to advantame acid (de-esterified advantame). Based on the data from studies with simulated gastric and intestinal fluids, the majority of this conversion occurs rapidly in the intestinal tract prior to absorption. Maximum plasma concentrations of advantame-associated radioactivity after oral dosing in rodents are reached within 15–45 minutes (T_{max}); this is similar to the T_{max} in fasted humans (1.25 hours) and contrasts with the T_{max} of 6–8 hours in fasted dogs. Overall bioavailability following oral doses is estimated to be less than 10% in rats, 8–15% in dogs and approximately 6% in humans.

Following oral dosing with radiolabelled advantame, the majority of advantame and/or its metabolites are found to be associated with the gastrointestinal tract, in particular the stomach and small and large intestine. The low levels of advantame-associated radioactivity found outside the gastrointestinal tract were consistent with the presence of these materials in plasma and provided no indication of tissue-specific distribution or accumulation. Based on autoradiography studies, advantame and/or its metabolites were not detected in the placentas or fetuses of pregnant rats after oral dosing. Human volunteers ingesting advantame daily over a 12-week period demonstrated no evidence of accumulation.

Advantame acid (de-esterified advantame) is generally the predominant metabolite found in plasma, urine and faeces of all species except dogs, where advantame acid accounts for a low proportion (<1%) of the total absorbed dose in plasma. In this species, a sulfate conjugate was postulated to be the predominant metabolite in plasma based on high-performance liquid chromatographic and mass spectrometric analyses. This conjugate, together with possible enterohepatic circulation of other metabolites, likely explains the longer terminal half-life of plasma radioactivity in the dog (advantame-associated radioactivity half-life of 74–85 hours in dogs compared with 6.0–8.1 hours in rats and 3.9 hours in humans). Sulfate conjugates were not detected in the plasma of rats or humans.

L-Phenylalanine methyl ester was identified as a minor (<1.0%) degradation product of advantame in beverages under low-pH storage conditions. When ingested, L-phenylalanine methyl ester would hydrolyse to L-phenylalanine and methanol. However, it was considered that any potential exposure to either chemical would be insignificant compared with the usual dietary exposure to these chemicals.

The oral median lethal dose (LD_{50}) of advantame administered by gavage to rats was greater than 5000 mg/kg body weight (bw). The subchronic and chronic toxicity of dietary advantame was assessed in mice (13 and 104 weeks), rats (4, 13 and 104 weeks) and dogs (4, 13 and 52 weeks). No-observed-adverse-effect levels (NOAELs) for each of these studies were established on the basis of an absence of adverse effects at the highest concentration tested (50 000 mg/kg in the diet, equal to doses ranging from approximately 2000 to 7400 mg/kg bw per day). A common observation in the subchronic and chronic rodent feeding studies was a significant decrease in body weight gain associated with the high-dose group (5% advantame in the diet) with an associated reduction in feed conversion efficiency, but not feed intake. A significant reduction in final body weight gain compared with controls, however, was noted in female mice in the high-dose group (50 000 mg/kg diet) in the chronic bioassay and occurred in the absence of a decrease in feed conversion efficiency. As this effect was mainly related to a decrease in body weight gain observed in senile mice (>78 weeks of age) and there was no significant difference in the final mean body weights, in the absence of any other adverse effects, the reduced body weight gain observed at the highest dose was attributed to the relatively high concentration of a non-caloric substance in the diet.

In the chronic bioassays designed to assess potential carcinogenicity in mice and rats, there was no treatment-related increase in tumour incidence at advantame doses of up to 5693 and 2621 mg/kg bw per day, respectively. There was no evidence of genotoxicity in any of the in vitro or in vivo tests

conducted with advantame. A number of minor degradation products of advantame (formed at levels of less than 1%) were also tested for genotoxicity potential in vitro. Only advantame-imide gave a weak positive response in vitro, which was not confirmed on in vivo testing.

In a two-generation study of reproductive toxicity in rats, there were no treatment-related effects on reproductive parameters (mating performance, fertility, gestation length/index and sperm quality), litter observations (size, survival, sex ratio and pup body weight) or measures of postnatal offspring development at dietary concentrations of advantame up to 50 000 mg/kg (equal to advantame doses in the range of 4000–6000 mg/kg bw per day during the period prior to mating and gestation and over 8000 mg/kg bw per day during lactation). The developmental toxicity of advantame was examined in rats (diet) and rabbits (gavage) at advantame doses of 0, 465, 1418 or 4828 mg/kg bw per day and 0, 500, 1000 or 2000 mg/kg bw per day, respectively. In neither species was there any evidence of embryotoxicity or teratogenicity up to the highest dose tested. In rats, there was a transitory decrease in feed consumption at the start of treatment, resulting in lower body weight gain and subsequent lower final body weights in high-dose dams; however, there was no adverse effect on survival, growth or fetal development. In the main rabbit developmental toxicity study, clinical signs of toxicity (lethargy, loss of coordination and locomotion, inappetence and body weight loss) leading to humane sacrifice were observed in the 1000 mg/kg bw per day ($n = 1$) and 2000 mg/kg bw per day ($n = 5$) dose groups. Necropsy findings of these animals included incidences of distended caecum with or without haemorrhagic walls, congestion of the gastrointestinal tract, kidneys reported with punctate cysts and/or foci on the surfaces and bladder filled with green-coloured urine. Based on the available data, it could not be concluded that the clinical symptoms necessitating humane sacrifice in maternal animals in the mid- and high-dose groups were not treatment related. In the high-dose group, there was an observation of an approximate 2-fold increase in post-implantation loss compared with controls. However, the Committee noted that this effect occurred without a significant reduction in the number of live offspring per litter and was within the historical control range for this strain of rabbits. Based on the similarity in clinical signs observed in gravid rabbits subject to humane sacrifice in the 1000 and 2000 mg/kg bw per day dose groups, a NOAEL for maternal toxicity of 500 mg/kg bw per day was assigned, whereas the NOAEL for developmental effects was 2000 mg/kg bw per day, the highest dose tested.

Studies of human tolerance of advantame included a single-dose pharmacokinetic study, a 4-week study in healthy males and a 12-week study in male and female diabetic subjects. There were no treatment-related adverse effects or withdrawals during the study periods. Advantame did not affect plasma levels of glucose or insulin in healthy subjects, exacerbate glucose tolerance

or insulin resistance or affect levels of glycosylated haemoglobin in diabetic subjects with acceptable blood glucose control. The consumption of a single or repeated dose of advantame up to 0.5 mg/kg bw per day was considered to be well tolerated by both healthy and diabetic individuals.

Assessment of dietary exposure

Advantame is intended for use as a high-intensity sweetener in a number of food categories, including use in tabletop sweeteners, where there are existing provisions in regulations for aspartame. At low concentrations, advantame can also be used as a flavour enhancer. Application of a modified budget method as a screening method indicated a theoretical maximum use level of 400 mg/kg for advantame, assuming use in one quarter of the food supply and half the beverage supply and an acceptable daily intake (ADI) for advantame of 0–5 mg/kg bw, as established by Food Standards Australia New Zealand (FSANZ) in 2011. The proposed use levels for advantame in chewing gum and tabletop sweeteners were at or above this maximum level, so further investigations were made.

In an additional screening method, mean dietary exposures to advantame were predicted, assuming total sugar replacement by advantame in the food supply and a sweetness relative to sucrose of 20 000:1. Using per capita data for the food group "Sugar, honey and candies" for the 17 GEMS/Food Cluster Diets (see Annex 3 for the countries included in the 17 Cluster Diets) or reported total sugar intakes for the population of the USA, known to have one of the highest sugar intakes in the world, the predicted mean population dietary exposures to advantame were all less than or equal to 0.2 mg/kg bw per day, assuming a 60 kg body weight. Dietary exposures to advantame were also predicted assuming replacement of permitted high-intensity sweeteners, by calculating the sucrose equivalent intakes derived from their known use and converting back to advantame use. Predicted mean dietary exposures to advantame were, as expected, lower than those for total sugar replacement, at 0.01–0.03 mg/kg bw per day for the general population and 0.03–0.05 mg/kg bw per day for high consumers, including people with diabetes, assuming a 60 kg body weight.

Dietary exposures to advantame were predicted from individual food consumption records from national nutrition surveys for a number of populations with a known use of foods containing high-intensity sweeteners (the USA, 22 European countries, Australia and New Zealand) and sponsor-proposed maximum use levels for each jurisdiction, assuming that brand-loyal consumers always select foods proposed to contain advantame. The proposed use levels were derived from existing maximum permitted levels for aspartame in the relevant jurisdiction and adjusting for the relative

sweetness of advantame to aspartame of 100:1, with further alterations based on taste perception, in some cases. The Committee noted that the maximum use levels proposed by the sponsor for the European Union (EU) were double those proposed for the USA in some food categories, as an additional factor of 2 had been applied to the advantame levels derived from aspartame maximum permitted levels. Sponsor-proposed use levels for the GSFA were derived by taking the highest value from the regulations in the USA or EU. Predicted mean dietary exposures to advantame for consumers only across the different population groups evaluated ranged from 0.03 mg/kg bw per day (mean consumers aged 15 years and over in New Zealand, assuming restricted use in beverages and tabletop sweeteners) to 1.45 mg/kg bw per day (mean consumers aged 2–6 years in Australia, assuming sponsor-proposed GSFA use levels). Predicted dietary exposures for high consumers ranged from 0.06 mg/kg bw per day (90th percentile consumers aged 15 years and over in New Zealand, assuming restricted use in beverages and tabletop sweeteners) to 2.16 mg/kg bw per day (90th percentile consumers aged 2–6 years in Australia, assuming proposed GSFA use levels). The predicted dietary exposures for European populations and the estimate for Australian children based on applicant-proposed GSFA use levels tended to be higher than those for the population in the USA due to higher maximum levels of advantame proposed for similar food categories and the fact that broader food categories were used in these estimates, which included foods for which no use of advantame is intended.

Evaluation

On the basis of the available studies, the Committee considered advantame to be a substance of low oral toxicity across a range of species, including humans. Appropriately conducted studies indicated that advantame is not carcinogenic, mutagenic or teratogenic or associated with any reproductive or developmental toxicity. The main treatment-related effect that was considered adverse was the occurrence of morbidity that necessitated early humane sacrifice of dams in the main rabbit developmental toxicity study (where dosing was by gavage) at and above an advantame dose of 1000 mg/kg bw per day. While these clinical observations were not observed in any other species dosed with similar levels of advantame via the diet, in the absence of pharmacokinetic data for gravid rabbits, it could not be concluded that the effect was not toxicologically relevant. The rabbit is considered the most sensitive species in the database, with a NOAEL for maternal toxicity of 500 mg/kg bw per day.

Although a developmental toxicity study is not considered to be representative of a long-term toxicity study, an additional safety factor was not considered necessary, based on the lack of adverse effects observed in long-term

dietary studies conducted with comparable levels of advantame in different species.

An ADI of 0–5 mg/kg bw is established for advantame on the basis of a NOAEL of 500 mg/kg bw per day for maternal toxicity in a developmental toxicity study in rabbits and use of a 100-fold safety factor for interspecies and intraspecies variability.

The Committee agreed that the ADI also applies to those individuals with phenylketonuria, as the formation of phenylalanine from the normal use of advantame would not be significant in relation to this condition.

Advantame is intended for use as a tabletop sweetener and in a large variety of solid and liquid foods. Conservative calculations based on its sweetness potency (20 000 times that of sucrose) suggest that a mean population dietary exposure to advantame of less than 0.2 mg/kg bw per day would result from total sugar replacement in the diet, even for the maximum reported mean intake of 160 g total sugars per day for the population of the USA, assuming a 60 kg body weight. Therefore, a total replacement of sugar with advantame would not lead to the ADI being exceeded. Using national dietary exposure estimates and making the "worst case" assumption that brand-loyal consumers always select foods intended to contain advantame at the sponsor-proposed maximum use levels for broad food categories suggest that the maximum mean dietary exposure to advantame would be 1.45 mg/kg bw per day (29% of the upper bound of the ADI), and the maximum high-percentile dietary exposure would be 2.16 mg/kg bw per day (43% of the upper bound of the ADI). The Committee considered these predicted dietary exposures to advantame to be overestimated due to the conservative assumptions made.

The proposed maximum use levels that the Committee considered for advantame for possible inclusion in the GSFA were not expected to lead to dietary exposures exceeding the upper bound of the ADI for any population group.

A toxicological monograph and a Chemical and Technical Assessment were prepared.

New tentative specifications were prepared, requesting, by the end of 2015, information on:

- the suitability of the headspace gas chromatographic method (using appropriate dissolution solvent) for determination of residual solvents, published in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*), and data, in a minimum of five batches, using the method;
- an alternative or improved high-performance liquid chromatographic method for the assay of advantame and advantame acid using a standard curve;

- additional data and analytical methods for the determination of palladium and platinum;
- information on the purity and availability of the commercial reference standards used in the assay of advantame and advantame acid.

3.1.2 *Glucoamylase from* Trichoderma reesei *expressed in* Trichoderma reesei

Explanation

At the request of CCFA at its Forty-fourth Session (*10*), the Committee evaluated the safety of the glucoamylase enzyme preparation (glucan 1,4-α-glucosidase; Enzyme Commission No. 3.2.1.3) from *Trichoderma reesei* expressed in *T. reesei*, which it had not evaluated previously. Glucoamylase catalyses the hydrolysis of terminal (1→4)-linked α-D-glucose residues successively from the non-reducing end of the chain with concomitant release of β-D-glucose in polysaccharide substrates. In this report, the expression "glucoamylase" refers to the glucoamylase enzyme and its amino acid sequence, and the expression "glucoamylase enzyme preparation" refers to the preparation formulated for commercial use. The glucoamylase enzyme preparation is used as a processing aid in the manufacture of sweeteners such as high-fructose corn syrup, in baking, in brewing and in the production of potable alcohol (spirits).

Genetic modification

Glucoamylase is produced from a genetically modified strain of *Trichoderma reesei* containing the glucoamylase gene from *T. reesei. Trichoderma reesei* is a mesophilic filamentous fungus that is ubiquitous in nature. It has a long history of use in the production of enzymes used in food processing, including enzymes from genetically engineered strains of the organism. Prior to the introduction of the glucoamylase gene, the *T. reesei* host strain was genetically modified through deletion of genes encoding cellobiohydrolase 1 and 2 and endoglucanase 1 and 2, resulting in a strain with a compromised ability to use cellulose as a carbon source. The modified host strain was then transformed using two expression cassettes containing the glucoamylase gene from *T. reesei*. The final recombinant production strain is genetically stable and free of any antibiotic resistance genes or vector deoxyribonucleic acid (DNA) used during transformation.

Chemical and technical considerations

Glucoamylase is produced by submerged aerobic, straight-batch or fed-batch pure culture fermentation of a genetically modified strain of *T. reesei* containing the gene coding for glucoamylase from *T. reesei.* The enzyme is secreted

into the fermentation broth and is subsequently purified and concentrated. The enzyme concentrate is formulated with glucose, sodium benzoate and potassium sorbate to achieve the desired activity and stability. The glucoamylase enzyme preparation contains commonly used food-grade materials and conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing (Annex 1, reference *154*). Glucoamylase activity is measured in glucoamylase units (GAU). One GAU is defined as the amount of enzyme that releases 1 g (5.6 mmol) of glucose per hour from soluble starch substrate (*p*-nitrophenyl-α-D-glucopyranoside) at pH 4.3 and a temperature of 30 °C. The mean activity of glucoamylase enzyme from three formulated batches of the enzyme preparation was 523 GAU per gram of glucoamylase enzyme preparation.

A typical commercial formulation of the glucoamylase enzyme preparation will contain 10–15% of enzyme as total organic solids (TOS). TOS includes the enzyme of interest and residues of organic materials, such as proteins, peptides and carbohydrates, derived from the production organism during the manufacturing process. The glucoamylase enzyme preparation is used at concentrations ranging from 0.05 to 0.32 g TOS per kilogram of food, depending on the proposed application. The glucoamylase enzyme is expected to be inactivated during processing and hence is not expected to remain in the final food.

Assessment of potential allergenicity

The glucoamylase from *T. reesei* was evaluated for potential allergenicity according to the bioinformatics criteria recommended by FAO/WHO. The amino acid sequence of glucoamylase was compared with the amino acid sequences of known allergens. A similarity search in the Structural Database of Allergenic Proteins (SDAP)[1] for matches showing greater than 35% identity over a window of 80 amino acids produced multiple matches with Sch c 1 protein of *Schizophyllum commune*. A similar search using the Allermatch database[2] also produced multiple matches with Sch c 1 protein and in addition produced one match with Pen ch 13 protein in *Penicillium chrysogenum*. The Sch c 1 and Pen ch 13 proteins are not identified as food allergens in the WHO–International Union of Immunological Societies (WHO-IUIS) list of allergens[3]. Using SDAP, a search for six contiguous amino acid sequences of the glucoamylase that could be present in allergenic proteins produced multiple matches as well. The vast majority of these matches are with various sections of the Sch c 1 protein of *Schizophyllum commune*, which was expected. The Sch c 1 protein is not identified as a food allergen in the WHO-IUIS list

[1] http://fermi.utmb.edu/SDAP/sdap_who.html
[2] http://www.allermatch.org/
[3] http://www.allergen.org/

of allergens. However, in addition to the Sch c 1 protein, a number of other allergenic proteins in SDAP were also found to share six contiguous amino acid sequence identity with glucoamylase. Therefore, the biological relevance of these matches was examined by investigating the distribution of these six contiguous amino acid sequences in proteins in general—that is, whether these sequence segments are present only in allergenic proteins or are present in both allergenic and non-allergenic proteins. This extended search was performed using the National Center for Biotechnology Information protein database[4], which contains the sequences of all known proteins. The search demonstrated that each of these six contiguous amino acid sequences of the glucoamylase that was found in other allergenic proteins is widely distributed in various prokaryotic and eukaryotic proteins, including proteins from non-allergenic sources, and even edible sources. This indicates that the six contiguous amino acid sequence matches found between the glucoamylase and various allergenic proteins occurred by chance and are not likely to be part of any allergenicity-associated epitopes. Therefore, the Committee considered that oral intake of glucoamylase is not anticipated to pose a risk of allergenicity.

Toxicological data

In a 13-week study of general toxicity in rats, no treatment-related adverse effects were seen when glucoamylase enzyme preparation was administered daily by gavage at doses up to 166 mg TOS per kilogram body weight per day. The glucoamylase enzyme preparation was not mutagenic in a bacterial reverse mutation assay in vitro and was not clastogenic in an assay for chromosomal aberrations in human lymphocytes in vitro.

Assessment of dietary exposure

A theoretical "worst case" dietary exposure estimate was made assuming that the enzyme remains in the food at its maximum concentration following its use as a processing aid in the production of sugars, bread/bakery items, beer and spirits and that it is present in 100% of each range of products. Based on these very conservative assumptions, the estimate of total dietary exposure was 1.73 mg TOS per kilogram body weight per day. However, the enzyme is not expected to remain in sugar, beer or spirit products following purification processes used in their manufacture, and it will be inactivated in bread and bakery products.

Evaluation

Based on its low toxicity and because it is reasonably anticipated that dietary exposure would be very low, the Committee established an ADI "not

[4] http://www.ncbi.nlm.nih.gov/protein

specified" for the glucoamylase enzyme preparation from *T. reesei* expressed in *T. reesei* used in the applications specified and in accordance with good manufacturing practice.

A toxicological monograph was prepared.

New specifications and a Chemical and Technical Assessment were prepared.

3.1.3 *Glycerol ester of gum rosin*

Explanation

At its seventy-first meeting (Annex 1, reference *196*), the Committee evaluated glycerol ester of gum rosin (GEGR) for use as an emulsifier/density adjustment agent for flavouring agents in non-alcoholic beverages and cloudy spirit drinks. The Committee established a group ADI of 0–25 mg/kg bw for GEGR and glycerol ester of wood rosin (GEWR). GEGR was evaluated based on the toxicity data for GEWR, the absence of toxicological effects of their corresponding non-esterified rosins and the qualitative similarity of the chemical components of GEGR and GEWR. However, in view of the limited toxicity data available for GEGR and the submission of only the summarized results of two 90-day oral toxicity studies in rats, the Committee concluded that the full reports of the two 90-day oral toxicity studies with GEGR were needed to confirm the validity of the comparison of GEGR with GEWR.

Further, at the seventy-first meeting, the specifications for GEGR were made tentative pending submission of additional data regarding the identity and compositional analysis of GEGR to establish the extent of the chemical similarity between GEGR and GEWR.

At its seventy-fourth meeting (Annex 1, reference *205*), the Committee noted that the requested full reports of the two 90-day oral toxicity studies on GEGR in rats had not been provided and that the validity of evaluating GEGR on the basis of toxicological data on GEWR still required confirmation. The Committee withdrew the group ADI for GEGR and GEWR and established a temporary group ADI for GEGR and GEWR of 0–12.5 mg/kg bw. The Committee noted that the temporary group ADI would be withdrawn if compositional information on GEGR as well as the full reports of the two 90-day oral toxicity studies on GEGR in rats were not submitted by the end of 2012.

Chemical and technical considerations

GEGR is a complex mixture of glycerol diesters and triesters of resin acids from gum rosin, with a residual fraction of glycerol monoesters. Gum rosin is an exudate of living pine trees.

Although the submitted analytical data included summarized information in relation to the composition of free resin acids and neutrals (non-acidic saponifiable and unsaponifiable substances) in GEGR, the Committee noted that the information on the composition and ester distribution of GEGR was incomplete and therefore could not confirm the claimed similarities to GEWR.

Evaluation

For the present meeting, the requested two unpublished 90-day oral toxicity studies on GEGR in rats were not submitted. Furthermore, complete information on the composition of GEGR was not submitted. As the requested data were not submitted, the Committee withdrew the temporary group ADI of 0–12.5 mg/kg bw for GEGR and GEWR.

The specifications were maintained as tentative pending the submission of additional information by the end of 2014. Additional data are requested to characterize GEGR in commerce in relation to the composition of 1) the refined gum rosin currently used as the source rosin with regard to the levels (%) of resin acids and neutrals, 2) the glycerol ester of gum rosin with regard to the levels (%) of a) glycerol esters, b) free resin acids and c) neutrals and 3) the total glycerol esters of resin acids with regard to the levels (%) of a) glycerol monoesters and b) the sum of glycerol diesters and triesters (assay). Validated methods for the determination of the substances considered in the specifications are also required.

No toxicological monograph was prepared.

3.1.4 *Glycerol ester of tall oil rosin*

Explanation

Glycerol ester of tall oil rosin (GETOR) was evaluated by the Committee at its seventy-first meeting (Annex 1, reference *196*) for proposed use as an emulsifier/density adjustment agent for flavouring agents in non-alcoholic beverages. The Committee concluded that, in principle, the data for GEWR, which had been evaluated previously, could be used for the evaluation of GETOR, provided the respective compositional data were sufficiently similar. Because the information on the composition of GETOR was inadequate to conclude that GETOR is sufficiently similar to GEWR, the Committee could not complete the evaluation and requested additional compositional data on the product in commerce, in order to clarify the extent and significance of any differences relative to other glycerol esters of rosins.

At the seventy-fourth meeting of the Committee (Annex 1, reference *205*), limited data on the composition of GETOR were provided. The claimed

similarities between GETOR and GEWR could not be confirmed. The Committee concluded that additional data were required to characterize the GETOR in commerce in relation to the composition of 1) the refined tall oil rosin used as the source rosin, 2) the glycerol esters of tall oil rosin, 3) the total glycerol esters of resin acids and 4) the neutrals. Validated methods for the determination of the substances considered in the specifications were also requested.

Evaluation

For the present meeting, no data on GETOR were submitted, and the Secretariat was informed that this compound is no longer supported by the previous data sponsor. Therefore, no evaluation was performed.

The tentative specifications were withdrawn.

No toxicological monograph was prepared.

3.1.5 *Glycerol ester of wood rosin*

Explanation

GEWR was previously considered by the Committee at its eighteenth, twentieth, thirty-third, thirty-seventh, forty-fourth, forty-sixth, seventy-first and seventy-fourth meetings (Annex 1, references *35*, *41*, *83*, *94*, *116, 122*, *196* and *205*). At its forty-sixth meeting, the Committee established an ADI of 0–25 mg/kg bw for GEWR. At its seventy-first meeting, the Committee extended this ADI to a group ADI of 0–25 mg/kg bw for GEGR and GEWR.

Prior to the seventy-fourth meeting, GEWR was evaluated based on the assumption that the substance was obtained from just one *Pinus* species (*Pinus palustris*). However, information received by the Committee at its seventy-fourth meeting indicated that the product in commerce is also produced from the species *Pinus elliottii.* Considering that the rosin source may have an impact on the composition of the final glycerol ester, the Committee decided that the specifications should include all the *Pinus* species from which the wood rosin is obtained. As the submitted information on GEWR did not adequately characterize the product in commerce, the Committee decided to withdraw the group ADI of 0–25 mg/kg bw for GEGR and GEWR and established a temporary group ADI of 0–12.5 mg/kg bw by applying an additional uncertainty factor of 2. The Committee requested additional data to characterize the GEWR in commerce in relation to the composition of 1) the refined wood rosin currently used as the source rosin for the production of GEWR, 2) the glycerol esters of wood rosin, 3) the total glycerol esters of resin acids and 4) the neutrals. Validated methods for the determination of the substances considered in the specifications were also requested. The Committee noted at the seventy-fourth

meeting that the temporary group ADI would be withdrawn unless additional compositional information on GEWR from *Pinus elliottii* and *Pinus palustris* as well as the full reports of two 90-day oral toxicity studies on GEGR in rats were submitted by the end of 2012.

Chemical and technical considerations

GEWR is a complex mixture of glycerol diesters and triesters of resin acids from wood rosin, with a residual fraction of glycerol monoesters. Wood rosin is obtained by solvent extraction of aged pine stumps.

The sponsor submitted the requested information on the composition of the wood rosin and GEWR, based on analyses of five production samples of the wood rosin and GEWR. The wood rosin was composed of resin acids and neutrals. GEWR was composed mainly of glycerol diesters and triesters (78.3–83.9%) and neutrals (11.4–17.6%), with lesser amounts of glycerol monoesters (1.5–3.2%) and free resin acids (2.3–2.8%). Further, the sponsor informed the Committee that throughout the history of the manufacture of GEWR, the wood rosin feedstock has always been based on a mixture of *P. palustris* and *P. elliottii*, which occur naturally in overlapping regions of the south-eastern USA. Considering this statement, in addition to the submitted compositional information, the Committee recognized that the GEWR used for each of the toxicological studies, just as the product now in commerce, was based on a mixture of the two species.

Based on this recognition, the specifications were revised to exclude both assays and limits for glycerol monoesters and neutrals and further to include gas chromatographic analysis for the confirmation of the presence of glycerol and major resin alcohols, abietic alcohols and dehydroabietic alcohols, generated by reductive reaction of GEWR.

Evaluation

At the present meeting, new information, including compositional data on GEWR, was submitted. Based on this information, the Committee concluded that the current product in commerce is equivalent to the GEWR with which the toxicological studies have been performed.

For the present meeting, the requested data on GEGR were not submitted. The Committee therefore withdrew the temporary group ADI of 0–12.5 mg/kg bw for GEGR and GEWR and re-established the ADI of 0–25 mg/kg bw for GEWR.

The existing tentative specifications were revised, and the tentative status was removed. A Chemical and Technical Assessment was prepared.

No toxicological monograph was prepared.

3.1.6 *Nisin*

Explanation

Nisin is a mixture of antimicrobial polypeptides produced by *Lactococcus lactis* subsp. *lactis*. Nisin preparations are currently used in commerce as an antimicrobial preservative in processed cheeses, pasteurized dairy products and processed meats. The Committee evaluated the safety of nisin at the twelfth meeting of JECFA (Annex 1, reference *17*) and established an ADI of 0–33 000 units of nisin per kilogram body weight.

At its Forty-fourth Session (*10*), CCFA requested JECFA to verify the calculation of the ADI for nisin; clarify the basis of the ADI for nisin; and provide the calculation to convert units of nisin to milligrams of nisin.

In the original JECFA evaluation of nisin, the ADI of 0–33 000 units of nisin per kilogram body weight was derived from the highest dose in a 2-year repeated-dose toxicity study (*11*), which the Committee interpreted as being 3 330 000 units of nisin per kilogram of body weight, but which was actually 3 330 000 units of nisin per kilogram of feed. As the ADI in the original JECFA evaluation was derived incorrectly, the present Committee undertook a re-evaluation of nisin, taking previously evaluated as well as new studies into account.

Chemical and technical considerations

Nisin is a mixture of closely related antimicrobial polypeptides that are 34 amino acids in length. Nisin is produced by strains of *Lactococcus lactis* subsp. *lactis* under appropriate fermentation conditions. The major polypeptide from the fermentation is nisin A. Nisin is produced in a sterilized medium of non-fat milk solids or non-milk-based fermentation sources, such as yeast extract and carbohydrate solids. The fermentation process is controlled for time and pH, until optimum nisin production has been achieved. Nisin is recovered, concentrated and purified from the fermentation medium by various methods, such as sterile injection, membrane filtration, acidification, salting out or spray-drying. The purified nisin is then standardized to make nisin preparation at the desired activity level. The remaining components of the preparation are milk solids and products of fermentation, which include proteins and carbohydrates. Nisin is commercially available as nisin preparation and contains commonly used food-grade materials. A typical batch of a commercial nisin preparation contains 2.5% (weight per weight [w/w]) nisin and approximately 75% (w/w) sodium chloride.

The activity of nisin in commercial nisin preparation has been described in the literature in Reading Units (RU) and International Units (IU). In 1970, the WHO Committee on Biological Standardization established the IU as

the international reference for units of nisin activity. One IU was defined as the amount of nisin required to inhibit the growth of one bacterial cell in 1 ml of broth. This amount is 0.025 μg of nisin (= 1 IU). Therefore, 1 μg of nisin is equivalent to 40 IU. The Committee at the current meeting reviewed the scientific literature in order to harmonize the RU and IU and concluded that they are equivalent (i.e. 1 IU is the same as 1 RU). The Committee at the current meeting clarified that the specification for the activity of nisin is reported as International Units and provided a conversion factor to obtain the quantity of active nisin in a given sample. The revised JECFA specifications for nisin include this conversion. The revised assay for nisin activity in the JECFA specifications is not less than 900 IU of nisin per milligram or not less than 22.5 μg of nisin per milligram. The revised specifications also removed the synonym "nisin preparation".

Toxicological data

In vitro studies demonstrated that nisin is inactivated by α-chymotrypsin. Nisin administered by gavage to rats was also hydrolysed and inactivated in the intestinal tract, with no biologically active nisin being detected in the colon or caecum. In a gavage study in dogs dosed with nisin (test material description not available) at 1000 mg/kg bw twice per day for 28 days, biologically active nisin was detected in blood serum in one of six dogs at a level of 0.54 μg/ml (limit of detection: 0.45 μg/ml). As the experimental design did not involve multiple time points to confirm the presence of biologically active nisin in plasma, the Committee did not find the results of this gavage dosing study to be conclusive evidence that nisin in food would result in systemic exposure to biologically active nisin.

A range of studies on the acute toxicity, short- and long-term toxicity, genotoxicity, and reproductive and developmental toxicity of nisin was taken into consideration for the safety assessment.

The oral LD_{50} of nisin preparation in mice was 6950 mg/kg bw, and the oral LD_{50} of purified nisin in rats was greater than 2000 mg/kg bw. The toxicity of orally administered (diet or gavage) nisin or nisin preparation was assessed in short-term studies in mice, short- and long-term studies in rats and short-term studies in dogs. A common observation in animals treated with nisin preparations (with ~75% [w/w] sodium chloride) was a significant increase in the absolute and relative kidney weights, coupled with high water consumption and increased urination. The increased kidney weight and minimal squamous cell hyperplasia of the limiting ridge in the forestomach that were seen in these studies in the nisin preparation–treated groups were also seen in the sodium chloride control groups, and these effects are known to be typical of high sodium chloride treatment. Slight but statistically significant changes in haematological parameters at high doses of nisin (2000 mg of purified nisin per

kilogram body weight per day in two studies and a 5% dietary level of nisin preparation in another study) were inconsistent in direction and magnitude.

In a 90-day toxicity study, rats were fed nisin preparation (with a nisin A potency of 3000 IU/mg, corresponding to a 7.5% nisin A content) in the diet at 0%, 0.2%, 1.0% or 5.0% (equal to 0, 117, 586 and 2996 mg of nisin preparation per kilogram body weight per day for males and 0, 129, 638 and 3187 mg/kg bw per day for females, respectively). A sodium chloride reference group was given sodium chloride at a dietary level of 3.712%, which was the same as that in the 5.0% nisin A diet. Significant increases in the absolute and relative kidney weights, coupled with high water consumption, increased urination and minimal squamous cell hyperplasia of the limiting ridge in the forestomach, were observed. These changes were also noted in the sodium chloride reference group and were considered to be related to sodium chloride intake. Other parameters that showed a statistically significant increase in the high-dose group were the red blood cell parameters (red blood cell count, haemoglobin, mean corpuscular haemoglobin, mean corpuscular volume, haematocrit value). The increase in these parameters was less than 4% and within the range of historical data and was not considered to be toxicologically relevant. Based on the lack of treatment-related adverse effects in the highest dose group, the NOAEL was identified as 5.0% of the nisin preparation in the diet, which was equal to 2996 mg/kg bw per day of the nisin preparation, or 224.7 mg/kg bw per day of nisin.

In three one-generation reproductive toxicity studies, the reproductive performance of the nisin-treated rats was unaffected. There were no perinatal or postnatal effects. Growth of the pups was normal and similar to that of the control group. In a three-generation reproductive toxicity study, a nisin preparation containing 2.5% nisin A was fed to rats in a standard diet containing 0%, 0.2%, 1.0% or 5.0% nisin preparation for 26 weeks. A further group of animals received a diet containing 3.8% sodium chloride, which was equivalent to the sodium chloride content of the 5.0% diet group. No treatment-related changes were observed in reproductive performance as assessed by pregnancy rate, gestation length, postpartum litter loss, litter size, mortality or necropsy findings. There were no treatment-related changes in organ weights or histopathology at the end of the study. A decrease in body weight gain was observed in males in the F_0 and F_2 generations, but not in the F_1 generation. Decreased body weight gain was not observed in females. Furthermore, a decrease in body weight gain in rats of both sexes was not observed in other studies. Therefore, the Committee considered this finding to be unrelated to nisin treatment.

In a developmental toxicity study in rats administered purified nisin by gavage at doses up to 50 mg/kg bw per day, no effects on any developmental end-points were observed.

Purified nisin was not genotoxic in reverse mutation, chromosomal aberration, mouse lymphoma or mouse bone marrow micronucleus assays. Nisin was not carcinogenic in the 2-year rat study at dietary concentrations up to 3.33 million units of nisin per kilogram diet. Based on the authors' statement that 1 g of nisin had an activity of approximately 40 million units and their assumptions that the average weight of the rats was 250 g and the average feed consumption of the rats was 15 g, this is equivalent to 83.3 mg of nisin per kilogram diet, or 5.0 mg/kg bw per day. This was the study from which the Committee derived the ADI at the twelfth meeting.

Assessment of dietary exposure

Nisin has been used commercially for over 25 years in a number of food types, primarily processed cheese and meat products. The Committee received information concerning dietary exposure patterns from one sponsor and independently obtained additional published information. The sponsor data had been submitted as part of a premarket evaluation of nisin for expanded uses in Japan in the mid-2000s. The additional information was taken from regulatory publications in Australia/New Zealand, Europe and the USA. Four national/regional estimates of dietary exposure to nisin were reviewed by the Committee: from the EU, Australia/New Zealand, Japan and the USA. The estimate of mean consumers-only dietary exposure for the EU from consumption of cheese, cream, desserts and egg products was 0.008 mg/kg bw per day, with exposure at the 97.5th percentile of 0.026 mg/kg bw per day. From FSANZ, the estimated consumers-only mean dietary exposures to nisin from consumption of cheese, cream, meat products, sauces, toppings and mayonnaise were 0.009 mg/kg bw per day (all ages) and 0.02 mg/kg bw per day (2- to 6-year-olds). Estimated consumers-only 95th percentile dietary exposures to nisin were lowest for New Zealanders aged 15 years and above, at 0.03 mg/kg bw per day, and highest for Australian children aged 2–6 years, at 0.07 mg/kg bw per day. The consumers-only dietary exposure estimate from the USA from consumption of cheese spreads, dressings, egg products and processed meat products was 0.04 mg/kg bw per day at the mean. The Committee also noted that a letter responding to a Generally Recognized as Safe notification in the USA for nisin use only in frankfurters included an estimate of consumer-only mean dietary exposure to nisin of 0.6 mg/day, or 0.01 mg/kg bw per day, with exposure at the 90th percentile of 1.1 mg/day, or 0.02 mg/kg bw per day. The Japanese per capita estimate was from consumption of cheeses, buns, meat and egg products, tofu and miso and was reported as 2.06 mg/person per day or approximately 0.04 mg/kg bw per day for a 50 kg individual. The FSANZ, Japanese and USA estimates were consistent and higher than the EU estimate due to broader food categories in which nisin could be applied. The Committee concluded that the use

of a dietary exposure of 0.07 mg/kg bw per day (95th percentile, Australian children, 2–6 years old) was appropriate for the safety evaluation of nisin.

Evaluation

At the meeting, the Committee provided clarifications on the identity of nisin and on the units of activity of nisin and a calculation to convert from International Units of nisin to micrograms of nisin based on the available data on different forms of nisin in commerce.

On the basis of the available studies, the Committee considered nisin to be a substance of low oral toxicity. Ingested nisin is inactivated in the upper part of the intestinal tract. Nisin is not carcinogenic or mutagenic and is not associated with any reproductive or developmental toxicity. The 2-year toxicity study was not considered to be an appropriate basis for establishing an ADI because it was not conducted to current standards and did not include an appropriate saline control group and because a number of later studies investigated higher doses of nisin.

After evaluating the new studies as well as the previously reviewed studies, the Committee concluded the 13-week subchronic toxicity study to be the pivotal study in the current safety evaluation of nisin because it was a higher-dose study and it took into consideration more parameters compared with other studies, such as the three-generation reproductive toxicity study. Based on the observation that there were no treatment-related adverse effects at the highest concentration tested, the 5% dietary level of nisin preparation (containing 7.5% nisin), a NOAEL of 224.7 mg of nisin per kilogram body weight per day was identified. Applying a safety factor of 100 to the NOAEL to account for interspecies and intraspecies variability, the Committee established an ADI for nisin of 0–2 mg/kg bw. The Committee did not consider it necessary to use an additional safety factor to account for the short duration of the study because no compound-related effects were observed at any dose in any of the other studies, including the reproductive toxicity study, and because ingested nisin is degraded in the upper part of the intestinal tract, such that systemic exposure to nisin is not likely to occur.

The highest estimated dietary exposure of 0.07 mg of nisin per kilogram body weight per day determined at the current meeting did not exceed the upper bound of the ADI.

The Committee withdrew the previous ADI of 0–33 000 units of nisin per kilogram body weight established at the twelfth meeting.

A toxicological monograph was prepared.

The specifications for nisin were revised.

3.1.7 *Octenyl succinic acid modified gum arabic*

Explanation

At its seventy-first meeting (Annex 1, reference *196*), the Committee evaluated the toxicological and chemical and technical data for octenyl succinic acid (OSA) modified gum arabic. In view of the similarities between OSA modified gum arabic and the parent gum arabic, toxicological information for gum arabic was included in the toxicological monograph. At that meeting, the Committee decided to allocate a temporary ADI "not specified" to OSA modified gum arabic, pending submission of data by the end of 2011 showing hydrolysis of OSA modified gum arabic in the gastrointestinal tract to confirm the validity of using toxicological data on gum arabic in the evaluation of OSA modified gum arabic.

At the seventy-fourth meeting (Annex 1, reference *205*), the Committee evaluated new data on the hydrolysis of OSA modified gum arabic and reviewed the specifications. The Committee concluded that the results from the experiments on the hydrolysis of OSA modified gum arabic did not unequivocally demonstrate that OSA modified gum arabic hydrolyses completely in the stomach into gum arabic and OSA. Furthermore, the hydrolysis experiments showed inconsistencies with the reported stability of OSA modified gum arabic in food. Therefore, the Committee deferred further evaluation of OSA modified gum arabic and requested that the following data be provided by the end of 2013:

- data resolving the concern about the stability of OSA modified gum arabic in food;
- data confirming that OSA modified gum arabic is (completely) hydrolysed in the gastrointestinal tract, to confirm the validity of using gum arabic data in the evaluation of OSA modified gum arabic.

The temporary ADI was retained and the specifications were revised with changes in the test methods for the degree of esterification and for residual OSA content.

At the present meeting, new data on the hydrolysis of OSA modified gum arabic in simulated gastric fluid, as well as the stability of OSA modified gum arabic in food, were evaluated by the Committee. The specifications were also reviewed.

Biochemical data

In an in vitro test, the hydrolysis of OSA modified gum arabic (lot no. 19705, purity not reported) in simulated gastric fluid (0.2% weight per volume [w/v] sodium chloride in 0.7% volume per volume [v/v] hydrochloric acid, without

pepsin, pH 1–2), simulated intestinal fluid (without pancreatin, USP XXII formulation, pH 7.5) and water was investigated. OSA modified gum arabic at a concentration of 3 mg/ml was incubated in simulated gastric fluid, simulated intestinal fluid or water for 0 or 60 minutes at 37 °C. The reactions were terminated by addition of a neutralizing agent, after which the OSA content was analysed by liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Incubation of OSA modified gum arabic at 3 mg/ml in simulated gastric fluid, simulated intestinal fluid or water for 0 and 60 minutes resulted in the formation of OSA free acid at concentrations of 353 and 364 µmol/l in simulated gastric fluid; 335 and 321 µmol/l in simulated intestinal fluid; and 275 and 292 µmol/l in water, respectively. In view of the high level of OSA free acid at 0 minutes, the study author concluded that hydrolysis of OSA modified gum arabic was immediate, with no apparent time dependence. However, the Committee questioned the effectiveness of the addition of a neutralizing agent to the reaction mixture to terminate the reaction, as marked hydrolysis of OSA modified gum arabic occurred in water. Following "termination" of the reaction, the mixture is processed for analysis by LC-MS/MS, which is reported to take at least 10 minutes and possibly longer. The formation of OSA free acid at a concentration of 353–364 µmol/l is equal to about 0.08 mg/ml, or 2.7% w/w of the starting material, which contains maximally 3% of OSA, according to the specifications. The study author considered that the study indicates virtually complete hydrolysis in simulated gastric fluid (*12*).

Stability in food

Data on the stability of OSA modified gum arabic in two model food systems were presented (*13*). The two model food systems used were beverage and salad dressing emulsions. Results of these studies demonstrate that OSA modified gum arabic is effective in forming stable emulsions in these foods over a given shelf life. The emulsion stability in the beverage model system was evaluated through particle size analysis at three pH levels (2.5, 3.6 and 4.5) and two temperatures (room temperature and 45 °C), ring test (over 30 days) and backscattering analysis (over 21 days). A standard formula for French salad dressing was used as the model system for the salad dressing. Emulsion stability was evaluated using backscattering analysis and viscosity. Backscattering analyses for 17.5% and 30% oil French dressings containing OSA modified gum arabic demonstrate stability over 4.4 and 5 months, respectively. Studies also demonstrate droplet size stability over 30 days in addition to stable viscosity.

Evaluation

The Committee noted that complete hydrolysis of OSA modified gum arabic under neutral pH conditions in simulated intestinal fluid or water, as

reported in the study submitted for the present meeting, was at variance with the claimed stability of the OSA ester linkage in aqueous solutions at the pH range of foods and beverages. The Committee considered that the spontaneous hydrolysis of OSA modified gum arabic in water was unlikely to occur, which therefore raised doubts about the validity of the observed hydrolysis in the presence of gastrointestinal enzymes. In view of this, the Committee considered that the present study does not unequivocally demonstrate that OSA modified gum arabic hydrolyses completely in the stomach into gum arabic and OSA and that the validity of using toxicological data on gum arabic in the evaluation of OSA modified gum arabic had not been confirmed.

The Committee also considered that the presented data demonstrate that OSA modified gum arabic provided a stable emulsion in the two model food systems evaluated. However, the data did not unequivocally demonstrate that the OSA modified gum arabic, at the molecular level, is stable in food and beverages.

The Committee noted that ongoing studies on the stability of OSA modified gum arabic in food may provide further information on its chemical state in food and aqueous solutions, which could help to explain the contradictory results of the hydrolysis study.

Therefore, the Committee decided to retain the temporary ADI "not specified" pending submission of additional data on the stability of OSA modified gum arabic in food by the end of 2013.

An addendum to the toxicological monograph was not prepared.

The Committee also reviewed the specifications and noted that the purity test of degree of esterification in the current specifications should be replaced by the degree of substitution and requested information for an analytical method to measure the degree of substitution and results of the analysis of at least five commercially available batches. The specifications were made tentative pending submission of these data by the end of 2013.

3.2 Revision of specifications

3.2.1 *Annatto extracts (solvent-extracted bixin and solvent-extracted norbixin)*

At the present meeting, the Committee considered information on the levels of residual solvents in commercial preparations of solvent-extracted annatto extracts of bixin and norbixin. The Committee noted that levels of methanol, isopropanol or acetone in many commercially available preparations exceeded those in the current specifications by a large margin. In the absence of sufficient information on residual solvent levels received

in response to the call for data, the Committee decided not to revise the provision for residual solvents in these substances. The Committee recommended that manufacturers supply residual solvent data from at least five batches of each of the solvent-extracted bixin and norbixin products to support the possible revision of the provision for residual solvents. The existing specifications were maintained.

The Committee also considered the suitability of the general method for the determination of residual solvents published in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*) for the analysis of solvent-extracted bixin and norbixin products. The Committee concluded that neither solvent listed in the method is suitable for the analysis of solvent-extracted bixin and norbixin by headspace gas chromatography. Accordingly, the Committee considered a method to allow the use of dimethyl formamide as the dilution solvent. This method will be published as tentative in FAO JECFA Monographs 14 (2013) and included in the online version of Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*). In order to evaluate the suitability of the method for the determination of residual solvents in annatto extracts dissolved in dimethyl formamide, the Committee recommends that manufacturers provide results from the analysis of samples of solvent-extracted bixin and norbixin products using both methods.

3.2.2 *Benzoe tonkinensis*

The specifications of Benzoe tonkinensis prepared at the seventy-fourth meeting of the Committee (Annex 1, reference *205*) were made tentative pending submission of the following data: complete composition of the ethanolic extract, data on microbiological contaminants, data on inorganic contaminants (lead, arsenic, antimony, chromium, mercury and cadmium) and an analytical method to distinguish between Benzoe tonkinensis and Benzoe sumatranus.

In response to a call for data, the Committee at the present meeting received only some of the requested data, including information on inorganic contaminants and a gas chromatographic–mass spectrometric method to determine cinnamic acid, used to distinguish between Benzoe tonkinensis and Benzoe sumatranus. The Committee noted that the data provided were not sufficient to revise the specifications and decided that the tentative specifications will be withdrawn if the complete data on the composition of the ethanolic extract and microbiological contaminants are not received by the end of 2013.

3.2.3 *Food additives containing aluminium and/or silicon*

The Committee at its seventy-sixth meeting (Annex 1, reference *211*) reviewed the analytical methods for food additives containing aluminium

and/or silicon and found that some test methods use potentially corrosive or hazardous reagents that may not be permitted in current laboratory safety protocols. The Committee also noted that aluminium silicate, calcium silicate and sodium aluminosilicate have no provisions for assay. Calcium aluminium silicate, aluminium silicate, calcium silicate and silicon dioxide were placed on the agenda of the current meeting for revision of their specifications. In addition, the Committee, at its current meeting, agreed that it was appropriate to revise the specification for sodium aluminosilicate, while noting that it had not been included in the call for data.

The Committee received limited information on the assay of aluminium silicate, calcium silicate and sodium aluminosilicate. However, other requested information was not received.

Specifications were revised and made tentative pending the submission of the requested information. Information required includes composition; methods of manufacture; data on loss on drying and loss on ignition; impurities (lead, cadmium, arsenic and mercury) soluble in hydrochloric acid (0.5 mol/l); and suitability of the proposed inductively coupled plasma – atomic emission spectrophotometric (ICP-AES) method for assay, as well as data on the assay. Details on information required will be included in the respective tentative specifications monographs (FAO JECFA Monographs 14 (2013)). The tentative specifications will be withdrawn unless the requested information is received by the end of 2014.

3.2.4 *Food additives containing phosphates: Analytical methods for the determination of phosphorus and revision of specifications*

At its seventy-sixth meeting (Annex 1, reference *211*), the Committee introduced an ICP-AES method while preparing the specifications for magnesium dihydrogen diphosphate, as the titrimetric and gravimetric methods incorporated in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*) were not reliable for the assay. The Committee requested information on the suitability of the ICP-AES method for the assay of other phosphate additives. The Committee, at its current meeting, agreed to publish the method in FAO JECFA Monographs 14 (2013) and updated the online version of Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*) accordingly.

The Committee noted that the general method used for the determination of cyclic phosphates in polyphosphates, as published in Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*), is lengthy and uses perchloric acid, which may not be permitted in current laboratory safety protocols. The Committee recommends that the method for the determination of cyclic phosphates be reviewed at a future meeting.

The Committee also noted that the specifications for some of the phosphate additives need updating and recommends placing these additives on the agenda at a future meeting.

3.2.5 *Mineral oil (medium viscosity)*

The Committee at its seventy-sixth meeting (Annex 1, reference *211*) drafted specifications for mineral oil (medium viscosity) from an existing monograph. In the call for data for the present meeting, the Committee requested information for the revision of provisions and methods of analysis in the specifications. In response to information received, the Committee agreed to replace the gas chromatographic method using a packed column for the determination of carbon number at 5% distillation with the proposed gas chromatographic method using a wide-bore column. The replacement method was introduced into the specifications and will be published in FAO JECFA Monographs 14 (2013). The method will be added to the online version of Volume 4 of the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*).

3.2.6 *Modified starches*

The specifications for modified starches cover 16 different modified starches, including starch sodium octenyl succinate. Modified starches were on the agenda of the present meeting due to a minor inconsistency in the specifications of starch sodium octenyl succinate. One of the provisions of starch sodium octenyl succinate concerns the percentage of octenyl succinate, whereas the associated analytical method provides the degree of substitution. The analytical method was therefore revised to calculate the percentage of octenyl succinate groups. The revised method will be published in FAO JECFA Monographs 14 (2013), and the online version will be amended accordingly.

3.2.7 *Paprika extract*

The sixty-ninth meeting of the Committee (Annex 1, reference *190*) prepared tentative specifications for paprika extract and required additional information in order to be able to remove the tentative status. At the present meeting, the Committee considered the detailed batch information received on composition, levels of capsaicinoids and levels of arsenic in paprika extract. The Committee considered the major coloured components and decided to remove capsorubin from the specifications because it appears to be a minor component of the article in commerce. The Committee also considered the levels of capsaicinoids in the samples in commerce and set a maximum content of 200 mg/kg; maximum arsenic levels were lowered to 1 mg/kg.

The Committee also noted that paprika extract was not soluble in water and accepted the proposal to use refined soya bean oil as the carrier for the

headspace gas chromatographic determination of the residual solvents. The specifications were revised, and the tentative status was removed. The Chemical and Technical Assessment prepared at the sixty-ninth meeting was modified to include the composition of commercial preparations.

3.2.8 *3-Phytase from* Aspergillus niger *expressed in* Aspergillus niger

The Committee at its seventy-sixth meeting (Annex 1, reference *211*) had prepared the specifications for 3-phytase from *Aspergillus niger* expressed in *A. niger*. CCFA at its Forty-fifth Session (*2*) requested some minor changes to the analytical method to measure the activity of 3-phytase. The Committee revised the specifications to incorporate the proposed changes.

3.2.9 *Potassium aluminium silicate*

Potassium aluminium silicate was on the agenda of the present meeting for the purpose of revising the tentative specifications. At its seventy-fourth meeting (Annex 1, reference *205*), the Committee prepared new tentative specifications for potassium aluminium silicate (PAS). PAS was referred to the Committee for evaluation as a carrier substrate for pearlescent pigments made with titanium dioxide and/or iron oxide. Information submitted indicated that PAS was not intended to be placed on the market as an additive itself; rather, it was only to be used as a carrier substrate as part of the pearlescent pigments.

At the seventy-fourth meeting, the Committee requested information on the preparation and purification of PAS, methods of identification, particle size distribution and inorganic impurities. The Committee also requested information on the suitability of the proposed ICP-AES method for the assay. At the present meeting, the Committee received sufficient information to revise the specifications. An identification test for aluminium and silicon based on alkali fusion followed by ICP-AES analysis was introduced. Individual specifications for metallic impurities were grouped together under the test "Impurities soluble in 0.5 M hydrochloric acid". The assay method based on alkali fusion followed by ICP-AES analysis was retained.

PAS was considered for evaluation as an anticaking agent at the twenty-eighth and twenty-ninth meetings of the Committee (Annex 1, references *66* and *70*). At that time, no information about the manufacture or use of PAS was provided, and therefore no ADI or specifications could be established. While no additional information regarding the use of PAS as an anticaking agent was submitted to the current meeting, the Committee noted that the Codex *Class Names and the International Numbering System for Food Additives* (*14*) includes PAS (INS No. 555) with the functional class of anticaking agent. The Committee was aware of possible uses of PAS as an anticaking

agent in certain cheese (sliced, cut, shredded or grated cheese) and cocoa products (cocoa–sugar mixture). Therefore, the functional use of anticaking agent was added to the specifications monograph for PAS.

The specifications were revised, and the tentative status was removed. A Chemical and Technical Assessment was prepared.

3.2.10 *Potassium aluminium silicate–based pearlescent pigments*

The Committee, at its seventy-fourth meeting (Annex 1, reference *205*), prepared new tentative specifications for potassium aluminium silicate–based pearlescent pigments (PAS-BPP) based on information received regarding the use of PAS as a carrier substrate for titanium dioxide and/or iron oxide. PAS-BPP are used as colours and are produced by the deposition of titanium and/or iron salts on PAS followed by calcination at high temperatures. The resulting pigment consists of PAS coated with titanium dioxide or iron oxide or a mixture of titanium dioxide and iron oxide.

At its seventy-fourth meeting, the Committee requested information on the manufacture, stability, particle size distribution and inorganic impurities of PAS-BPP. The Committee also requested information on the suitability of the proposed ICP-AES method for the assay.

At the present meeting, PAS-BPP was on the agenda for the purpose of the revision of tentative specifications. Sufficient information was received to revise the specifications. The Committee decided to split the combined tentative specifications prepared at the seventy-fourth meeting into three separate specifications for PAS-BPP based on the type of material deposited on PAS. The three specifications are defined as follows: 1) PAS-BPP, Type I: PAS coated with titanium dioxide only; 2) PAS-BPP, Type II: PAS coated with iron oxide only; and 3) PAS-BPP, Type III: PAS coated with both titanium dioxide and iron oxide. An identification test for titanium and/or iron was introduced based on alkali fusion followed by ICP-AES analysis. Individual specifications for metallic impurities were grouped together under the test "Impurities soluble in 0.5 M hydrochloric acid". The assay method based on alkali fusion followed by ICP-AES analysis was retained. However, specifications for pH and particle size, present in the tentative combined specifications monograph prepared at the seventy-fourth meeting, were removed, as the Committee considers that these tests could be removed without affecting the identification and quality features of the specifications. A general statement under the definition section in all three monographs was included indicating that particles of PAS-BPP smaller than 100 nm should not be present.

Although a method of assay was included for all three monographs, an assay value was not provided, as each of the three PAS-BPP monographs encompasses a wide range of pearlescent pigments for each type with different

contents of PAS, titanium dioxide and/or iron oxide based on the desired properties of the pearlescent pigment. As a result, a value of “as labelled” was provided under the assay to allow for the variability expected for the multiple types of available pearlescent pigments.

The specifications were revised, and the tentative status was removed. A Chemical and Technical Assessment was prepared.

4. Contaminants

4.1 Cadmium: Assessment of exposure from cocoa and cocoa products

Explanation

Cadmium was evaluated by the Committee at its sixteenth, thirty-third, forty-first, fifty-fifth, sixty-first, sixty-fourth and seventy-third meetings (Annex 1, references *30*, *83*, *107*, *149*, *166*, *176* and *202*). At the sixty-first and sixty-fourth meetings, the Committee noted that the estimated total mean population dietary exposure to cadmium from all foods, derived from per capita data from the five GEMS/Food regional diets, ranged from 40% to 60% of the provisional tolerable weekly intake (PTWI) applicable at that time, 7 μg/kg bw. The seven commodity groups that contributed significantly to total dietary exposure to cadmium were rice, wheat, root vegetables, tuber vegetables, leafy vegetables, other vegetables and molluscs (40–85% of the total dietary exposure to cadmium across the five regional diets).

At its seventy-third meeting, the Committee re-evaluated cadmium and established a provisional tolerable monthly intake (PTMI) of 25 μg/kg bw, reflecting the long half-life of cadmium in humans. The estimates of mean dietary exposure to cadmium from all foods reported from national estimates for adults ranged from 2.2 to 12 μg/kg bw per month, or 9–48% of the PTMI; for European children up to 12 years of age, the mean dietary exposure to cadmium was 11.9 μg/kg bw per month (47% of the PTMI). High-percentile dietary exposures to cadmium for adults were reported to range from 6.9 to 12.1 μg/kg bw per month (28–48% of the PTMI), and for children aged 0.5–12 years, from 20.4 to 22.0 μg/kg bw per month (82–88% of the PTMI). Cadmium occurrence data and consumption of foods containing cocoa and its derivatives were included in these estimates.

CCCF, at its Sixth Session (*8*), requested that the Committee conduct an assessment of dietary exposure to cadmium from cocoa and cocoa products. The Committee considered the exposure to cadmium from foods containing cocoa and its derivatives in the context of overall dietary exposure as reported at the seventy-third meeting of the Committee.

Occurrence data for cadmium in cocoa and cocoa products

The Committee received occurrence data on cadmium in cocoa and cocoa products from 13 countries (Australia, Czech Republic, Denmark, Ecuador, Estonia, France, Germany, New Zealand, Romania, Singapore, Slovakia, Sweden and the USA). In total, 3919 individual samples collected from 2002 to 2011 were analysed, the majority of which were reported for products available in the European region. Aggregated mean and median cadmium occurrence data were submitted from Australia, Ecuador, Singapore and New Zealand, with information on sample size, but these were not used in the dietary exposure assessment. The Committee classified the submitted data using five GEMS/Food identifiers: cocoa bean, cocoa powder, cocoa mass, cocoa beverage and other cocoa products (including chocolate). Fifty per cent of the samples were for other cocoa products, and 33% were for cocoa powder. Of the total number of samples, 452 were below the limit of quantification (LOQ). These data were assigned a value of the LOQ, as there was no significant difference between estimates made using an upper-bound (replacing samples below the LOQ by the LOQ) or a lower-bound (replacing samples below the LOQ by 0) occurrence value. The Committee noted that no occurrence data for cocoa butter were submitted. The occurrence data are summarized in Tables 1 and 2. The guidelines for conducting international dietary exposure assessments for contaminants in foods (*9*) recommend that when the distribution of contaminant occurrence data is skewed, the median or geometric mean, rather than the arithmetic mean, should be used in the dietary exposure estimate. For cadmium occurrence data where there are a small number of non-detect values (<LOQ), the use of the geometric mean was considered by the Committee to be appropriate. As cocoa beans and cocoa mass are not consumed without further processing, these data were not used in the national dietary exposure assessments.

Assessment of dietary exposure

International estimates

The guidelines for conducting international dietary exposure assessments for contaminants in foods using GEMS/Food diets recommend that per capita data for each Cluster Diet be matched with average contaminant values for foods containing the food chemical of interest derived as summary values from occurrence data for the relevant countries in that cluster (*9*). However, in this case, cocoa is grown in a restricted area in the world, such that individual products made from cocoa and its derivatives would tend to have the same cadmium levels wherever they are offered for purchase. The Committee therefore decided to use the summary occurrence data for cocoa mass, as given in Table 2, to best represent products containing cocoa and its derivatives at the raw commodity level for the international dietary exposure estimates,

Table 1
Summary of cadmium occurrence data for cocoa and cocoa products

Cocoa product	*N* (total)	Minimum concentration (µg/kg)	Maximum concentration (µg/kg)	*N* > 100 µg/kg (%)	*N* > 300 µg/kg (%)	*N* > 500 µg/kg (%)	*N* > 1000 µg/kg (%)
Cocoa bean	451	ND	5239	392 (86.9%)	324 (71.8%)	245 (54.3%)	119 (26.4%)
Cocoa beverage	137	ND	290	13 (0.0%)	0	0	0
Cocoa mass	85	15	593.8	36 (37.9%)	6 (6.3%)	4 (4.2%)	0
Cocoa powder	1292	ND	1910	669 (47.4%)	55 (3.9%)	21 (1.5%)	6 (0.5%)
Other cocoa products (including chocolate)	1954	ND	1073	408 (20.8%)	78 (4.0%)	7 (0.4%)	1 (0.05%)

ND, not detected

Table 2
Summary of statistical descriptors for cadmium occurrence data

Cocoa product	Concentration (µg/kg)			
	Mean	Geometric mean	Median	97.5th percentile
Cocoa bean	751	467	570	2190
Cocoa beverage	35	22	21	160
Cocoa mass	136	103	88	537
Cocoa powder	130	86	130	430
Other cocoa products (including chocolate)	76	34	32	361

as cocoa beverage, cocoa powder and other cocoa products are made from cocoa mass exported from the producing countries. Per capita food amounts for cocoa and its derivatives ranged from 0.1 to 7.5 g/day across the 17 Cluster Diets (see Annex 3 for a list of countries included in each of the 17 Cluster Diets). The geometric mean of the occurrence levels for cocoa mass was multiplied by the corresponding per capita figure to estimate mean population dietary exposure to cadmium from cocoa products for each cluster of countries. These estimates were extrapolated to a monthly basis by multiplying the daily exposures by 30, then considered relative to the PTMI.

The estimates of mean population dietary exposure to cadmium from cocoa and its derivatives ranged from 0.005 µg/kg bw per month (Cluster 13) to 0.39 µg/kg bw per month (Cluster 7), assuming a 60 kg body weight, which equated to 0.2–1.6% of the PTMI.

National estimates

The Committee considered a number of exposure calculation scenarios for preparing the national estimates of dietary exposure to cadmium. These included combining weighted mean and high-percentile food consumption data with the geometric mean or high-percentile occurrence data. Two scenarios were selected from the options considered to best represent dietary exposure to cadmium from products containing cocoa and its derivatives: mean dietary exposures for consumers only were estimated by combining the geometric mean occurrence data for cadmium for cocoa beverages, cocoa powder and other cocoa products with the relevant mean food consumption data for consumers; and 97.5th percentile dietary exposures for consumers only were estimated by combining geometric mean occurrence data for cadmium for cocoa beverages, cocoa powder and other cocoa products with the relevant 97.5th percentile food consumption data for consumers. The Committee considered that it was not appropriate to combine the 97.5th percentile food consumption data for consumers only with the 97.5th percentile occurrence data for a chronic dietary exposure estimate.

The Committee used summary food consumption data derived from individual records from a total of 36 different surveys on national consumption submitted by Brazil, China and the European Food Safety Authority (EFSA) for the national dietary exposure estimates. For the European data (22 countries, 34 surveys), the consumption data for cocoa beverages, cocoa powder and other cocoa products for the whole population (mean amount) and consumers only (mean and 97.5th percentile food consumption amounts) were combined with the appropriate geometric mean occurrence data to prepare the dietary exposure estimates for six age groupings taken from the EFSA data set: toddlers (2–6 years of age), other children (7–11 years of age), adolescents (12–19 years of age), adults (20–65 years of age), elderly (65–75 years of age) and very elderly (>75 years of age). Dietary exposures for the general population and women of childbearing age in Brazil and China, as well as for children in China, were also estimated. National dietary exposure estimates for cadmium from cocoa beverages, cocoa powder and other cocoa products are summarized in Table 3, with data presented on the mean dietary exposure for the whole population, for consumers of each product only and for the 97.5th percentile of exposure for consumers of each product.

Estimated mean dietary exposures to cadmium for the whole population across different age groups from cocoa beverages ranged from 0.02 to

Table 3
Dietary exposure estimates for cocoa derivatives

Cocoa product	Country/ region	Age group	Dietary exposure (µg/kg bw per month)		
			Whole population	Consumers only	
				Mean	97.5th percentile
Cocoa beverages	EU	Infants	—	—	—
		Toddlers[a]	—	2.0	—
		Other children	0.058	2.3	11.9
		Adolescents	0.138	1.8	6.2
		Adults	0.037	1.2	5.2
		Elderly	0.020	1.5	4.7
		Very elderly	0.017	1.1	2.8
Cocoa powder	EU	Infants[a]	—	0.4	—
		Toddlers	0.035	0.6	5.1
		Other children	0.085	0.6	12.0
		Adolescents	0.076	0.4	2.4
		Adults	0.006	0.1	2.2
		Elderly	0.004	0.1	0.6
		Very elderly	0.005	0.2	2.0
	China	General population	0.001	1.6	4.5
		Children[b]	—	—	—
		Women of childbearing age	0.002	2.3	8.8
	Brazil	General population	0.118	1.0	3.2
		Women of childbearing age	0.127	0.9	2.5
Other cocoa products	EU	Infants[a]	0.006	0.8	1.5
		Toddlers	0.302	1.0	3.7
		Other children	0.461	0.8	5.6
		Adolescents	0.257	0.5	4.4
		Adults	0.109	0.3	3.7
		Elderly	0.052	0.2	1.1
		Very elderly	0.056	0.2	1.4
	China	General population	0.001	0.5	1.8
		Children	0.005	1.1	7.8
		Women of childbearing age	0.001	0.3	1.6
	Brazil	General population	0.051	0.9	4.4
		Women of childbearing age	0.067	0.9	4.2

[a] Number of consumers <11.
[b] One consumer reported.

0.14 μg/kg bw per month (0.08–0.6% of the PTMI); from cocoa powder, from 0.001 to 0.13 μg/kg bw per month (0.004–0.5% of the PTMI); and from other cocoa products, from 0.001 to 0.46 μg/kg bw per month (0.004–1.8% of the PTMI). Estimated mean dietary exposures across different population age groups for consumers of cocoa beverages ranged from 1.1 to 2.3 μg/kg bw per month (4–9% of the PTMI); for consumers of cocoa powder, from 0.1 to 2.3 μg/kg bw per month (0.4–9% of the PTMI); and for consumers of other cocoa products, from 0.2 to 1.1 μg/kg bw per month (0.8–4% of the PTMI). Estimated 97.5th percentile dietary exposures to cadmium across different population age groups for consumers only of cocoa beverages ranged from 2.8 to 11.9 μg/kg bw per month (11–48% of the PTMI); for consumers only of cocoa powder, from 0.6 to 12.0 μg/kg bw per month (2–48% of the PTMI); and for consumers only of other cocoa products, from 1.1 to 7.8 μg/kg bw per month (4–31% of the PTMI).

Evaluation

The estimates of mean population dietary exposure to cadmium from products containing cocoa and its derivatives for the 17 GEMS/Food Cluster Diets ranged from 0.005 to 0.39 μg/kg bw per month, which equated to 0.02–1.6% of the PTMI. This represents an estimate of mean dietary exposure to cocoa and its derivatives for the whole population. Similar mean population cadmium dietary exposures for individual cocoa products were estimated from national data, ranging from 0.001 to 0.46 μg/kg bw per month (0.004–1.8% of the PTMI).

On a national level, it was also possible to estimate dietary exposures for consumers of cocoa products (cocoa beverages, cocoa powder and other cocoa products). As expected, due to the smaller population of consumers of each product, these were higher than the population mean dietary exposures. Estimated mean and 97.5th percentile cadmium dietary exposures for consumers of cocoa beverages and cocoa powder were higher than the corresponding exposures for consumers of other cocoa products.

The Committee assessed the potential dietary exposure to cadmium for high consumers of products containing cocoa and its derivatives in addition to cadmium derived from other foods by adding the highest 97.5th percentile dietary exposure estimate for adults and children out of the three cocoa food groups for any of the countries considered to the mean population dietary exposure estimate for cadmium for adults and children from the whole diet, as previously estimated at the seventy-third meeting. For adults, the total cadmium dietary exposure for a high consumer of products containing cocoa and its derivatives was estimated to be 7.4–17.2 μg/kg bw per month (2.2–12 μg/kg bw per month for mean exposure from all foods plus 5.2 μg/kg bw

per month from the highest 97.5th percentile exposure from cocoa beverages), or 30–69% of the PTMI. For children aged 0.5–12 years, the total cadmium dietary exposure for a high consumer of products containing cocoa and its derivatives was estimated to be 23.9 µg/kg bw per month (11.9 µg/kg bw per month for mean exposure from all foods plus 12 µg/kg bw per month for the highest 97.5th percentile exposure from cocoa powder), or 96% of the PTMI. The Committee noted that this total cadmium dietary exposure for high consumers of cocoa and cocoa products was likely to be overestimated, because the estimate for dietary exposure to cadmium from the whole diet also included a contribution from products containing cocoa and its derivatives. The Committee did not consider contributions from products containing cocoa and its derivatives to total cadmium exposure for high consumers of these products to be of concern.

No addendum to the toxicological monograph was prepared.

Detailed information on cadmium occurrence data and national food consumption data used in the evaluation are available on the JECFA web site[5].

[5] http://www.who.int/foodsafety/chem/jecfa/publications/reports/en/index.html

5. Future work and requests for data

Advantame

New tentative specifications were prepared, pending the submission of information, **by the end of 2015**, on:

- the suitability of the headspace gas chromatographic method (using appropriate dissolution solvent) for determination of residual solvents, published in Volume 4 of the *Combined Compendium of Food Additive Specifications*, and data, in a minimum of five batches, using the method;
- an alternative or improved high-performance liquid chromatographic method for the assay of advantame and advantame acid using a standard curve;
- additional data and analytical methods for the determination of palladium and platinum;
- information on the purity and availability of the commercial reference standards used in the assay of advantame and advantame acid.

Analytical method for the determination of carbon number at 5% distillation point

The Committee recommended that a note be included in Volume 4 of the *Combined Compendium of Food Additive Specifications* to indicate the availability of a newer method. The Committee further recommended that the suitability of this method for use in the analysis of similar substances be evaluated at a future meeting.

Analytical method for the determination of residual solvents by headspace gas chromatography

The Committee recommended that the issue of the suitability of dissolution solvents for the determination of residual solvents in food additives be investigated at a future meeting.

Annatto extracts (solvent-extracted bixin and solvent-extracted norbixin)

The Committee recommended that manufacturers supply residual solvent data from at least five batches of each of the solvent-extracted bixin and norbixin products to support the possible revision of the provision for residual solvents. To evaluate the suitability of the method for the determination of residual solvents in annatto extracts dissolved in dimethyl formamide, the Committee also recommended that manufacturers provide results from the analysis of samples of solvent-extracted bixin and norbixin products using this method as well as the general method for the determination of residual solvents published in Volume 4 of the *Combined Compendium of Food Additive Specifications*.

Benzoe tonkinensis

The tentative specifications will be withdrawn if the complete data on the composition of the ethanolic extract and microbiological contaminants are not received **by the end of 2013**.

Food additives containing aluminium and/or silicon

Specifications were made tentative pending the submission of information on composition; methods of manufacture; data on loss on drying and loss on ignition; impurities (lead, cadmium, arsenic and mercury) soluble in hydrochloric acid (0.5 mol/l); and suitability of the proposed ICP-AES method for assay, as well as data on the assay. Details on information required are included in the respective tentative specifications monographs. The tentative specifications will be withdrawn unless the requested information is received **by the end of 2014**.

Glycerol ester of gum rosin

The specifications were maintained as tentative pending the submission of additional information **by the end of 2014**. Additional data are requested to characterize GEGR in commerce in relation to the composition of 1) the refined gum rosin currently used as the source rosin with regard to the levels (%) of resin acids and neutrals, 2) the glycerol ester of gum rosin with regard to the levels (%) of a) glycerol esters, b) free resin acids and c) neutrals and 3) the total glycerol esters of resin acids with regard to the levels (%) of a) glycerol monoesters and b) the sum of glycerol diesters and triesters (assay). Validated methods for the determination of the substances considered in the specifications are also required.

Octenyl succinic acid modified gum arabic

The Committee noted that ongoing studies on the stability of OSA modified gum arabic in food may provide further information on its chemical state in

food and aqueous solutions, which could help to explain the contradictory results of the hydrolysis study submitted to the Committee at the present meeting. The Committee decided to retain the temporary ADI "not specified" pending submission of additional data on the stability of OSA modified gum arabic in food **by the end of 2013**.

The Committee noted that the purity test of degree of esterification in the current specifications should be replaced by the degree of substitution and requested information for an analytical method to measure the degree of substitution and results of the analysis of at least five commercially available batches. The specifications were made tentative pending submission of these data **by the end of 2013**.

Phosphates: Analytical methods for the determination of phosphorus and revision of specifications

The Committee noted that the general method used for the determination of cyclic phosphates in polyphosphates, as published in Volume 4 of the *Combined Compendium of Food Additive Specifications*, is lengthy and uses perchloric acid, which may not be permitted in current laboratory safety protocols. The Committee recommends that the method for the determination of cyclic phosphates be reviewed at a future meeting.

The Committee also noted that the specifications for some of the phosphate additives need updating and recommends placing these additives on the agenda at a future meeting.

6. Recommendations

Annatto extracts (solvent-extracted bixin and solvent-extracted norbixin)

The Committee recommends that manufacturers supply residual solvent data from at least five batches of each of the solvent-extracted bixin and norbixin products to support the possible revision of the provision for residual solvents.

In order to evaluate the suitability of a method for the determination of residual solvents in annatto extracts dissolved in dimethyl formamide for the analysis of solvent-extracted bixin and norbixin products, the Committee recommends that manufacturers provide results from the analysis of samples of solvent-extracted bixin and norbixin products using this method as well as the general method for the determination of residual solvents published in Volume 4 of the *Combined Compendium of Food Additive Specifications* for the analysis of solvent-extracted bixin and norbixin products.

Requirements for submission of analytical methods

In order to assess and ensure the accuracy and reliability of the data submitted, the Committee recommends the use of methods that are appropriately validated. It also recommends that in relevant cases, the detailed analytical method be provided, together with validation data, in response to specific JECFA calls for data.

Acknowledgements

The Committee wishes to thank Ms M. Sheffer, Ottawa, Canada, for her assistance in the preparation of the report. The Committee also expresses its appreciation to Ms Clélia Bianchi, Intern, Department of Food Safety and Zoonoses, WHO, Geneva, for her presentation on the new GEMS/Food Cluster Diets.

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Annex 1

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

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212. *Safety evaluation of certain food additives.* WHO Food Additives Series, No. 67, 2012.

213. *Compendium of food additive specifications.* FAO JECFA Monographs 13, 2012.

Annex 2
Toxicological and dietary exposure information and information on specifications

Food additives considered for specifications only

Food additive	Specifications[a]
Aluminium silicate	R, T
Annatto extracts (solvent-extracted bixin)	M
Annatto extracts (solvent-extracted norbixin)	M
Benzoe tonkinensis	M, T
Calcium aluminium silicate	R, T
Calcium silicate	R, T
Food additives containing phosphates	R[b]
Mineral oil (medium viscosity)	R
Modified starches	R[c]
Paprika extract	R[d]
Phytase from *Aspergillus niger* expressed in *Aspergillus niger*	R
Potassium aluminium silicate	R[d]
Potassium aluminium silicate–based pearlescent pigments, Type I	N[e]
Potassium aluminium silicate–based pearlescent pigments, Type II	N[e]
Potassium aluminium silicate–based pearlescent pigments, Type III	N[e]
Silicon dioxide, amorphous	R, T
Sodium aluminosilicate	R, T

[a] M, existing specifications maintained; N, new specifications; R, existing specifications revised; T, tentative specifications.

[b] The inductively coupled plasma – atomic emission spectrophotometric (ICP-AES) method for the assay of phosphate additives was added to the *Combined Compendium of Food Additive Specifications*.

[c] The method for determination of percentage of octenyl succinate groups in starch sodium octenyl succinate was revised.

[d] The tentative status of the specifications was removed.

[e] The existing combined specifications for potassium aluminium silicate–based pearlescent pigments were split into three separate specifications (Type I: coated with titanium oxide only, Type II: coated with iron oxide only and Type III: coated with both titanium dioxide and iron oxide). The tentative status of the specifications was removed.

Food additives evaluated toxicologically, assessed for dietary exposure and considered for specifications

Food additive	Specifications[a]	Acceptable daily intakes, other toxicological recommendations and dietary exposure assessment
Advantame	N, T	**The Committee established an acceptable daily intake (ADI) of 0–5 mg/kg body weight (bw) for advantame** on the basis of a no-observed-adverse-effect level (NOAEL) of 500 mg/kg bw per day for maternal toxicity in a developmental toxicity study in rabbits and application of a 100-fold safety factor to account for interspecies and intraspecies variability. The Committee agreed that the ADI also applies to those individuals with phenylketonuria, as the formation of phenylalanine from the normal use of advantame would not be significant in relation to this condition. Using the proposed maximum use levels and conservative assumptions, the maximum mean dietary exposure to advantame would be 1.45 mg/kg bw per day (29% of the upper bound of the ADI), and the maximum high-percentile dietary exposure would be 2.16 mg/kg bw per day (43% of the upper bound of the ADI).
Glucoamylase from *Trichoderma reesei* expressed in *Trichoderma reesei*	N	Based on its low toxicity and because it is reasonably anticipated that dietary exposure would be very low, **the Committee established an ADI "not specified"[b] for the glucoamylase enzyme preparation from *T. reesei* expressed in *T. reesei*** used in the applications specified and in accordance with good manufacturing practice.
Glycerol ester of gum rosin (GEGR)	R, T	As the requested two unpublished 90-day oral toxicity studies on GEGR in rats and complete information on the composition of GEGR were not submitted, **the Committee withdrew the temporary group ADI of 0–12.5 mg/kg bw for GEGR and glycerol ester of wood rosin (GEWR)** (see below).
Glycerol ester of tall oil rosin (GETOR)	W	No data on GETOR were submitted, and the Secretariat was informed that this compound is no longer supported by the previous data sponsor. Therefore, **the Committee did not evaluate GETOR**.
Glycerol ester of wood rosin (GEWR)	R[c]	As the requested data on GEGR were not submitted, **the Committee withdrew the temporary group ADI of 0–12.5 mg/kg bw for GEGR and GEWR and re-established the ADI of 0–25 mg/kg bw for GEWR.**

Food additive	Specifications[a]	Acceptable daily intakes, other toxicological recommendations and dietary exposure assessment
Nisin	R	**The Committee established an ADI for nisin of 0–2 mg/kg bw** on the basis of a NOAEL of 224.7 mg of nisin per kilogram body weight per day from a 13-week study in rats and application of a safety factor of 100 to account for interspecies and intraspecies variability. The Committee did not consider it necessary to use an additional safety factor to account for the short duration of the study because no compound-related effects were observed at any dose in any of the toxicity studies, including a reproductive toxicity study in rats, and because ingested nisin is degraded in the upper part of the intestinal tract, such that systemic exposure to nisin is not likely to occur. The highest estimated dietary exposure of 0.07 mg of nisin per kilogram body weight per day determined at the current meeting did not exceed the upper bound of the ADI. **The Committee withdrew the previous ADI of 0–33 000 units of nisin per kilogram body weight established at the twelfth meeting**.
Octenyl succinic acid (OSA) modified gum arabic	R, T	**The Committee decided to retain the temporary ADI "not specified"[b]** pending submission of additional data on the stability of OSA modified gum arabic in food by the end of 2013, which may help to explain contradictory hydrolysis data.

[a] M, existing specifications maintained; N, new specifications; R, existing specifications revised; T, tentative specifications; W, existing specifications withdrawn.

[b] ADI "not specified" is used to refer to a food substance of very low toxicity that, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary exposure to the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice—i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

[c] The tentative status of the specifications was removed.

Contaminants

Cadmium: Assessment of exposure from cocoa and cocoa products

The Codex Committee on Contaminants in Foods, at its Sixth Session, requested that the Committee conduct an assessment of dietary exposure to cadmium from cocoa and cocoa products.

The estimates of mean population dietary exposure to cadmium from products containing cocoa and its derivatives for the 17 new Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/

Food) Cluster Diets (see Annex 3) ranged from 0.005 to 0.39 μg/kg bw per month, which equated to 0.02–1.6% of the provisional tolerable monthly intake (PTMI) of 25 μg/kg bw. Similar mean population cadmium dietary exposures for individual cocoa products were estimated from national data, ranging from 0.001 to 0.46 μg/kg bw per month (0.004–1.8% of the PTMI).

The potential dietary exposures to cadmium for high consumers of products containing cocoa and its derivatives in addition to cadmium derived from other foods were estimated to be 30–69% of the PTMI for adults and 96% of the PTMI for children 0.5–12 years of age. The Committee noted that this total cadmium dietary exposure for high consumers of cocoa and cocoa products was likely to be overestimated and did not consider it to be of concern.

Detailed information on cadmium occurrence data and national food consumption data used in the evaluation will be available on the JECFA web site.

Annex 3
GEMS/Food Cluster Diets 2012

Cluster/country	Cluster/country	Cluster/country	Cluster/country	Cluster/country
G01	Togo	Nicaragua	Democratic	Ethiopia
Afghanistan	Zambia	Panama	People's	Gambia
Algeria		Peru	Republic of	Haiti
Azerbaijan	**G04**	Seychelles	Korea	Kenya
Iraq	Antigua and	South Africa	Guinea Bissau	Malawi
Jordan	Barbuda	Suriname	Indonesia	Mali
Libya	Bahamas	Tajikistan	Lao People's	Namibia
Mauritania	Barbados	The former	Democratic	Niger
Mongolia	Brunei Darussalam	Yugoslav	Republic	Nigeria
Morocco	French Polynesia	Republic of	Myanmar	Senegal
Occupied	Grenada	Macedonia	Nepal	Somalia
Palestian	Israel	Trinidad and	Philippines	Sudan
Territory	Jamaica	Tobago	Sierra Leone	Swaziland
Pakistan	Kuwait	Venezuela,	Thailand	United Republic of
Syrian Arab	Netherlands	Bolivarian	Timor Leste	Tanzania
Republic	Antilles	Republic of	Viet Nam	Zimbabwe
Tunisia	Saint Kitts and			
Turkmenistan	Nevis	**G06**	**G10**	**G14**
Uzbekistan	Saint Lucia	Armenia	Belarus	Comoros
Yemen	Saint Vincent and	Cuba	Bulgaria	Fiji Islands
	the Grenadines	Egypt	Canada	Kiribati
G02	Saudi Arabia	Greece	Croatia	Papua New Guinea
Albania	United Arab	Iran, Islamic	Cyprus	Solomon Islands
Bosnia and	Emirates	Republic of	Estonia	Sri Lanka
Herzegovina		Lebanon	Italy	Vanuatu
Georgia	**G05**	Turkey	Japan	
Kazakhstan	Argentina		Latvia	**G15**
Kyrgyzstan	Bolivia,	**G07**	Malta	Czech Republic
Montenegro	Plurinational	Australia	New Zealand	Denmark
Republic of	State of	Bermuda	Republic of Korea	Hungary
Moldova	Brazil	Finland	Russian	Ireland
Ukraine	Cape Verde	France	Federation	Lithuania
	Chile	Iceland	United States of	Portugal
G03	Colombia	Luxembourg	America	Romania
Angola	Costa Rica	Norway		Serbia and
Benin	Djibouti	Switzerland	**G11**	Montenegro
Burundi	Dominican	United Kingdom	Belgium	Slovakia
Cameroon	Republic	Uruguay	Netherlands	Slovenia
Congo	Ecuador			Sweden
Côte d'Ivoire	El Salvador	**G08**	**G12**	
Democratic	Guatemala	Austria	Belize	**G16**
Republic of the	Guyana	Germany	Dominica	Gabon
Congo	Honduras	Poland		Rwanda
Ghana	India	Spain	**G13**	Uganda
Guinea	Malaysia		Botswana	
Liberia	Maldives	**G09**	Burkina Faso	**G17**
Madagascar	Mauritius	Bangladesh	Central African	Samoa
Mozambique	Mexico	Cambodia	Republic	Sao Tome and
Paraguay	New Caledonia	China	Chad	Principe

Evaluation of certain food additives and contaminants

This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of various food additives and a food contaminant with a view to concluding as to safety concerns and to preparing specifications for identity and purity.

The first part of the report contains a general discussion of the principles governing the toxicological evaluation of and assessment of dietary exposure to food additives. A summary follows of the Committee's evaluations of technical, toxicological and dietary exposure data for seven food additives (advantame; glucoamylase from *Trichoderma reesei* expressed in *Trichoderma reesei*; glycerol ester of gum rosin; glycerol ester of tall oil rosin; glycerol ester of wood rosin; nisin; and octenyl succinic acid modified gum arabic) and an assessment of dietary exposure to cadmium from cocoa and cocoa products.

Specifications for the following food additives were revised: annatto extracts (solvent-extracted bixin and solvent-extracted norbixin); Benzoe tonkinensis; food additives containing aluminium and/or silicon; mineral oil (medium viscosity); modified starches; paprika extract; phosphates (analytical methods for the determination of phosphorus and revision of specifications); 3-phytase from *Aspergillus niger* expressed in *Aspergillus niger*; potassium aluminium silicate; and potassium aluminium silicate–based pearlescent pigments.

Annexed to the report are tables summarizing the Committee's recommendations for dietary exposures to and toxicological evaluations of the food additives and contaminant considered.

ISBN 978-92-4-120983-0