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956

EVALUATION OF CERTAIN FOOD ADDITIVES

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

Food and Agriculture Organization of the United Nations

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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. WHO Food Additives Series, No. 62, 2010.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications. FAO JECFA Monographs 7, 2009.

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met in Geneva from 16 to 24 June 2009. The meeting was opened by Dr Keiji Fukuda, Assistant Director General ad interim, Health Security and Environment Cluster of the World Health Organization (WHO), on behalf of the Directors General of the Food and Agriculture Organization of the United Nations (FAO) and WHO. Dr Fukuda noted the more than 50 years of successful work of the Committee and emphasized the role that the Committee plays in improving and guaranteeing the safety of the global food supply, by providing independent scientific advice as a basis for food standards. As a result of the increasing globalization of food trade, illustrated by last year's melamine food contamination incident, this work is of increasing importance. Dr Fukuda emphasized that work on the provision of international scientific advice on food safety and other related topics remains an important and high priority for FAO and WHO. The Committee was then welcomed by Dr Jørgen Schlundt, Director of the Department of Food Safety and Zoonoses of WHO, who explained recent organizational changes within WHO to reinforce the department's ability to better reflect the farm-to-table approach for food safety assurance.

1.1 Declarations of interests

The Secretariat informed the Committee that all experts participating in the seventy-first meeting had completed declaration of interest forms and that no conflicts had been identified. The following declared interests and potential conflicts were discussed by the Committee. Professor Ron Walker had consulted in the past on some safety aspects for crystalline lycopene and hence did not participate in the discussions on the subject. Dr Brian Whitehouse declared that he had provided consultations for the preparation of a dossier for octenyl succinic acid modified gum arabic. The Committee decided that Dr Whitehouse would not participate in the discussions on this substance.

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 70 previous meetings of the Committee (Annex 1). The present meeting was convened on the basis of a recommendation made at the sixty-ninth meeting (Annex 1, reference *190*).

The tasks before the Committee were:

- to elaborate further principles for evaluating the safety of food additives (section 2);
- to undertake toxicological evaluations of certain food additives (section 3 and Annex 2);
- to review and prepare specifications for certain food additives (section 3 and Annex 2).

2.1 Modification of the agenda

The Committee considered the names of the compounds branching enzyme from *Rhodothermus obamensis* and expressed in *Bacillus subtilis*, lycopene oleoresin extract from tomato and OSA (octenyl succinic acid)-modified acacia gum (gum arabic), which were on the agenda for evaluation for the first time, to be inappropriate. The Committee renamed them, respectively, branching glycosyltransferase from *Rhodothermus obamensis* expressed in *Bacillus subtilis*, lycopene extract from tomato and octenyl succinic acid modified gum arabic.

A temporary acceptable daily intake (ADI) "not specified" was allocated to the food additive cyclotetraglucose and cyclotetraglucose syrup at the sixty-eighth meeting of the Committee (Annex 1, reference *187*) pending submission of information on the identity of the bacterial strain used to produce the 6-α-glucosyltransferase and α-isomaltosyltransferase (6-GT/IMT) enzyme preparation and evidence of its lack of pathogenicity and toxicogenicity. The specifications for cyclotetraglucose syrup were made tentative pending additional information on the total saccharide content and test methods and on

the unidentified saccharide fraction. The Committee received the information requested, and the substances were therefore added to the agenda.

The Committee made recommendations at its sixty-fifth and sixty-seventh meetings (Annex 1, references *178* and *184*) regarding the need to re-evaluate certain alkane hydrocarbon solvents, particularly hexanes, as it was noted that products in commerce could differ from the material originally evaluated. As the recommendations were not sufficiently clear as to the scope of the re-evaluation to be undertaken, the Committee decided to add this item to the agenda with the aim to provide further clarification. In addition, during the evaluation of lycopene extract from tomato, it became apparent that the assessment of this extract depends on the evaluation of lycopene from all sources. Therefore, the Committee decided to add lycopene from all sources to the agenda.

The food additives ethyl lauroyl arginate, pectins, titanium dioxide and triethyl citrate were added to the agenda for minor revisions of specifications. The specifications monograph for glycerol ester of wood rosin was revised as a result of the evaluation of two additional glycerol esters of rosins at the present meeting.

2.2 Report from the forty-first session of the Codex Committee on Food Additives (CCFA)

The Chairperson of the Codex Committee on Food Additives (CCFA), Dr Junshi Chen, informed the Committee of the main achievements and outcomes of the forty-first session of CCFA (Shanghai, China, 16–20 March 2009), including details on texts forwarded to the thirty-second session of the Codex Alimentarius Commission (CAC) for adoption.

Dr Chen briefly summarized the decisions taken by the forty-first session of CCFA related to the recommendations of the sixty-ninth meeting of JECFA (Annex 1, reference *190*) and described the status of development of the Codex General Standard for Food Additives (GSFA). In view of the amount of work still necessary for its completion, the next session of CCFA will consider ways to expedite work on the GSFA. The Committee was informed that CCFA had completed work on inconsistencies identified between the names of the substances listed in the International Numbering System (INS) and in the Codex Specifications for Identity and Purity of Food Additives. In order to prevent more inconsistencies in the future, CCFA recommended that JECFA carefully consider the names of compounds listed in the INS for use in the specifications and, when they are considered not to be appropriate, to clearly indicate the reasons in order to facilitate follow-up actions by CCFA. A series of specific requests, included in the report of the forty-first session of CCFA, would be addressed by JECFA in a future meeting.

Finally, the forty-first session of CCFA agreed to a priority list of compounds for evaluation/re-evaluation by JECFA and also agreed to revise the text of the Circular Letter on Priority List of Food Additives Proposed for Evaluation by JECFA to allow an indication of the names of the country either where the compound is legally traded or where it has been approved and to include more details on data to be submitted by JECFA.

2.3 Principles governing the 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 Environmental Health Criteria, No. 70 (EHC 70), *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated subsequently at a number of its meetings (Annex 1, references *77*, *83*, *88*, *94*, *107*, *116*, *122*, *131*, *137*, *143*, *149*, *152*, *154*, *160*, *166*, *173*, *176*, *178*, *184*, *187* and *190*), including the present one. EHC 70 contains the most important observations, comments and recommendations made, up to the time of its publication, by the Committee and associated bodies in their reports on the safety assessment of food additives.

2.3.1 *Codex GSFA-related questions*

The Committee received two questions from the United States of America (USA), which arose when the USA was preparing a paper on the Codex GSFA for the next session of CCFA.

Sodium and potassium sulfates

The Committee was asked whether the ADI for sodium sulfate also applied to sodium hydrogen sulfate and whether the ADI for potassium sulfate also covered potassium hydrogen sulfate. The Committee had previously evaluated sodium and potassium sulfate; the sulfate ion was allocated an ADI "not specified" at the twenty-ninth meeting (Annex 1, reference *70*). In evaluating sodium hydrogen sulfate at the present meeting, the Committee considered that the principles elaborated at the twenty-ninth meeting for fully ionizable salts were applicable. It further considered that this approach could also be used in evaluating other fully ionizable sulfates, including food-grade potassium sulfate and potassium hydrogen sulfate. In conclusion, the ADI "not specified" for potassium sulfate is also applicable to potassium hydrogen sulfate.

Nisin and nisin preparation

In response to the question as to whether the ADI refers to nisin or nisin preparation, the Committee noted that when the name had been changed from

nisin to nisin preparation at the sixty-eighth meeting of the Committee (Annex 1, reference *187*), no modification was made that would impact the ADI. The Committee at this meeting, after reconsideration, decided to rename the specifications monograph "nisin" (see section 3.2.4).

The Committee also considered the question on a reporting basis for the nisin maximum levels in the Codex GSFA. It was noted that the ADI is expressed based on activity (units/kg body weight [bw]) for nisin and that the activity of individual commercial products may vary significantly.

2.3.2 *JECFA periodic re-evaluation of food additives*

JECFA has repeatedly noted the importance of reviewing substances previously evaluated when new data on those substances become available and in light of further developments in science and risk assessment methodologies. This was brought to the attention of the forty-first session of CCFA (*2*), which requested the JECFA Secretariat to prepare a discussion paper on the topic for consideration at the next session of CCFA.

The JECFA Secretariat presented to the Committee a draft discussion paper on the periodic review of JECFA evaluations of food additives for brief consideration and comments. The paper indicated that, since its establishment, JECFA has evaluated more than 600 food additives (excluding flavouring agents) and that approximately 30% of JECFA evaluations are more than 30 years old. The periodic review mechanisms established by the Codex Committee on Pesticide Residues (CCPR) for pesticide residue evaluations carried out by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the ongoing re-evaluation of food additives by the European Food Safety Authority (EFSA) were also noted.

The Committee noted that many re-evaluations have already been undertaken, based on specific requests from Member States and CAC, and considered that it will be necessary to develop criteria for a periodic review of substances. Criteria that may trigger a review have already been published in EHC 70, and revised criteria will be published in the updated principles and methods document, which is currently being finalized. These may serve as a basis for further consideration, and the revised criteria are repeated here:

> Periodic review of past decisions on safety is made necessary by one or more of the following developments:
>
> - a new manufacturing process for the food additive;
> - a new specification;
> - new data on the biological properties of the compound;
> - new data concerning the nature and/or the biological properties of the impurities present in a food additive;

- advances in scientific knowledge relevant to the nature or mode of action of food additives;
- changes in consumption patterns or level of use of a food additive; and
- improved requirements for safety evaluation. This is made possible by new scientific knowledge and the quality and quantity of safety data considered necessary in the case of food additives and residues of pesticides and veterinary drugs.

The Committee further noted that it is important to take existing assessments into account in the re-evaluation of a food additive and that a process must be developed by which the information needed for the re-evaluation can be provided.

2.3.3 *Data adjustment using food frequency questionnaires to better account for long-term dietary exposure*

Risk characterizations for long-term toxicity compare dietary exposure estimates with the relevant health-based values established for a lifetime. In previous meetings, the Committee often raised the fact that the use of short-term food consumption data to represent long-term dietary habits could lead to an overestimation of the amount of food consumed per day, in particular for foods consumed infrequently.

Typically, chronic dietary exposures are based on food consumption data collected over a period of 1–7 days. The use of surveys of duration longer than 1 day allows the averaging of the amount of food consumed per day to give the amount usually consumed. This will reduce the overestimation of the dietary exposure for chemicals occurring in foods consumed infrequently.

During the current meeting, the Committee examined a submission for an additive for which the "usual" food consumption data collected over a period of 2 days had been adjusted to better describe long-term dietary exposures by the use of food frequency questionnaires that estimated the number of eating occasions for each food over a period of 30 days for a comparable population. In this case, data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES), which reports 2 days of food consumption, had been combined with data from the NHANES III 30-day food frequency survey for the population in the USA.

To better assess chronic dietary exposure, the Committee recommends the use of food consumption data collected over a period of more than 1 day with an averaging of the amounts of food consumed per day. Moreover, the Committee recommends that food consumption data collected over a few days be adjusted by using food frequency questionnaires on a comparable population where these data are available. This approach would better represent long-term consumption for foods consumed infrequently. The

Committee noted, however, that the food categories covered by a food frequency questionnaire are necessarily less numerous and far broader than those in a food recall or record survey. It would be simpler to apply this frequency adjustment to broad food categories (e.g. seafood) rather than to very specific ones (e.g. chocolate-filled biscuit). However, even in the latter case, the number of eating occasions recalled or recorded for the detailed food category could be adjusted relative to the number of eating occasions per month from the broad category.

2.3.4 *Guidelines for the safety evaluation of enzymes produced by genetically modified microorganisms*

At its sixty-fifth meeting (Annex 1, reference *178*), the Committee concluded that guidelines need to be developed on the safety evaluation of enzymes produced by genetically modified microorganisms (GMMs). At the sixty-eighth meeting (Annex 1, reference *187*), the Committee noted the ongoing international initiatives to elaborate guidelines for the safety evaluation of enzymes (including those from GMMs) and microorganisms intended for food applications. At the present meeting, the Committee discussed the new regulation for enzymes enacted by the European Parliament (*3*) and related guidance documents (*4*, *5*).

The Committee decided to update the General Specifications and Considerations for Enzymes Used in Food Processing (*6*) to expand recommendations for microbiology and molecular biology information to be submitted in dossiers for enzymes from microorganisms (including those from GMMs) and to discuss toxicological and other safety studies for enzymes from all sources.

The Committee recommended that the JECFA Secretariat establish a working group to update the current guidance document on enzymes for discussion at a future meeting.

2.4 Hexanes

At the sixty-fifth and sixty-seventh meetings of the Committee (Annex 1, references *178* and *184*), it was noted that the specifications for hexanes should be revised, as the material of commerce, a light petroleum fraction, was a mixture of components of different chain lengths with potential differences in toxicity. At the current meeting, the Committee was made aware that there were new data on the toxicity of *n*-hexane and that the composition of commercially available solvents containing *n*-hexane may not comply with the existing specifications. The Committee concluded that these new data indicate that the specifications and toxicity of hexanes should be reconsidered at a future meeting and reiterated the recommendations made in this regard at the sixty-fifth and sixty-seventh meetings.

3. Specific food additives

The Committee evaluated nine food additives for the first time and re-evaluated a number of others. Information on the safety evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and other information required for certain substances are given in Annex 3.

3.1 Safety evaluations

3.1.1 *Branching glycosyltransferase from* Rhodothermus obamensis *expressed in* Bacillus subtilis

Explanation

At the request of CCFA at its fortieth session (*7*), the Committee evaluated the enzyme branching glycosyltransferase (1,4-α-glucan branching enzyme; Enzyme Commission number 2.4.1.18), which it had not evaluated previously. Branching glycosyltransferase catalyses the transfer of a segment of a 1,4-α-D-glucan chain to a primary hydroxy group in a similar glucan chain to create 1,6-linkages. The enzyme is intended for use in starch processing to obtain modified starch with an increased number of branch points and improved functional properties.

Genetic modification

Branching glycosyltransferase is manufactured by pure culture fermentation of a genetically modified strain of *Bacillus subtilis* containing a synthetic gene coding for branching glycosyltransferase from *Rhodothermus obamensis*. *Bacillus subtilis* is a Gram-positive bacterium that is widely distributed in nature and is considered to be non-pathogenic and non-toxigenic. It has a long history of use in the production of enzymes used in food processing, including enzymes from genetically engineered strains. It has also been granted a Qualified Presumption of Safety status by EFSA.

The gene encoding branching glycosyltransferase was originally cloned from *R. obamensis*, a thermophilic bacterium that was isolated from a marine

hydrothermal vent. Based on the amino acid sequence of branching glycosyltransferase translated from the *R. obamensis* gene, a synthetic gene was designed. The synthetic gene encodes branching glycosyltransferase with the same amino acid sequence as that of the native *R. obamensis* enzyme. The gene was subsequently placed under deoxyribonucleic acid (DNA) regulatory sequences derived from several *Bacillus* species and introduced into the *B. subtilis* host strain JA1343 by transformation. The chloramphenicol resistance gene (*cat*) was used in transformation as a selectable marker, but it was subsequently deleted to make the production strain marker free.

Chemical and technical considerations

Branching glycosyltransferase is secreted during fermentation into the fermentation broth and is subsequently purified and concentrated. The final product is formulated with sorbitol, glycerol and water and standardized to a desired activity. The total organic solids (TOS) content of the branching glycosyltransferase preparation is approximately 4%. The branching glycosyltransferase enzyme preparation complies with the General Specifications and Considerations for Enzyme Preparations Used in Food Processing.

The branching glycosyltransferase preparation is intended for use in the production of modified starch with improved functional properties, such as higher solubility, lower viscosity and reduced retrogradation (undesirable structural changes). The recommended use levels range from 0.4 to 40 kg of the enzyme preparation per tonne of starch dry substance. The branching glycosyltransferase is likely to be inactivated and/or removed during starch processing steps. The enzyme is not added directly to food, and any carryover to food products formulated with modified starch is expected to be very low.

Assessment of potential allergenicity

Branching glycosyltransferase was assessed for potential allergenicity by comparing its amino acid sequence with the sequences of known allergens according to the bioinformatics criteria recommended in the report of the Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology. A 35% homology within a sliding window of 80 amino acids to α-amylase from *Aspergillus oryzae* was identified. *Aspergillus oryzae* is recognized as the occupational allergen Asp o 21 and was also reported to cause allergy symptoms in a few individuals after ingestion. However, no homology between branching glycosyltransferase and α-amylase from *A. oryzae* was found at the level of six contiguous amino acid sequences. In addition, branching glycosyltransferase is a bacterial protein, whereas nearly all known allergens are of eukaryotic origin. Thus, branching glycosyltransferase does not seem to have the characteristics of a potential food allergen.

Toxicological data

Toxicological studies were performed with branching glycosyltransferase using a representative batch (PPY 27209), which was produced according to the procedure used for commercial production. The liquid enzyme preparation used in the toxicological studies was a mixture of three preparations from fermentation sub-batches. The final preparation (specific gravity 1.065 g/ml) had an activity of 89 200 branching enzyme units per gram and a TOS value of 7.3%.

In a 13-week study of general toxicity in rats, no toxicologically relevant effects were seen when branching glycosyltransferase was administered daily by gavage at doses up to 769 mg TOS/kg bw per day. This dose, the highest dose tested, was therefore taken to be the no-observed-adverse-effect level (NOAEL).

Branching glycosyltransferase was not mutagenic in an assay for mutagenicity in bacteria in vitro and was not clastogenic in an assay for chromosomal aberrations in human lymphocytes in vitro.

Assessment of dietary exposure

Branching glycosyltransferase can be used in a wide range of foodstuffs, but it is not expected to be present in the final product. The following estimation is based on the worst-case assumption that the enzyme is used in all processed food and beverages and remains in the products consumed. The maximum amount of TOS added to food is 48 mg/kg. Assuming a daily consumption of 750 g of food (50%) and 1500 g of beverages (25%), according to the budget method, the amount of TOS ingested would be about 2 mg/kg bw per day for an adult weighing 60 kg.

Evaluation

The Committee allocated an ADI "not specified" for branching glycosyltransferase from this recombinant strain of *B. subtilis* (JA1343) used in the specified applications and in accordance with Good Manufacturing Practice. A toxicological monograph was prepared.

A Chemical and Technical Assessment and new specifications were prepared.

3.1.2 *Cassia gum*

Explanation

At the request of CCFA at its fortieth session (*7*), the Committee evaluated cassia gum, which it had not evaluated previously. Cassia gum is related to

guar gum, locust (carob) bean gum and tara gum in terms of structure and chemical properties. The galactomannans of guar gum, locust (carob) bean gum and tara gum have mannose to galactose ratios of 2:1, 4:1 and approximately 3:1, respectively. Each of these three gums was previously allocated an ADI "not specified" (Annex 1, references *39*, *57* and *74*).

Chemical and technical considerations

Cassia gum is the purified flour from the endosperm of the seeds of *Cassia tora* and *Cassia obtusifolia*, which belong to the Leguminosae family. Cassia gum is composed of at least 75% high relative molecular mass (approximately 200 000–300 000) polysaccharide, consisting primarily of a linear chain of 1,4-β-D-mannopyranose units with 1,6-linked α-D-galactopyranose units. The saccharides are composed of mannose (77.2–78.9%), galactose (15.7–14.7%) and glucose (7.1–6.3%). The ratio of mannose to galactose is 5:1.

The manufacture of cassia gum includes cleaning of the source material, by which the content of *Cassia occidentalis* (which is a naturally occurring contaminant) is reduced to less than 0.05%, de-husking and de-germing by thermal mechanical treatment, followed by milling and screening of the endosperm. The ground endosperm is further purified by extraction with isopropanol. The concentration of anthraquinones in cassia gum is below the 0.5 mg/kg detection limit. The food additive under evaluation is cassia gum that is refined and complies with the specifications established at the current meeting.

Cassia gum is used as a thickener, emulsifier, foam stabilizer, moisture retention agent and/or texturizing agent in processed cheese, frozen dairy desserts and mixes, meat products and poultry products.

Toxicological data

Most available toxicological studies have been performed with semi-refined cassia gum, which is produced similarly to the cassia gum currently under evaluation, with the exception of an additional isopropanol extraction step to significantly reduce the level of anthraquinones in the latter. Semi-refined cassia gum contains approximately 70 mg total anthraquinones/kg.

Although specific absorption, distribution, metabolism and excretion data were not available for cassia gum, the Committee concluded, based on data on related galactomannans, that cassia gum will be largely excreted unchanged, although fermentation by gut microflora may occur to some extent. If hydrolysis of cassia gum occurs, the resulting oligosaccharides or monosaccharides would be expected to be absorbed and metabolized in normal biochemical pathways.

Cassia gum is of low acute oral toxicity in rats and mice. It was also of low oral toxicity in a 28-day study in rats, a 90-day study in dogs and a 90-day study in cats. In these studies, administration of semi-refined cassia gum at dietary concentrations up to 50 000 mg/kg in rats (equal to doses of 4960 mg/kg bw per day for males and 4590 mg/kg bw per day for females), 25 000 mg/kg in dogs (equal to doses of 3290 mg/kg bw per day for males and 3890 mg/kg bw per day for females) and 25 000 mg/kg in cats (equal to doses of 2410 mg/kg bw per day for males and 2740 mg/kg bw per day for females) did not result in adverse effects. The decrease in food consumption and accompanying decrease in body weight gain noted in the 28-day rat study and the increase in water consumption observed in the 90-day dog study were considered to be related to the viscous nature of cassia gum and not considered to be of toxicological relevance. Therefore, the NOAELs in rats and dogs were 4590 and 3290 mg/kg bw per day, respectively, the highest doses tested. The no-observed-effect level (NOEL) in cats was 2410 mg/kg bw per day, the highest dose tested.

Cassia gum and/or semi-refined cassia gum were tested in reverse mutation assays in bacteria and in a chromosomal aberration assay and a gene mutation assay in mammalian cells. Cassia gum was also tested in an in vivo sperm abnormality test and an in vivo micronucleus test in mice. From these studies, the Committee concluded that cassia gum is not genotoxic. Cassia gum was not tested in a carcinogenicity study, but, given the lack of genotoxicity and the negative results obtained in assays of carcinogenicity of locust (carob) bean gum and tara gum, the Committee did not consider a study of long-term toxicity and/or carcinogenicity necessary for the safety evaluation of cassia gum.

Semi-refined cassia gum was tested in reproductive toxicity studies in the rat (two-generation study) at dietary concentrations up to 50 000 mg/kg (equal to a dose of 5280 mg/kg bw per day for males and 6120 mg/kg bw per day for females) and in the cat (one-generation study) at dietary concentrations up to 25 000 mg/kg (equal to a dose of 2470 mg/kg bw per day in males and 2950 mg/kg bw per day in females). In the cat study, high mortality in the control group resulted in a high litter loss, impairing appropriate comparison between control and treatment groups. Therefore, this cat study was considered not suitable for use in the evaluation. In the two-generation reproductive toxicity study in rats, the only effects observed were a slightly reduced pregnancy rate (which was not observed in a subsequent second mating resulting in an F_{1b} generation) and a slight, but not significant, decrease in pup weights of the F_{1a} and F_2 generations at the highest dose level. Therefore, 50 000 mg/kg feed (equal to 5280 mg/kg bw per day), the highest dose tested, was taken to be the NOEL.

Semi-refined cassia gum was also tested in studies of developmental toxicity in the rat and the rabbit at doses up to 1000 mg/kg bw per day. In the rat study, food intake was statistically significantly reduced in the pregnant animals of the highest dose group, accompanied by a statistically significant reduction in mean body weight gain. In the rabbit study, a reduction in mean daily food consumption was reported, as well as a slight reduction in mean fetal weights at the highest dose level, but these reductions were not statistically significant. These effects are probably related to the viscous nature of cassia gum and were not considered to be of toxicological relevance. No embryotoxicity or teratogenicity was observed. The NOAELs were 1000 mg/kg bw per day, the highest dose tested, in both rats and rabbits.

The findings of overall low toxicity for cassia gum are in line with the findings for the related food additives guar gum, locust (carob) bean gum and tara gum. The Committee noted that in the toxicological studies available on cassia gum and semi-refined cassia gum, no indications for anthraquinone-related toxicity were found.

Assessment of dietary exposure

The Committee received an assessment of dietary exposure to cassia gum and additionally accessed data on dietary exposure from the EFSA web site.

An EFSA opinion published in 2006 contained an assessment of dietary exposure to cassia gum. Per capita food consumption figures for yogurt and yogurt drinks, ice cream, desserts, processed cream cheese, and canned/preserved meat and poultry items were combined with cassia gum concentrations at the suggested maximum use levels, resulting in an estimated dietary exposure of approximately 195 mg/person per day. Assuming a default body weight of 60 kg, dietary exposure was 3.2 mg/kg bw per day. The EFSA opinion also contained a dietary exposure estimate prepared using individual dietary records for consumers of foods that may contain cassia gum in the USA. Maximum use levels in nine broad food categories were combined with reported food consumption, yielding an estimated mean dietary exposure of 2.1 mg/kg bw per day. Dietary exposure at the 90th percentile was 4.9 mg/kg bw per day.

A sponsor supplied an estimate of dietary exposure to cassia gum from its proposed use in four broad food categories: processed cheese at a maximum cassia gum level of 3000 mg/kg food; frozen desserts at up to 2500 mg/kg food; and meat products and poultry products at up to 3500 mg/kg food. Food consumption data from the USA (the 2003–2004 NHANES) were used for this analysis. As this survey contains dietary records for 2 non-consecutive days of food consumption, it likely overestimates exposure. To better estimate "usual" consumption, the sponsor proportionally adjusted the 2-day

average intakes to 30-day averages using a factor calculated from the number of days on which a food was reported to be consumed over an additional 30-day survey period. The adjusted mean dietary exposure was 2.7 mg/kg bw per day; at the 90th percentile, dietary exposure was 5.4 mg/kg bw per day.

The Committee concluded that the estimated 90th-percentile dietary exposure to cassia gum from the proposed uses would be less than 6 mg/kg bw per day.

Evaluation

Comparing the conservative exposure estimate of 6 mg/kg bw per day with the lowest reported NOAEL of 1000 mg/kg bw per day (the highest dose tested) derived from the developmental toxicity studies in rats and rabbits, the margin of exposure is at least 160. The Committee noted that in a 28-day study in rats, in 90-day studies in dogs and cats and in a two-generation study in rats, no adverse effects were observed at doses up to, respectively, 4590, 3290, 2410 and 5280 mg/kg bw per day, the highest doses tested in these studies.

Considering the low toxicity and the negative genotoxicity results, the Committee allocated an ADI "not specified" for cassia gum that complies with the tentative specifications established at the current meeting, when used in the applications specified and in accordance with Good Manufacturing Practice.

As the method for determination of anthraquinones at a level of 0.5 mg/kg and below was not considered to be suitable for inclusion in the specifications, the Committee decided to make the specifications tentative pending submission of data on a suitable and validated method by the end of 2010.

A toxicological monograph was prepared. A Chemical and Technical Assessment and new tentative specifications were prepared.

3.1.3 *Cyclamic acid and its salts: dietary exposure assessment*

Explanation

Cyclamic acid and its sodium and calcium salts are food additives commonly termed "cyclamates". Cyclamates are used in over 50 countries as intense sweeteners in a range of food categories.

The fortieth session of CCFA in 2008 (*7*) requested an evaluation by JECFA of the impact on dietary exposures to cyclamates of different maximum levels of use of cyclamates in the Codex GSFA Food Category 14.1.4, Water-based flavoured drinks, including "sport", "energy" or "electrolyte" drinks and particulated drinks, which includes all carbonated and non-carbonated varieties and concentrates, products based on fruit and vegetable

juices[1] and coffee-, tea- and herbal-based drinks. The different use levels to be considered were 250, 500, 750 and 1000 mg/kg. While there are provisions for the use of cyclamates in the GSFA in a wide range of food categories, the GSFA does not currently have a provision for the use of cyclamates in Food Category 14.1.4.

Cyclamates were evaluated at the eleventh, fourteenth, twenty-first, twenty-fourth and twenty-sixth meetings of the Committee (Annex 1, references *14*, *22*, *44*, *53* and *59*). An ADI of 0–11 mg/kg bw for cyclamates was established at the twenty-sixth meeting, based on testicular atrophy induced by the metabolite cyclohexylamine in rats, with a NOAEL of 100 mg/kg bw per day. Cyclohexylamine can be formed from unabsorbed cyclamates by the intestinal flora in certain individuals.

Assessment of dietary exposure

The Committee received a submission from Australia containing an analysis of the impact of various maximum use levels for cyclamates in beverages covered by Food Category 14.1.4 on overall dietary exposure to cyclamates. Additionally, the Committee considered published information concerning dietary exposure analyses for intense sweeteners in general, and cyclamates in particular.

The Committee noted two important considerations in the analysis of the impact of the variable maximum use levels for cyclamates in beverages covered by Food Category 14.1.4. First, the current uses of cyclamates in beverages (although not in the Codex GSFA, many countries allow the use of cyclamates in the beverages covered by Food Category 14.1.4) are at or near their maximum levels. This may be a result of their relatively low intensity of perceived sweetness (30 times that of sucrose) compared with other intense sweeteners (200 times that of sucrose for aspartame and 600 times that of sucrose for sucralose). It is noted that maximum use levels for cyclamates are not sufficient to allow complete sugar replacement in beverages covered by Food Category 14.1.4 and that it is necessary to use other intense sweeteners in conjunction with cyclamates to achieve the desired sweetness profile. Second, in countries where regulated cyclamate levels in beverages covered by Food Category 14.1.4 have been reduced in the past decade, published analyses have shown that overall dietary exposure has decreased. For example, dietary exposures to cyclamates decreased in Denmark following a change in European Union legislation in 2004 that reduced the maximum use level for beverages covered by Food Category 14.1.4 from 400 to 250 mg/kg; dietary exposures to cyclamates also decreased in Australia when the maximum use level for these beverages was reduced from 1200 to 600 mg/kg in 1999 and further lowered to 350 mg/kg in 2007.

[1] Fruit and vegetable juices per se are found in Codex GSFA Food Categories 14.1.2.1 and 14.1.2.2, respectively.

Published dietary exposure analyses for cyclamates were available for several countries. Those reported specifically for consumers of products containing intense sweeteners are summarized in Table 1.

Table 1.
Dietary exposure estimates for consumers of cyclamates

Country (year)	Survey type	Source of concentration data[a]	Population group	Dietary exposure to cyclamates (mg/kg bw per day)
Australia (1995)	1993 intense sweetener survey, 128 respondents, 7-day diary	TUL, matched by brand and flavour	Mean (12–39 years)	2.5
			90th percentile (12–39 years)	11.8
			Mean (12–17 years)	3.8
			90th percentile (12–17 years)	14.6
Australia (2004)	2003 intense sweetener survey, 263 respondents, 7-day diary	TUL, matched by brand and flavour	Mean (12+ years)	3.1
			90th percentile (12+ years)	8.2
			95th percentile (12+ years)	9.9
Australia (2007)	1995 National Nutrition Survey, 24-h recall, 1921 respondents aged 2–11 years, 10% consumers	TUL, except for 14.1.4 beverages, for which MUL of 350 mg/kg used	Mean (2–11 years)	3.6–4.1
			90th percentile (2–11 years)	8.1–8.9
			95th percentile (2–11 years)	10.1–11.0
Brazil (1995)	1990–1991 survey across two seasons, 673 consumers of intense sweeteners selected from two regions, 67% cyclamate users	Analysis and labels	Mean (consumers)	4.0
			Maximum (consumers)	17.9
Germany (1992)	1988–1989 survey, 24-h recall, 2291 respondents, 31% cyclamate users	TUL, labels, some analysis	Mean (consumers)	3.0
			90th percentile (consumers)	6.4
Italy (1999)	1996 survey, teenagers aged 13–19 years, 212 respondents, 6% cyclamate users	TUL, matched by brand and flavour	Mean (consumers)	0.2
			Maximum (consumers)	0.6

Table 1. continued

Country (year)	Survey type	Source of concentration data[a]	Population group	Dietary exposure to cyclamates (mg/kg bw per day)
Italy (2004)	2000–2001 survey, 270 respondents aged 14–17 years, 6% cyclamate users (17% females)	TUL, matched by brand and flavour	Mean (consumers) Maximum (consumers)	0.05 1.2
New Zealand (2004)	2003 intense sweetener survey, 137 respondents, 7-day diary	TUL, matched by brand and flavour	Mean (12+ years) 90th percentile (12+ years) 95th percentile (12+ years)	2.2 7.5 8.8
Spain (1996)	1992 survey, 2450 respondents aged 6–75 years, two 24-h recalls, food frequency, two different seasons, 18% cyclamate users	TUL	Mean (consumers) 90th percentile (consumers)	2.4 4.7
United Kingdom (2003)	2003 survey, 7-day diary, children aged 1.5–4.5 years, 1110 consumers of drinks with intense sweeteners only	TUL, analysis of dilutable drinks, matched by brand and flavour	Mean (consumers) 97.5th percentile (consumers)	4.5 14.1

MUL, maximum use level; TUL, typical manufacturers' use level.

[a] Manufacturers' use level is usually a mean value or matched to brand and flavour. Where products were analysed, mean values for product categories or values for individual products by brand and flavour were used.

In some subgroups of populations, primarily children, the ADI of 0–11 mg/kg bw was exceeded at high percentiles of the exposure distribution. Exceedances of the ADI were also reported in earlier studies for the general population conducted when maximum use levels for cyclamates were higher than current provisions and in one study for people with diabetes or on weight control diets. In several other studies for people with diabetes who were consumers of products containing cyclamates, dietary exposures were similar to those for the rest of the population and did not exceed the ADI; however, the

proportion of consumers in this group was higher. In all these studies, the beverages covered by Food Category 14.1.4 had provisions for cyclamates.

In the one submission from Australia, three analyses were performed:

1) The first assumed Codex GSFA maximum use levels in the low-joule (low-energy) version of all food categories, including beverages covered by Food Category 14.1.4 (where identified), and in the whole food category, for which the version was not identified. Individual body weights were used in the calculations.

2) The second assumed the above was true, except for beverages covered by Food Category 14.1.4, for which it was assumed that cyclamates were added to all these beverages.

3) The third assumed typical use levels for cyclamates in Australia for the low-joule versions of all food categories and the proposed GSFA use levels for low-joule beverages covered by Food Category 14.1.4.

Dietary exposures were presented for all models for the baseline (i.e. no cyclamates in beverages covered by Food Category 14.1.4) and maximum use levels of 250, 500, 750 and 1000 mg/kg, as well as for a level of 350 mg/kg, which is the current permitted level of use in Australia and New Zealand for this category of beverages. The same food consumption data derived from individual records from the 1995 Australian National Nutrition Survey were used for estimating dietary exposures to cyclamates for all the models. For the whole population aged 2 years and over who were consumers of beverages covered by Food Category 14.1.4, mean consumption amounts ranged from 375 to 560 g/day, and 90th-percentile amounts ranged from 625 to 1040 g/day. For children aged 2–6 years who were consumers of beverages covered by Food Category 14.1.4, mean consumption amounts ranged from 230 to 420 g/day, and 90th-percentile amounts ranged from 320 to 900 g/day.

For the first model, for the whole population aged 2 years and over, mean and 90th-percentile dietary exposures for consumers of products containing cyclamates were below the ADI of 0–11 mg/kg bw (25–30% of the ADI for mean consumers, 55–75% of the ADI for 90th-percentile consumers). For children aged 2–6 years, mean dietary exposures to cyclamates for consumers were also below the ADI (60–65% of the ADI). However, in this age group, dietary exposures to cyclamates exceeded the ADI at the 90th percentile of exposure at baseline and for all optional levels of cyclamates in beverages covered by Food Category 14.1.4 (120–150% of the ADI). The higher dietary exposures expressed per kilogram body weight for young children compared with adults are to be expected, owing to relatively higher levels of consumption of food per kilogram body weight; additionally, members of this age group are relatively high consumers of fine bakery wares, juices and juice

nectars, which were all assumed to contain cyclamates, as the low-joule version could not be identified. In reality, very few of these products do contain the sweetener. Hence, the predicted dietary exposures to cyclamates based on Codex GSFA levels were considered by the Committee to be overestimates.

In many populations, the proportion of people consuming beverages covered by Food Category 14.1.4 containing high-intensity sweeteners is increasing compared with those consuming sugar-sweetened drinks. As the Australian food consumption data were collected in 1995, patterns of consumption of these drinks are likely to be out of date. For this reason, the second model was a more conservative dietary exposure analysis for the Australian population, assuming that cyclamates were added to all beverages covered by Food Category 14.1.4. In this analysis, for the whole population aged 2 years and over, mean dietary exposures for consumers remained below the ADI at all maximum use levels for beverages covered by Food Category 14.1.4 (30–55% of the ADI), but dietary exposures for 90th-percentile consumers exceeded the ADI at the 750 and 1000 mg/kg maximum use levels. For children aged 2–6 years, predicted mean dietary exposures to cyclamates for consumers were 70–130% of the ADI; exposures were below the ADI at use levels for cyclamates up to 500 mg/kg in beverages covered by Food Category 14.1.4, but exceeded the ADI at higher use levels. In this age group, exposures of 90th-percentile consumers exceeded the ADI for cyclamates at all use levels (140–270% of the ADI).

In the third, more realistic dietary exposure assessment for cyclamates for 2- to 11-year-old children using typical use levels for cyclamates in low-joule products in the Australian analysis, two food categories ("fine bakery wares and mixes" and "juices and fruit nectars") were excluded, as they do not contain cyclamates in Australia. Beverages covered by Food Category 14.1.4 contributed 70–90% of total dietary exposure to cyclamates. In this analysis, 90th-percentile consumers in this age group were predicted to have dietary exposures to cyclamates that exceeded the ADI only at maximum use levels for cyclamates of 400 mg/kg and above in beverages covered by Food Category 14.1.4; at 350 mg/kg, dietary exposures were less than the ADI.

Evaluation

Potential dietary exposures to cyclamates are directly influenced by the maximum use levels in legislation, the number and type of food categories for which provisions to add cyclamates are given, as well as food consumption patterns. The reason for this is that typical use levels for cyclamates as an intense sweetener to replace sugar in products tend to be close to maximum use levels, because of the low sucrose equivalence of cyclamates compared

with other intense sweeteners. As beverages covered by Food Category 14.1.4 are major contributors to dietary exposure to intense sweeteners, the concentration of cyclamates in these products can considerably influence total dietary exposures.

Most reported mean dietary exposures to cyclamates were below the ADI of 0–11 mg/kg bw; however, several studies reported population subgroups for which exposures for high consumers approached or exceeded the ADI when cyclamate levels in beverages covered by Food Category 14.1.4 were 400 mg/kg or over, particularly for children and in one study for people with diabetes. Theoretical models for the Australian population indicated that maximum use levels for cyclamates of 500 mg/kg and under in all foods with Codex GSFA provisions and in beverages in Food Category 14.1.4 would be protective of all populations, except for young children who were high consumers. However, these estimates were likely to overestimate dietary exposure, as it was assumed that all low-joule soft drinks contained cyclamates and that all fruit juices, juice nectars and fine bakery wares contained cyclamates, which in reality would not be the case. A more accurate estimate for the Australian population using typical use levels for cyclamates indicated that maximum use levels for cyclamates of 400 mg/kg and above in beverages covered by Food Category 14.1.4 would result in dietary exposures to cyclamates that exceeded the ADI of 0–11 mg/kg bw for children up to 11 years of age who were high consumers.

Conclusion

Of the four maximum use levels (250, 500, 750 and 1000 mg/kg) that the Committee considered at the request of CCFA for cyclamates in beverages covered by Codex GSFA Food Category 14.1.4, only the lowest level of 250 mg/kg was not likely to lead to dietary exposures exceeding the ADI for high consumers, including children. Moreover, it was noted that a maximum use level of 350 mg/kg also resulted in dietary exposures for high consumers, including children, that were less than the ADI.

A dietary exposure monograph was prepared.

3.1.4 *Cyclotetraglucose and cyclotetraglucose syrup*

At its sixty-eighth meeting (Annex 1, reference *187*), the Committee evaluated cyclotetraglucose and cyclotetraglucose syrup for use as a stabilizer and carrier. Cyclotetraglucose and cyclotetraglucose syrup are produced from hydrolysed food-grade starch by the action of a mixture of 6-GT and IMT derived from *Sporosarcina globispora* and cyclodextrin glycosyltransferase derived from *Bacillus stearothermophilus*. The Committee allocated a temporary ADI "not specified" for cyclotetraglucose and cyclotetraglucose syrup

pending submission of additional data on the identity of the bacterial strain used to produce 6-GT/IMT enzyme preparation and evidence of its lack of pathogenicity and toxigenicity. The specifications for the syrup were made tentative pending submission of further information on the total saccharide content and test methods and on the unidentified saccharide fraction.

In response to the Committee's request, the sponsor provided data that support taxonomic classification of the bacterial strain N75 used in the production of the 6-GT/IMT enzyme preparation as *Bacillus globisporus*, described in Bergey's Manual of Systematic Bacteriology (*8*). *Bacillus globisporus* was subsequently reclassified as *Sporosarcina globispora* (*9*). The sponsor also conducted a literature search, which did not reveal evidence of either the pathogenicity or the toxigenicity of *S. globispora*, and attested that *S. globispora* has been used in the production of the 6-GT/IMT enzyme preparation for several years without any indication of an occupational hazard. *Sporosarcina globispora* has been deposited in the American Type Culture Collection and the German Federal Institute for Occupational Safety (Ausschuss für Biologische Arbeitstoffe) and classified as a biosafety level 1 organism (i.e. not known to cause disease in healthy adult humans).

The Committee concluded that the bacterial strain of *S. globispora* used to produce the 6-GT/IMT enzyme preparation was identified and classified correctly and that there is no evidence of pathogenic or toxigenic potential. The Committee therefore removed the temporary designation and established an ADI "not specified" for cyclotetraglucose and cyclotetraglucose syrup.

The Committee also received the requested information in relation to the tentative specifications for cyclotetraglucose syrup. The Committee found the information sufficient, revised the specifications and removed the tentative designation.

3.1.5 *Ferrous ammonium phosphate*

Explanation

At the present meeting, the Committee evaluated the safety of and established specifications for ferrous ammonium phosphate for use in food fortification, at the request of CCFA at its fortieth session (*7*). The Committee had not previously evaluated ferrous ammonium phosphate. The Committee had, however, at its ninth and twenty-third meetings, evaluated a large number of food acids and salts and was of the opinion that ADIs for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions (Annex 1, references *11* and *50*).

Ferrous ammonium phosphate consists of iron(II), ammonium and phosphate ions in a 1:1:1 molar ratio, with the iron content ranging between 24% and 30%. Ferrous ammonium phosphate is intended for use as an alternative to currently permitted iron fortification compounds. Ferrous ammonium phosphate is stable in foods but readily dissociates to iron(II), ammonium and phosphate ions when subjected to the low pH conditions of the stomach.

Iron was evaluated at the twenty-seventh meeting (Annex 1, reference *62*) and assigned a group provisional maximum tolerable daily intake (PMTDI) of 0.8 mg/kg bw, which applies to iron from all sources except for iron oxides used as colouring agents, supplemental iron taken during pregnancy and lactation, and supplemental iron for specific clinical requirements. The sodium iron salt of ethylenediaminetetraacetate (EDTA) was evaluated by the Committee at its forty-first and fifty-third meetings (Annex 1, references *107* and *144*). At the last evaluation, the Committee concluded that sodium iron EDTA could be considered safe for use in supervised food fortification programmes. At the sixty-first meeting (Annex 1, reference *167*), the Committee evaluated the safety of ferrous glycinate (processed with citric acid) as a source of iron for dietary supplementation. The Committee concluded that ferrous glycinate was suitable for use as a source of iron for supplementation and fortification, provided that total intake of iron does not exceed the PMTDI of 0.8 mg/kg bw.

Phosphoric acid and phosphate salts were evaluated by the Committee at its sixth, seventh, eighth, ninth, thirteenth, fourteenth, seventeenth and twenty-sixth meetings (Annex 1, references *6*, *7*, *8*, *11*, *19*, *22*, *32* and *59*). A group maximum tolerable daily intake (MTDI) of 70 mg/kg bw, expressed as phosphorus, was established at the twenty-sixth meeting and applies to the sum of phosphates present naturally in food and those present as additives.

The Committee has also previously evaluated ammonium salts. At its twenty-sixth meeting (Annex 1, reference *59*), the Committee evaluated the safety of ammonium carbonate and ammonium hydrogen carbonate and allocated an ADI "not specified", while noting that although toxicological data for these ammonium salts were limited, extrapolation of results from studies with ammonium compounds (primarily ammonium chloride) and with sodium or potassium carbonate provided a basis for evaluation. At its twenty-ninth meeting (Annex 1, reference *70*), the Committee prepared a table giving the ADIs for a large number of combinations of cations and anions, including ammonium salts. No restriction was placed on the intake of ammonium from ammonium salts, provided that the contribution made to food is assessed and considered acceptable.

Chemical and technical considerations

Ferrous ammonium phosphate is manufactured by mixing phosphoric acid, iron powder and ammonium hydroxide. Iron powder and phosphoric acid are combined in demineralized water with stirring to form a suspension. The mixture is heated until no further gas is evolved. Ammonia solution is added to the resultant slurry to yield ferrous ammonium phosphate. The product is then spray dried and milled to obtain a greyish-green fine powder.

Toxicological data

The toxicological data related specifically to ferrous ammonium phosphate are limited. The Committee received a submission containing unpublished studies on the bioavailability of iron from ferrous ammonium phosphate and studies on the constituent ions—iron, ammonium and phosphate. The submission included new toxicological data on iron, phosphate and ammonium salts that have become available subsequent to the latest evaluations conducted by the Committee, as well as older studies not previously reviewed by the Committee. The latest toxicological information on ammonium and phosphate salts was discussed in order to identify whether the new information would indicate a need to revise the Committee's previous opinions on these components. It was concluded that the safety of ferrous ammonium phosphate depended primarily on the iron component.

In one of the few studies available on ferrous ammonium phosphate, the bioavailability of iron from ferrous ammonium phosphate in humans was shown to be similar to that of other iron salts used for fortification purposes. In this study, no gastrointestinal complaints or other adverse effects were reported following consumption of a milk product fortified with ferrous ammonium phosphate, providing a total iron dose of 5 mg.

Results of acute toxicity studies in rodents indicate that large doses of iron (as ferrous sulfate) produce adverse effects that consist largely of gastrointestinal disturbances, such as diarrhoea. The oral median lethal dose (LD_{50}) values for iron derived from ferrous sulfate were reported to be approximately 250 mg/kg bw in mice, to range from 300 to 1100 mg/kg bw in rats and to be greater than 200 mg/kg bw in dogs.

Results of short-term studies of toxicity in rodents, including studies specifically designed to produce iron overload, indicate that repeated administration of large doses of iron in the diet (mainly in the form of ferrous sulfate or carbonyl iron), in the range of 37.5 mg iron/kg bw per day or greater, was associated with hepatic changes. Consistent observations in these studies included a reduction in body weight gain, increases in serum indicators of hepatic toxicity and increased hepatic microsomal lipid peroxidation, coupled

with increases in hepatic iron content. However, these findings in the liver were not accompanied by histopathological abnormalities.

In a rat carcinogenicity study, dietary administration of iron lactate at 167 mg iron/kg bw per day, but not at 82 mg/kg bw per day, resulted in an increased incidence of hyperplasia in the pancreatic acinar cells and endometrium. There was no increase in tumour incidence at either dose. A number of in vitro and in vivo genotoxicity studies have been conducted using ferrous sulfate and ferrous fumarate. No genotoxic effects were seen, except for infrequent non-concentration-dependent effects that were observed in the presence of cytotoxicity. The Committee concluded that ferrous sulfate and ferrous fumarate are not genotoxic.

In reproductive toxicity studies, iron supplementation of the diets of pregnant rats did not affect fetal growth. Pups supplemented via breast milk and then the diet at doses of 500 mg iron/kg bw per day and greater showed significant retardation of growth.

The additional toxicological studies on iron reviewed in this evaluation support the safety of iron in the diet, which was evaluated by the Committee at its twenty-seventh meeting (Annex 1, reference *62*).

The Committee noted previously that healthy individuals have taken supplements of 50 mg iron/day as ferrous sulfate for long periods of time without any adverse effects. Repeated oral iron supplementation at dosages greater than 50 mg iron/day may lead to adverse gastrointestinal effects. Gastrointestinal symptoms such as abdominal discomfort, diarrhoea, constipation and darkened stools were observed in studies where iron was provided at dose levels equal to or greater than 50 mg/day, with the frequency of effects increasing with the dose. These observations are consistent with the previous evaluation of iron and derivation of the PMTDI (Annex 1, references *62* and *63*). Studies with ferrous iron supplements in pregnant women (up to 60 mg/day) and infants (up to 66 mg/day) did not result in adverse birth outcomes or adverse effects on growth or development.

Individuals with iron storage disorders such as haemochromatosis are particularly at risk from exposure to iron, primarily as a result of an increased rate of iron absorption, even under conditions of normal iron stores.

The Committee concluded that the latest toxicological information on ammonium and phosphate salts did not indicate a need to revise the Committee's previous evaluations on these ions.

Assessment of dietary exposure

The Committee received a submission detailing the potential dietary exposure to ferrous ammonium phosphate. Food consumption data based on individual dietary records were combined with expected ferrous ammonium phosphate concentrations in various foods to produce assessments based on dietary patterns in the United Kingdom and the USA.

For the population in the United Kingdom, the highest mean dietary exposure to iron from consumption of ferrous ammonium phosphate for consumers only was estimated to be 1.0 mg/person per day (15 µg/kg bw per day),[1] and the highest 97.5th-percentile dietary exposure to iron was 5.1 mg/person per day (90 µg/kg bw per day). For the population in the USA, for consumers only, the mean dietary exposure to iron from ferrous ammonium phosphate was estimated to be 3.9 mg/person per day (74 µg/kg bw per day), and the 90th-percentile exposure was 8.7 mg/person per day (181 µg/kg bw per day). For both population groups, the intakes of phosphate and ammonium ions were insignificant when compared with background dietary exposures.

Overall, the dietary exposure calculations for both the United Kingdom and the USA, covering all the proposed food uses of ferrous ammonium phosphate and using use levels that reflect current fortification programmes in the respective communities, indicate levels of consumption of each of the individual components (iron, ammonium and phosphate) that fall well below acceptable amounts previously established by the Committee.

As ferrous ammonium phosphate is intended to replace current sources of ferrous iron in national fortification programmes, the Committee concluded that its introduction into the food supply will result in no increase in estimates of dietary exposure to iron.

Evaluation

The newly available information on the toxicity of iron did not identify any toxicological effects additional to those previously identified by the Committee and did not indicate a need to revise the PMTDI. On the basis of the available data on the bioavailability of iron from ferrous ammonium phosphate and consideration of the toxicity of its constituent ions, the Committee concluded that ferrous ammonium phosphate is acceptable for use as a source of iron for dietary fortification, provided that the total intake of iron does not exceed the PMTDI for iron of 0.8 mg/kg bw.

[1] All of the dietary estimates shown in parentheses were derived using the actual body weights of the participants of the surveys and are not estimates based on standard body weight assumptions.

Products, including ferrous ammonium phosphate, that are intended to provide a source of additional iron should not be consumed by individuals with any type of iron storage disease, except under medical supervision.

Consideration of the toxicity of ammonium or phosphate did not indicate a need to revise the Committee's previous evaluations on these ions.

A toxicological monograph was prepared. A Chemical and Technical Assessment and new specifications were prepared.

3.1.6 *Glycerol ester of gum rosin*

Explanation

Glycerol ester of gum rosin (GEGR) was placed on the agenda of the current meeting at the request of CCFA at its fortieth session (*7*). The Committee had not previously evaluated GEGR. However, the Committee previously considered, at its eighteenth, twentieth, thirty-third, thirty-seventh, forty-fourth and forty-sixth meetings (Annex 1, references *35*, *41*, *83*, *94*, *116* and *122*), a related substance, glycerol ester of wood rosin (GEWR). At its forty-sixth meeting, the Committee allocated an ADI for GEWR of 0–25 mg/kg bw.

GEGR is intended to be used as an emulsifier/density adjustment agent for flavouring substances in non-alcoholic beverages and cloudy spirit drinks.

Chemical and technical considerations

GEGR is a complex mixture of triglycerol and diglycerol esters of resin acids from gum rosin (GR), with a residual fraction of monoglycerol esters. It is obtained by the esterification of refined GR under a nitrogen atmosphere with food-grade glycerol and purified by direct countercurrent steam distillation. Refined GR is obtained by extracting oleoresin gum from living pine trees and refining it through washing, filtration and distillation.

The refined rosin contains approximately 90% resin acids and 10% neutrals. The resin acid fractions are a complex mixture of isomeric diterpenoid monocarboxylic acids having the empirical formula $C_{20}H_{30}O_2$ and grouped into three main classes: abietane, pimarane and isopimarane. The resin acids of these classes are similar in structure, differing only in the number and arrangement of double bonds or in the stereochemistry of the C-13 position. The neutral fraction is composed of esters of resin acids, esters of fatty acids and various unsaponifiable materials. The composition of the resin acid portion of the esters in the neutral fraction is similar to that of the resin acids of the acid fraction; the fatty acid portion of the esters in the neutral fraction is predominantly C_{18} or higher straight-chain acids with varying degrees of unsaturation.

The chemical composition of GEGR varies depending on the pine species, environmental factors, geographical differences and the techniques used in the processes of rosin purification and refinement. During the esterification procedure, because of the high temperature and severe conditions employed, some isomerization and dehydration reactions of the resin acids also occur, so that the resin acid distribution in the final ester is different from that in the original rosin. Limited data were available on the variability of the resin acid composition of GEGR in commerce. According to submitted data, the major resin acids found in GEGR are abietic, dehydroabietic, communic, pimaric and isopimaric acids.

Toxicological data

At the present meeting, the Committee evaluated the information available on the chemical composition of GR, the toxicological studies with GR, which included acute toxicity, 90-day toxicity and 2-year toxicity/carcinogenicity studies, and a summary statement from the sponsor about the results of two unpublished 90-day toxicity studies with GEGR. There are no data available on the absorption, distribution, metabolism or excretion of GR or GEGR.

Acute oral LD_{50} values for GR in mice, rats and guinea-pigs were reported to be 4600, 7600 and 4100 mg/kg bw, respectively.

Results of the 90-day oral toxicity study with GR demonstrated that Sprague-Dawley rats given diets with the highest concentration of 5.0% GR experienced drastic reductions in body weights and died during the first 7 days of the treatment period. The mortality was associated with feed refusal. At dietary concentrations up to 1.0% (equivalent to 500 mg/kg bw per day), there was no mortality, and there were no treatment-related effects on haematology, urinalysis, or gross or microscopic histopathology. Body weight gain and feed consumption were reduced, particularly during the first few weeks of the study. Decreases in organ weights in the 1.0% dietary concentration group were not accompanied by histopathological changes and were not considered to be of toxicological significance.

Results of the 2-year toxicity/carcinogenicity study in rats at dietary concentrations of 0.05% or 1.0% GR indicate that at the 1.0% dietary concentration (equivalent to 500 mg/kg bw per day), body weights were significantly lower than those of controls throughout the study, which again was attributed to lower feed consumption. Some sporadic differences in the ratios of organ weight to body weight were noted but, in the absence of any accompanying pathology, were not considered to be of toxicological significance. No significant dose-related systemic toxicity was noted in rats. In the same study, there was no evidence of carcinogenicity in rats fed GR at dietary concentrations of either 0.05% or 1.0%.

In the 2-year toxicity study, GR fed to Beagle dogs at dietary concentrations of 0.05% or 1.0% had no effect on growth, feed consumption, survival, organ weights, haematology, urinalysis, liver or kidney function, or gross or microscopic histopathology. No significant dose-related systemic toxicity was noted in dogs. The NOEL in this study was 1.0% in the diet (equivalent to 250 mg/kg bw per day).

The results of the studies with GR were compared with those of the related substance wood rosin (WR). The Committee concluded that the results of the studies with GR were consistent with those of the 90-day toxicity and 2-year toxicity/carcinogenicity studies with WR in rats that were previously evaluated (Annex 1, reference *116*). Furthermore, the results from the 90-day toxicity studies with GEWR indicate that the feed acceptance was improved. This effect is reflected by the absence of deaths even in the highest GEWR dose group (2500 mg/kg bw per day).

The Committee was informed by the sponsor of the results of two 90-day toxicity studies with GEGR in rats for which the NOEL was claimed to be 1.0% in the diet. However, the full reports were not available for evaluation by the Committee.

The variations in the amounts of both the individual resin acids and the components of the neutral fraction were considered to be of no toxicological consequence.

In its previous evaluation of GEWR at the forty-sixth meeting, the Committee concluded that GEWR is metabolically stable in the gastrointestinal tract, with more than 95% being recovered unchanged in the faeces. Only a minor fraction, most probably the monoglycerol ester fraction, undergoes partial hydrolysis (Annex 1, reference *116*). Although the proportion of the monoglycerol esters is dependent upon the ratio of the GR and the glycerol used in the esterification process, the variations observed in the monoglycerol esters of GEGR are comparable with those observed in the monoglycerol esters of GEWR.

The Committee also considered the previous evaluation of the absorption studies in rats with tritiated resin acids—namely, dehydroabietic, tetrahydroabietic and isopimaric acids—which indicated that these resin acids were primarily recovered from the faeces within 2 weeks (most within 4 days) after oral administration. The small amount of dehydroabietic acid absorbed appeared to have been metabolized in the liver to three or four uncharacterized metabolites, which were then excreted in the bile and urine. There was limited evidence to show that tetrahydroabietic and isopimaric acids were metabolized.

In its previous evaluation of GEWR, the Committee concluded that GEWR is not genotoxic in several in vitro test systems.

At the forty-sixth meeting, the Committee allocated an ADI for GEWR of 0–25 mg/kg bw based on the 13-week toxicity study in rats. The NOEL was 2500 mg/kg bw per day, the highest dose tested.

Assessment of dietary exposure

GEGR is intended to be used as an emulsifier/density adjustment agent for flavouring substances in non-alcoholic beverages and cloudy spirit drinks at a maximum use level of 100 mg/kg. This amount is expected to be present in the final product.

For the purpose of the current assessment, the maximum use level was combined with the total consumption of soft drinks in Australia (1995 Australian National Nutrition Survey), Europe (EFSA Concise European Food Consumption Database) and the USA (2003–2004 NHANES) for adults, consumers only. The median values were calculated for both the mean and the 95th percentile of the consumption distribution across the 19 countries considered and were 340 and 990 g/day, respectively.

Based on these figures, the mean and the high percentile for dietary exposure to GEGR would be 34 and 99 mg/day, respectively, corresponding to 0.57 and 1.65 mg/kg bw per day, respectively, for a 60-kg adult.

Evaluation

The Committee concluded that the data from GEWR could be used in the evaluation of GEGR because of the absence of toxicological effects of their respective rosins and the qualitative similarity of the chemical components of GEGR and GEWR. In addition, these esters undergo very limited hydrolysis in the gastrointestinal tract.

The Committee decided to include GEGR in the ADI for GEWR of 0–25 mg/kg bw, thereby establishing a group ADI of 0–25 mg/kg bw for GEWR and GEGR.

The Committee requested that it be provided with full reports of the two 90-day toxicity studies with GEGR in rats fed dietary concentrations of up to 1.0% to confirm the validity of the comparison of GEWR with GEGR.

The Committee considered that although GEWR and GEGR are chemically similar, they are produced from different sources, processed using different procedures and conditions, and not identical in composition. The Committee therefore developed separate specifications for GEGR. The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional

information on methods that enable the identification of the individual rosin esters and their differentiation. This information should be submitted by the end of 2010.

A toxicological monograph on GEGR was prepared. Tentative new specifications were prepared.

3.1.7 *Glycerol ester of tall oil rosin*

Explanation

Glycerol ester of tall oil rosin (GETOR) was placed on the agenda of the current meeting at the request of CCFA at its fortieth session (*7*). The Committee had not previously evaluated GETOR. However, the Committee previously considered, at its eighteenth, twentieth, thirty-third, thirty-seventh, forty-fourth and forty-sixth meetings, a related substance, GEWR (Annex 1, references *35*, *41*, *83*, *94*, *116* and *122*). At its forty-sixth meeting, the Committee allocated an ADI for GEWR of 0–25 mg/kg bw.

GETOR is intended to be used as an emulsifier/density adjustment agent for flavouring substances in non-alcoholic beverages.

Chemical and technical considerations

GETOR is a complex mixture of triglycerol and diglycerol esters of resin acids from tall oil rosin (TOR), with a residual fraction of monoglycerol esters. It is obtained by the esterification of TOR under a nitrogen atmosphere with food-grade glycerol and purified by steam stripping. TOR is obtained as a by-product of the kraft (paper) sulfate pulping process.

TOR contains approximately 90% resin acids and 10% neutrals. The resin acid fractions are a complex mixture of isomeric diterpenoid monocarboxylic acids having the empirical formula $C_{20}H_{30}O_2$ and grouped into three main classes: abietane, pimarane and isopimarane. Resin acids of these classes are similar in structure, differing only in the number and arrangement of double bonds or in the stereochemistry of the C-13 position. The neutral fraction is composed of esters of resin acids, esters of fatty acids and various unsaponifiable materials. The composition of the resin acid portion of the esters in the neutral fraction is similar to that of the resin acids of the acid fraction; the fatty acid portion of the esters in the neutral fraction is predominantly C_{18} or higher straight-chain acids with varying degrees of unsaturation.

The chemical composition of GETOR varies depending on the pine species, environmental factors, geographical differences and the techniques used in the processes of rosin purification and refinement. During the esterification procedure, because of the high temperature and severe conditions employed,

some isomerization and dehydration reactions of the resin acids also occur, so the resin acid distribution in the final ester is different from that in the original rosin. Additionally, the quality and consistency of TOR will depend upon the quality of the crude tall oil by-product from which it is distilled. Characteristic impurities in GETOR are sulfur compounds, which are derived from the use of sulfate in the kraft paper-making process. No data were available on the resin acid composition of GETOR in commerce.

Toxicological data

At the present meeting, the Committee evaluated the information available on the chemical composition of TOR, the toxicological studies with TOR, which included acute toxicity, 90-day toxicity and 2-year toxicity/carcinogenicity studies, and two acute toxicity studies with GETOR. There are no data available on the absorption, distribution, metabolism or excretion of TOR or GETOR.

Acute oral LD_{50} values for TOR in mice, rats and guinea-pigs were reported to be 4600, 7600 and 4600 mg/kg bw, respectively.

Results of the 90-day oral toxicity study with TOR demonstrate that Sprague-Dawley rats given diets with the highest concentration of 5.0% TOR experienced drastic reductions in body weight and died during the first 7 days of the treatment period. The mortality was associated with feed refusal. At dietary concentrations up to 1.0% (equivalent to 500 mg/kg bw per day), there was no mortality, and there were no treatment-related effects on haematology, urinalysis, or gross or microscopic histopathology. Body weight gain and feed consumption were reduced, particularly during the first few weeks of the study. Decreases in organ weights in the 1.0% dietary level group were not accompanied by histopathological changes and were not considered to be of toxicological significance.

Results of the 2-year toxicity/carcinogenicity study in rats at dietary concentrations of 0.05–1.0% with TOR indicate that at the 1.0% dietary concentration (equivalent to 500 mg/kg bw per day), body weights were significantly lower than those of controls throughout the study, which again was attributed to lower feed consumption. No significant dose-related systemic toxicity was noted in rats. In the same study, there was no evidence of carcinogenicity in rats fed TOR at dietary concentrations up to 1.0%.

In the 2-year toxicity study, TOR fed to Beagle dogs at a dietary concentration of 0.05% or 1.0% had no significant effect on growth, survival, organ weights, haematology, urinalysis, liver or kidney function, or gross or microscopic histopathology. The feed intake was slightly lower in the high-dose group than in the control dogs. No significant dose-related systemic toxicity was

noted in dogs. The NOEL in this study was 1.0% in the diet (equivalent to 250 mg/kg bw per day).

The results of the studies with TOR were compared with those of the related substance WR. The Committee concluded that the results of the studies with TOR were consistent with those of both the 90-day toxicity and 2-year toxicity/carcinogenicity studies with WR, which were previously evaluated (Annex 1, reference *117*). Furthermore, the results from the 90-day toxicity studies with GEWR indicate that the feed acceptance was improved. This effect is reflected by the absence of deaths even in the highest GEWR dose group (2500 mg/kg bw per day).

In its previous evaluation of GEWR at the forty-sixth meeting, the Committee concluded that GEWR is metabolically stable in the gastrointestinal tract, with more than 95% recovered unchanged in the faeces. Only a minor fraction, most probably the monoglycerol ester fraction, undergoes partial hydrolysis (Annex 1, reference *117*). Although the proportion of the monoglycerol esters is dependent upon the ratio of TOR to glycerol used in the esterification process, the variations observed in the monoglycerol esters of GETOR are comparable with those observed in the monoglycerol esters of GEWR.

The Committee also considered the previous evaluation of the absorption studies with tritiated resin acids in rats—namely, dehydroabietic, tetrahydroabietic and isopimaric acids—which indicated that these resin acids were primarily recovered in faeces within 2 weeks (most within 4 days) after oral administration. The small amount of dehydroabietic acid absorbed appeared to have been metabolized in the liver to three or four uncharacterized metabolites, which were then excreted in the bile and urine. There was limited evidence to show that tetrahydroabietic and isopimaric acids were metabolized.

The Committee also noted the compositional differences that are unique to TOR. The Committee noted that several sulfur compounds have been detected in crude tall oil. These include sodium sulfate, hydrogen sulfide, methyl mercaptan, dimethyl sulfide and dimethyl disulfide. However, it is unlikely that the four latter compounds, which are volatile, would be retained during the harsh conditions of subsequent refining and purification. The most likely residual sulfur compounds in TOR would be sodium sulfate with possible traces of dimethyl sulfide and dimethyl disulfide. However, there are no data to confirm the identity of the sulfur compounds and whether their presence in trace amounts would pose any toxicological concern.

In its previous evaluation of GEWR, the Committee concluded that GEWR is not genotoxic in several in vitro test systems.

The Committee at its forty-sixth meeting allocated an ADI for GEWR of 0–25 mg/kg bw based on the 13-week toxicity study in rats. The NOEL was 2500 mg/kg bw per day, the highest dose tested.

Assessment of dietary exposure

GETOR is intended to be used as an emulsifier/density adjustment agent for flavouring substances in non-alcoholic beverages at a maximum use level of 100 mg/kg. This amount is expected to be present in the final product.

For the purpose of the current assessment, the maximum use level was combined with the total consumption of soft drinks in Australia (1995 Australian National Nutrition Survey), Europe (EFSA Concise European Food Consumption Database) and the USA (2003–2004 NHANES) for adults, consumers only. The median values were calculated for both the mean and the 95th percentile of the consumption distribution across the 19 countries considered and were 340 and 990 g/day, respectively.

Based on these figures, the mean and the high percentile for dietary exposure to GETOR would be 34 and 99 mg/day, respectively, corresponding to 0.57 and 1.65 mg/kg bw per day, respectively, for a 60-kg adult.

Evaluation

The Committee concluded in principle that the data from GEWR could be used in the evaluation of GETOR because of the absence of any toxicological effects of their respective rosins and because these esters undergo very limited hydrolysis in the gastrointestinal tract. However, the Committee did not have adequate information on the composition of GETOR, considering that the source material and production processes are different, which may result in different by-products. Therefore, the Committee decided that it could not evaluate GETOR without additional information on its composition in order to clarify the extent and significance of any differences relative to other glycerol esters of rosins.

The Committee considered that although GEWR and GETOR are chemically similar, they are produced from different sources, processed using different procedures and conditions, and not identical in composition. The Committee therefore developed separate specifications for GETOR. The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual rosin esters and their differentiation. The Committee also requested information on the identity of the sulfur compounds in the commercial products. This information should be submitted by the end of 2010.

A toxicological monograph on GETOR was prepared. New tentative specifications were prepared.

3.1.8 *Lycopene from all sources*

Explanation

During the Committee's evaluation of lycopene extract from tomato, performed at the request of CCFA at its fortieth session (*7*), it became apparent that the assessment of this extract depends on the evaluation of lycopene from other sources. The Committee therefore reconsidered all the available toxicological studies on lycopene, including a new 28-day toxicity study completed after the sixty-seventh meeting (Annex 1, reference *184*), when it last evaluated synthetic lycopene and lycopene derived from the fungus *Blakeslea trispora* for use as a food colour.

Toxicological data

When lycopene was administered orally to rats as a formulation containing 10% synthetic lycopene, its LD_{50} was more than 5000 mg/kg bw.

The toxicity of synthetic lycopene, lycopene extract from tomato and lycopene derived from *Blakeslea trispora* was evaluated in short-term toxicity studies in rats and dogs and long-term studies in rats. In most studies of toxicity, there were no statistically significant or consistent differences in body weights, food or water consumption, or organ weights or in parameters of haematology, clinical chemistry or urine analysis between the treated and control groups. In the absence of any toxicologically relevant effects, the NOAELs were always established at the highest dose tested (up to 586 mg/kg bw per day in a 90-day rat study). A 100-day toxicity study in the rat at a lycopene dose of 1000 mg/kg bw per day (only one dose level tested) that was completed in 1958 and a more recent (1996) limited 1-month toxicity study in the rat at the same dose provided supporting evidence for the absence of any adverse effects at high doses.

In a 52-week study of toxicity in rats, slight increases in the group mean activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were recorded at week 13 at the highest dose only (250 mg/kg bw per day). At weeks 26 and 52, group mean activities of these enzymes were increased in a dose-dependent manner in males (up to 1.7-fold and 2.6-fold, respectively) and females (up to 1.4-fold and 2-fold, respectively) at the lowest, intermediate and highest doses (10, 50 and 250 mg/kg bw per day, respectively), although increases were not always statistically significant and were generally without progression between week 26 and week 52. At the end of a 13-week treatment-free period, AST and ALT activities had declined,

but they still tended to be higher in the highest dose group than in the control group.

Slightly elevated levels of AST and ALT, which achieved statistical significance among male rats after 3 or 12 months of exposure to the highest tested dose (500 and 250 mg/kg bw per day, respectively), were considered not to be adverse because of the lack of concordance with other important measures usually associated with liver damage, such as increased organ weight and histopathological lesions.

As the doses of lycopene were increased in short-term studies in rats, a discoloration of the faeces owing to excretion of the test substance was observed. Macroscopically, all treated animals in the feeding studies showed a discoloration of the liver and adipose tissue. The observed discoloration in the liver was associated with pigment deposits in the hepatocytes; however, there was no histopathological evidence of liver damage. Observations made in short-term studies of toxicity in dogs were consistent with the findings in rats. The Committee considered that the changes observed in the repeated-dose studies of toxicity did not represent adverse effects.

In a study of carcinogenicity in which rat diets were mixed with synthetic lycopene at doses up to 50 mg/kg bw per day, the treatment resulted in a discoloration of the faeces, gastrointestinal tract and connective tissue at the intermediate and/or highest dose (10 and 50 mg/kg bw per day, respectively). Pigment deposits were observed in the liver, kidneys (especially in females at the highest dose) and mesenteric and mandibular lymph nodes (at all doses). The liver pigmentation was observed mainly in hepatocytes and histiocytes in females and, to a lesser degree, in histiocytes in males. Histopathologically, the liver pigmentation was associated with a greater incidence and severity of eosinophilic foci in males and of normochromic and basophilic foci in females, especially at the intermediate and highest doses, albeit without a consistent dose–response relationship. There was no apparent evidence of hepatotoxicity. Also, no increase in the incidence of liver tumours was observed, nor was treatment with lycopene associated with an increase in the incidence of tumours in any other tissue or organ. The histopathological alterations of liver foci, observed mainly at the intermediate and highest doses, were considered to be treatment related but of no toxicological consequence because they did not progress to tumours.

On the basis of the results of the carcinogenicity study in rats and an adequate range of genotoxicity tests, the Committee concluded that lycopene has no genotoxic or carcinogenic potential when protected against oxidative processes.

In a two-generation study of reproductive toxicity in rats, adults receiving lycopene at a dietary dose of up to 500 mg/kg bw per day showed no evidence of toxicity. The discoloured faeces and staining of fur/skin/fat/abdominal organs observed were attributed to the presence of lycopene in the diet. Mating performance, fertility, and survival and growth of the pups were not affected by treatment with lycopene. The NOAELs for parental, reproductive and offspring toxicity were all 500 mg/kg bw per day, the highest dose tested.

In studies of developmental toxicity in rats and rabbits, no teratogenicity was observed. Similarly, there were no treatment-related increases in the overall number of external, visceral or skeletal abnormalities and variations. In all developmental studies, the dams showed discoloured faeces, and the contents of the gastrointestinal tract appeared discoloured in the gavage studies. Given the absence of any adverse toxicological findings, the NOAELs for maternal and developmental toxicity were at the highest tested doses in both rats and rabbits, 1000 and 400 mg/kg bw per day, respectively.

Studies in humans, although not specifically designed to assess the safety of lycopene, revealed no adverse effects after administration of dietary lycopene. There are, however, case reports of skin discoloration (lycopenodermia) and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and/or supplements, those effects being reversible upon cessation of lycopene ingestion.

Assessment of dietary exposure

Dietary exposure to lycopene naturally present in food is likely to be up to 10 mg/day in adults. Lycopene used as a food colour can be derived from a number of different sources, such as synthetic lycopene, lycopene derived from *Blakeslea trispora* and lycopene extract from tomato. However, it is likely that lycopene from these sources will be substituted for one another as food colours when used in accordance with Good Manufacturing Practice. Therefore, the dietary exposure to lycopene from all these sources will be similar. Based on the proposed use levels, dietary exposure to lycopene added as a food colour is estimated to be up to 5 times higher than the upper end of the range of the background exposure, 10 mg/day.

Evaluation

Lycopene is a normal constituent of the human diet, and the background dietary exposure to lycopene from vegetables and fruits is up to 10 mg/person per day. The available data indicate that dietary lycopene is generally well tolerated in humans. After prolonged high intake of lycopene-rich food and/or supplements, the effects were limited to skin discoloration and/or gastrointestinal discomfort. The Committee reconsidered the available toxicological data, including a new 28-day study, together with the dietary exposure

to lycopene that occurs naturally in food and lycopene used as a food colour from all sources. The Committee decided to revise the group ADI established at the sixty-seventh meeting and replace it with a group ADI "not specified" for lycopene from all sources. Hence, the previous group ADI of 0–0.5 mg/kg bw for lycopene has been withdrawn.

The group ADI "not specified" applies to synthetic lycopene, lycopene derived from the fungus *Blakeslea trispora* and lycopene extract from tomato that comply with the specifications, when used in accordance with Good Manufacturing Practice.

A toxicological monograph was prepared that consolidates the available toxicological data on lycopene from all sources.

3.1.9 *Lycopene extract from tomato*

Explanation

At the request of CCFA at its fortieth session (*7*), the Committee evaluated lycopene extract from tomato for safety and specifications for its intended use as a food colour. The substance was originally placed on the agenda under the name "Lycopene oleoresin extract from tomato"; however, the Committee decided that "Lycopene extract from tomato" should be the name under which it would be evaluated, because the compound is not a lycopene oleoresin, but an extract that contains lycopene and other constituents dissolved and suspended in the tomato's lipids. Lycopene is the functional component of the extract intended for use as a food colour. Lycopene extract from tomato is obtained by ethyl acetate extraction of the pulp of a non-genetically modified variety of ripe tomatoes (*Lycopersicon esculentum* L.) that has a high lycopene content (6%).

The Committee previously evaluated lycopene for use as a food colour at its eighth, eighteenth and twenty-first meetings (Annex 1, references *8*, *35* and *44*). A lack of adequate information precluded the Committee from developing specifications and establishing an ADI for lycopene as a food colour. At its sixty-seventh meeting (Annex 1, reference *184*), the Committee evaluated both synthetic lycopene and lycopene derived from *Blakeslea trispora* and developed specifications and established a group ADI of 0–0.5 mg/kg bw. Under consideration at the present meeting was a lycopene extract from tomato. During the evaluation of this lycopene extract from tomato, it became apparent that the assessment of this extract depends on the evaluation of lycopene from other sources. The Committee therefore reviewed all the available toxicological studies on lycopene, including a new 28-day toxicity study completed after the sixty-seventh meeting.

Chemical and technical considerations

Lycopene extract is obtained from ripe tomatoes with a high lycopene content by first crushing the tomatoes and then extracting the pulp with ethyl acetate. The solvent is removed, and the remaining extract is a dark red viscous liquid containing 5–15% lycopene, of which at least 86% is all-*trans*-lycopene; the balance of the extract is made up primarily of other naturally occurring fatty acids (72%), waxes (6%) and flavour components. Minor amounts of *cis* isomers of lycopene and other carotenoids and related substances, including β-carotene, phytofluene, phytoene and tocopherols, are also present. Because lycopene is susceptible to chemical changes such as isomerization and degradation when exposed to light, heat or oxygen, lycopene extract from tomato is packed under nitrogen and stored at low temperatures.

Lycopene extract from tomato is intended for use as a food colour in dairy products, non-alcoholic flavoured drinks, cereal and cereal products, bread and baked goods, and spreads, providing colour shades from yellow to red.

Toxicological data

The existing toxicological database for lycopene is comprehensive and described in section 3.1.8. The toxicity of lycopene extract from tomato was assessed in 10-week and 13-week studies in rats and a 6-week study in human volunteers. As the major non-lycopene constituents present in the extract from tomato were naturally occurring fatty acids (72%), it was anticipated that the toxicity profile of this lycopene extract would be similar to those of synthetic lycopene and lycopene derived from *Blakeslea trispora*. Consistent with the results of all toxicity studies on synthetic lycopene and lycopene derived from *B. trispora*, no toxicologically relevant effects were observed in the studies using lycopene extract from tomato.

Assessment of dietary exposure

Dietary exposure to lycopene naturally present in food is likely to be up to 10 mg/day in adults. Based on the proposed use levels, dietary exposure to lycopene added as a food colour is estimated to be up to 5 times higher than the upper end of the range of the background exposure, 10 mg/day.

Evaluation

The Committee evaluated the toxicity of lycopene extract from tomato together with dietary exposure to lycopene naturally occurring in food and lycopene from all sources that is used as a food colour and concluded that, based on lycopene's very low toxicity, there was no need to establish a numerical ADI for lycopene. The Committee established a group ADI

"not specified" for synthetic lycopene, lycopene derived from the fungus *Blakeslea trispora* and lycopene extract from tomato that comply with the specifications established at the sixty-seventh and the current meetings, when used in accordance with Good Manufacturing Practice.

A toxicological monograph entitled "Lycopene from all sources" was prepared that consolidates all the available toxicological data on lycopene. A Chemical and Technical Assessment and new specifications for lycopene extract from tomato were prepared.

3.1.10 *Mineral oil (low and medium viscosity) class II and class III*

Mineral oils were last evaluated by the Committee at its fifty-ninth meeting (Annex 1, reference *160*). At that meeting, the Committee noted that the new information reviewed indicated that the observed effects in rats on which the temporary group ADI is based for low- and medium-viscosity mineral oil classes II and III may be strain and sex specific. The Committee therefore extended the temporary group ADI of 0–0.01 mg/kg bw for classes II and III medium- and low-viscosity mineral oils until 2006, pending the submission of information on the relevance to humans of the response of Fischer 344 and Sprague-Dawley rats to these materials.

The re-evaluation of the safety of mineral oils (low and medium viscosity) classes II and III was scheduled for the sixty-ninth meeting of the Committee (Annex 1, reference *190*). Information was received from the sponsor that relevant studies are being undertaken, and the Committee agreed to maintain the temporary group ADI until the end of 2009, awaiting submission of the additional data.

The Committee at its current meeting received further information from the sponsor that studies are under way but that technical problems had been encountered that will delay the finalization of the studies. The Committee received confidential information on the studies and nature of the problems and, based on this, decided to further extend the temporary group ADI. The Committee noted that the temporary group ADI will be withdrawn at the end of 2011 if the data are not submitted by that time.

3.1.11 *Octenyl succinic acid modified gum arabic*

Explanation

At the request of CCFA at its fortieth session (*7*), the Committee evaluated octenyl succinic acid (OSA) modified gum arabic, which it had not evaluated previously. OSA modified gum arabic (gum arabic hydrogen octenylbutanedioate, Chemical Abstracts Service No. 455885-22-0) is produced by

controlled esterification of the polysaccharide in gum arabic with octenyl succinic acid anhydride, analogous to the production of starch sodium octenyl succinate (OSA modified food starch). The Committee considered safety data on OSA modified gum arabic together with safety data on the related food additives gum arabic and starch sodium octenyl succinate, which the Committee had previously reviewed at its twenty-sixth and thirty-fifth (gum arabic only) meetings (Annex 1, references *59* and *88*).

Chemical and technical considerations

OSA modified gum arabic is produced by esterifying gum arabic *Acacia seyal* or gum arabic *Acacia senegal* in aqueous solution with not more than 3% of octenyl succinic acid anhydride. It is subsequently spray dried. The degree of esterification of OSA modified gum arabic is not more than 0.6%, and residual octenyl succinic acid is not more than 0.3%.

OSA modified gum arabic is a cold water–soluble hydrocolloid used as an emulsifier. The introduction of lipophilic groups to the polysaccharide in gum arabic results in enhanced emulsifying properties for OSA modified gum arabic relative to the parent compound.

Toxicological data

No absorption, distribution, metabolism or excretion data are available for OSA modified gum arabic. Gum arabic is not significantly digested by laboratory animals or humans, but experiments with rats and humans show that gum arabic can be fermented by bacteria in the caecum/colon. According to the sponsor, OSA modified gum arabic is expected to be de-esterified in the stomach to gum arabic and to be fermented in the colon as well. However, there are no experimental data available on the de-esterification of OSA modified gum arabic, such as in vitro data on hydrolysis under simulated gastric conditions.

Toxicological studies have been performed with different batches of OSA modified gum arabic, which can be considered to be representative of the OSA modified gum arabic under evaluation. OSA modified gum arabic is of low acute oral toxicity in rats. In a 90-day study of toxicity in rats, no significant treatment-related effects were seen when OSA modified gum arabic was administered at dietary concentrations up to 50 000 mg/kg feed. Therefore, 50 000 mg/kg feed (equal to 3410 mg/kg bw per day), the highest dose tested, was taken to be the NOEL.

OSA modified gum arabic was not mutagenic in an assay for mutagenicity in bacteria in vitro. It was not tested in any assay of genotoxicity with mammalian cells. From studies of genotoxicity in vitro and in vivo with gum

arabic, reviewed by the Committee at its twenty-sixth meeting (Annex 1, reference *60*), it was concluded that mutagenicity studies in a number of test systems, including host-mediated assay, Ames test, *Saccharomyces cerevisiae,* dominant lethal test and *Drosophila*, were negative. In another series of in vivo genotoxicity assays that were not considered in the previous evaluation, gum arabic was reported to induce dominant lethal effects in male rats (although no clear dose–response was observed), but not in male mice at considerably higher doses. In addition, gum arabic did not cause heritable chromosomal effects in male mice. Overall, the Committee concluded that gum arabic is not genotoxic, but it did not extend this conclusion to OSA modified gum arabic.

Assessment of dietary exposure

The Committee received one dietary exposure analysis for OSA modified gum arabic. Additionally, the Committee evaluated information submitted to the United States Food and Drug Administration as part of a Generally Recognized as Safe (GRAS) Notice for the use of OSA modified gum arabic.

OSA modified gum arabic is intended to replace gum arabic in a number of food applications. It is proposed for use as an emulsifier for flavouring agents in baked goods, beverages (non-alcoholic and alcoholic), breakfast cereals, processed cheese, chewing gum, flour confectionery and icings, egg products, fish products, frozen dairy, fruit ices, gelatines and puddings, gravies, imitation dairy products, instant coffee and tea, jams and jellies, meat products, milk products, other grains, processed poultry, processed fruit juices, processed vegetable juices, snack foods, soft candy, soups and sweet sauces at levels up to 500 mg/kg of the food. OSA modified gum arabic is also proposed for use as an emulsifier in some fruit-flavoured drinks, fruit juices and some other beverages (carbonated juice and energy drinks), salad dressing, sauces, icing, some breads (whole-grain and high-fibre breads) and some cereals (high-fibre, low-sugar and low-fat adult cereals) at levels up to 10 000 mg/kg of the food.

The dietary exposure analysis received by the Committee used individual dietary records from both the United Kingdom and the USA. The food consumption data from the United Kingdom were taken from the 2000–2001 National Diet and Nutrition Survey. The food consumption data from the USA were taken from the 2003–2004 NHANES. The mean dietary exposure estimated using the data from the United Kingdom was 326 mg/person per day (4.3 mg/kg bw per day), with an estimated 97.5th-percentile dietary exposure of 859 mg/person per day (12 mg/kg bw per day). In the parallel analysis using the food consumption data from the USA, the mean dietary exposure was 524 mg/person per day (9 mg/kg bw per day), and the 90th-percentile exposure was 964 mg/person per day (17 mg/kg bw per day).

The Committee concluded that the estimated dietary exposure to OSA modified gum arabic from the proposed uses would be less than 20 mg/kg bw per day.

Evaluation

Only limited data were available for OSA modified gum arabic. The Committee concluded that the available data on OSA modified gum arabic indicate a very low toxicity, comparable with the toxicities of traditional gum arabic and starch sodium octenyl succinate (OSA modified food starch), both of which were previously reviewed by the Committee and allocated ADIs "not specified".

Comparing the exposure estimate of 20 mg/kg bw per day with the NOEL from the 90-day study of oral toxicity in rats (3410 mg/kg bw per day, the highest dose tested), the margin of exposure is at least 170. The Committee decided to allocate a temporary ADI "not specified" to OSA modified gum arabic, used in the applications specified and in accordance with Good Manufacturing Practice. The Committee decided to make the ADI temporary pending submission of data by the end of 2011 showing hydrolysis of OSA modified gum arabic to confirm the validity of using gum arabic data in the evaluation of OSA modified gum arabic.

A toxicological monograph was prepared. A Chemical and Technical Assessment and new specifications were prepared.

3.1.12 *Sodium hydrogen sulfate*

Explanation

At the present meeting, the Committee evaluated sodium hydrogen sulfate for use as an acidifier, at the request of CCFA at its fortieth session (*7*). The Committee was asked for a safety assessment and revision of specifications. At its sixty-eighth meeting, the Committee considered sodium hydrogen sulfate for use in the preparation of acidified sodium chlorite, an antimicrobial washing solution, and established specifications, but did not evaluate it for safety (Annex 1, reference *187*). At its ninth and twenty-third meetings, the Committee evaluated a large number of food acids and salts and was of the opinion that ADIs for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions (Annex 1, references *11* and *50*).

The sulfate ion was evaluated at the twenty-ninth meeting of the Committee (Annex 1, reference *70*), when an ADI "not specified" was established, as sulfate is a natural constituent of food and is a product of sulfur metabolism

in animals. Sodium sulfate was evaluated at the fifty-third, fifty-fifth and fifty-seventh meetings (Annex 1, references *144*, *149* and *154*), when an ADI "not specified" was established.

Chemical and technical considerations

Sodium hydrogen sulfate is manufactured by mixing sodium chloride with sulfuric acid at elevated temperatures to form molten sodium hydrogen sulfate. The molten sodium hydrogen sulfate is sprayed and cooled to form a solid product with uniform particle size.

Toxicological data

When sodium hydrogen sulfate is added to food products containing water or after ingestion of sodium hydrogen sulfate, it ionizes to sodium ions, hydrogen ions and sulfate ions. The Committee received a submission containing unpublished studies on sodium hydrogen sulfate, including a study on its acute toxicity and studies on inhalation toxicity, skin irritation and corrosivity, and freshwater ecotoxicity. A literature search identified no published studies of the toxicity of sodium hydrogen sulfate. Additional information identified by a literature search related to sulfate, as the Committee decided to assess sodium hydrogen sulfate in terms of the sulfate component because of its dissociation to the constituent ions and given that sodium and hydrogen ions are ubiquitous and natural constituents of foods.

In an acute toxicity study, the oral LD_{50} of sodium hydrogen sulfate in rats was determined to be 2800 mg/kg bw in males and >2500 mg/kg bw in females. The additional studies received as part of the submission were not considered relevant to the evaluation of the oral toxicity of sodium hydrogen sulfate.

In studies evaluating the effect of inorganic sulfate on bowel function, the body weight and kidney weight of neonatal pigs administered up to 2000 mg/l in a liquid diet for 18 days were unaffected. In a 16-day study, the concentration of added sulfate in the diet at which 50% of the piglets developed non-pathogenic diarrhoea was estimated to be between 1600 and 1800 mg/l. No differences in bowel movements were noted in adult volunteers receiving sulfate in the drinking-water at concentrations up to 1200 mg/l for 3 consecutive days.

The additional studies identified on sulfate did not raise concern about its toxicity.

Assessment of dietary exposure

Sodium hydrogen sulfate is typically added to beverages, confectionery, fillings, syrups, processed cheeses, salad dressings, sauces, jams and jellies, and processed vegetable products at levels ranging from 500 to 4000 mg/kg. For beverages, sodium hydrogen sulfate is generally used in non-citrus-flavoured soft drinks, tea, and chocolate-flavoured and coffee-flavoured drinks, as it does not impart a sour or citric taste, as do other acidifiers.

Based on poundage data for the USA, where the food additive has the highest reported production levels, mean per capita exposures for the population in the USA for current production volumes and for increased production volumes in the future, as predicted by the sponsor, were estimated to be 20 and 50 mg/day, respectively, assuming that all members of the population were consumers of products containing the additive.

From the limited data submitted by the sponsor on the proposed use of sodium hydrogen sulfate as a food acid, potential mean and high-consumer dietary exposures (derived from consumption for two food groups with highest dietary exposure at the 95th percentile plus mean for population for all other food groups) for 19 European populations (aged 16–64 years) were calculated based on typical use levels, assuming that the additive was used in all foods in each of the broad food categories identified above. Potential mean per capita dietary exposures for this "worst case" scenario ranged from 400 to 1160 mg/day for the whole population and from 1090 to 6340 mg/day for high consumers of foods containing sodium hydrogen sulfate. Potential dietary exposures based on individual dietary records and use of sodium hydrogen sulfate in food subcategories specified by the sponsor were submitted for the Australian population. Potential mean dietary exposures for Australians were lower than those for Europeans but of the same order of magnitude (mean per capita dietary exposure of 700 mg/day for the whole Australian population and 1210 mg/day for high consumers at the 90th percentile). The Committee considered that the predicted dietary exposures for the European and Australian populations were overestimates, a view supported by the much lower per capita estimates reported for the population in the USA. The actual use of sodium hydrogen sulfate would be restricted to subcategories within the broader food group and to foods within these subcategories where a low pH was required and/or for drinks where an acidic or citric taste was undesirable.

Evaluation

Considering that the available evidence did not provide any indication of toxicity, the Committee allocated an ADI "not specified" for sodium hydrogen sulfate, in line with the principles established for ionizable salts at its

twenty-ninth meeting, when used in the applications specified and in accordance with Good Manufacturing Practice.

A toxicological monograph was prepared. Specifications were revised to include the new technological use. A Chemical and Technical Assessment for sodium hydrogen sulfate was prepared.

3.1.13 *Sucrose oligoesters type I and type II*

Explanation

At the request of CCFA at its thirty-ninth session (*10*), the Committee evaluated sucrose oligoesters (SOE), which are separated into two types, SOE type I and type II. SOE type I and type II are produced by interesterification of sucrose with methyl esters of fatty acids derived from edible fats and oils, including hydrogenated fats and oils such as stearic acid and palmitic acid. A sucrose molecule has eight hydroxyl groups, and so it can produce mono- to octa-esters (Table 2). "Sucrose esters of fatty acids" consist mainly of sucrose mono- to tri-esters, whereas SOE type I consists mainly of sucrose tetra- to octa-esters and SOE type II consists of sucrose mono- to octa-esters. The lipophilic character of these constituents increases according to the increasing degree of esterification and the increasing chain length of the fatty acids. Other physical and chemical properties of the products also vary depending on the degree of esterification and the chain length of the fatty acids.

Table 2.
Classification of sucrose fatty acid esters

Property	Group	Composition of esters (%)			
		Mono–tri	Tetra–octa	Hepta+octa	Octa
Hydrophilic	Sucrose esters of fatty acids	80–100	0–20	–	–
↓	Sucrose oligoesters type II	20–80	20–80	0–20	0–10
↓	Sucrose oligoesters type I	0–20	80–100	0–50	0–20
Lipophilic	Olestra[a]	–	–	97–100	70–100

[a] The monograph for olestra in the sixth edition of the Food Chemicals Codex specifies the following distribution for the number of esters: octa-esters, not less than 70%; hexa-, hepta- and octa-esters, not less than 97%; hexa-esters, not more than 1%; and penta-esters, not more than 0.5%. Olestra is used as a replacement for fats in food.

SOE type I and type II are lipophilic emulsifiers as well as stabilizers and tableting aids for foods presented in tablet form. They are authorized for use in a number of countries, including Japan, the USA, China and the Republic of Korea.

The Committee had previously evaluated low-range sucrose esters of fatty acids, which principally include mono-, di- and tri-esters, at its thirteenth, seventeenth, twentieth, twenty-fourth, thirty-fifth, thirty-ninth, forty-fourth and forty-ninth meetings (Annex 1, references *19*, *32*, *41*, *53*, *88*, *101*, *116* and *131*). At the forty-ninth meeting, the Committee established a group ADI of 0–30 mg/kg bw for sucrose esters of fatty acids and sucroglycerides on the basis of potential laxative effects in humans.

For the present evaluation of SOE type I and type II, the Committee considered the available data on the safety of SOE type I and type II in view of the Committee's previous evaluation of low-range sucrose esters of fatty acids.

Toxicological data

The Committee considered studies of the absorption, distribution, metabolism and elimination (ADME) of components of SOE type I—i.e. tetra-, hexa- and octa-esters of fatty acids, each separately radiolabelled in both the fatty acid and sucrose moieties. These studies indicated that the tetra-, hexa- and octa-esters of sucrose with stearic acid were very slowly hydrolysed prior to intestinal absorption of the hydrolysis products, but only the tetra-ester was hydrolysed and absorbed to any appreciable extent. These data were consistent with pharmacokinetic data on mono-, di- and tri-esters of sucrose with stearic and palmitic acids, which were reviewed at the forty-fourth meeting. Small amounts of mono-esters were absorbed intact, but the di- and tri-esters were not. Although specific ADME data for SOE type II were not available, their metabolic fate can be predicted by the demonstrated inverse relationship between hydrolysis and the degree of esterification of sucrose esters of fatty acids.

Toxicological studies, including a 28-day range-finding study and a combined 12-month toxicity and 2-year carcinogenicity study, were available for SOE type I fed to rats at dietary concentrations of up to 50 000 mg/kg (equal to 2370 mg/kg bw per day in males and 2800 mg/kg bw per day in females in the toxicity study; equal to 2120 mg/kg bw per day in males and 2420 mg/kg bw per day in females in the carcinogenicity study). In these studies, no significant toxicological or tumorigenic effects were reported. The NOEL from the 12-month toxicity study was 2370 mg/kg bw per day, the highest dose tested. The NOEL from the 2-year carcinogenicity study was 2120 mg/kg bw per day, the highest dose tested.

No studies of reproductive or developmental toxicity were available for SOE type I or type II. However, in a two-generation reproductive and developmental toxicity study of sucrose polyester (a mixture of 8.2% hexa-, 33% hepta- and 58% octa-esters of edible-grade fatty acids with sucrose) fed to rats at up to 10% of their diet, no adverse effects on reproductive or developmental parameters were reported.

SOE type II tested negative in a reverse mutation assay in bacterial cells. No genotoxicity data were available for SOE type I.

Assessment of dietary exposure

SOE type I and type II are used as emulsifiers in fats and oils, chocolate, cream, seasonings and condiments, and some tablet forms of hard sweets and dietary supplements, with typical use levels ranging from 2000 to 10 000 mg/kg and a maximum use level of 20 000 mg/kg. There are several other additives available that perform the same function in foods, so SOE type I and type II are expected to capture only a small proportion of the total market for emulsifiers (≤10%). As the functional uses of SOE type I and type II are similar and there is common use across some food categories, the dietary exposure was estimated for SOE type I and type II combined.

Use of the budget method indicated that detailed dietary exposure estimates were required for SOE type I and type II, as the theoretical maximum permitted use level of 4800 mg/kg was less than that expected to be used in some food categories (maximum 20 000 mg/kg).

Per capita estimates of dietary exposure to SOE type I and type II from use as an emulsifier based on poundage data were 60 and 110 mg/day for the USA and Japan, respectively. The Committee noted that this was an overestimate for Japan owing to the inclusion of sucrose esters of fatty acids in the reported data. The estimate for the USA assumed 10% of all production of emulsifiers to be SOE type I and type II, which was supported by the industry submission that indicated that SOE type I and type II would capture no more than 10% of the emulsifier market in the USA.

From the limited data submitted by the sponsor on the dietary exposure to SOE type I and type II based on national nutrition survey food consumption data, estimated mean dietary exposures for two populations where a wide range of processed foods are available, Japan and the USA, ranged from 115 to 150 mg/day (1.9–2.5 mg/kg bw per day), assuming typical SOE use across different food categories. Estimated mean dietary exposures for Japan and the USA, assuming maximum SOE type I and type II use levels across different food categories, ranged from 220 to 270 mg/day (3.7–4.6 mg/kg bw per day). However, the Committee considered these dietary exposures predicted for Japan and the USA to be overestimates because of assumptions made in the calculations, as not all products in each category will contain SOE type I or type II, and consumers will not consistently select those foods containing SOE type I and type II over a lifetime.

Another estimation of dietary exposures based on individual dietary records for the population in the USA was evaluated, where mean dietary exposure

to SOE type I and type II was 45 mg/day (0.8 mg/kg bw per day) and 90th-percentile exposure was 98 mg/day (1.6 mg/kg bw per day), assuming a maximum use level of 5000 mg/kg for all food categories included in the assessment. This mean dietary exposure estimate for the USA was of the same order of magnitude as the per capita estimates for the population in the USA based on poundage data.

Evaluation

The available ADME data for the components of SOE type I and for low-range sucrose esters of fatty acids indicate that only the lower esters were hydrolysed to any appreciable extent. The Committee concluded that these data and the results of the newly available 12-month toxicity study and 2-year carcinogenicity study on SOE type I did not identify any effects of toxicological concern at the highest dose tested.

The Committee noted that some of the components of sucrose esters of fatty acids may be present in significant amounts in SOE type I and type II. The Committee also noted that the group ADI of 0–30 mg/kg bw allocated to sucrose esters of fatty acids and sucroglycerides was based on a potential laxative effect in humans. The Committee therefore considered that it was appropriate to include SOE type I and type II in a group ADI of 0–30 mg/kg bw for sucrose esters of fatty acids, sucroglycerides and SOE type I and type II. Estimated dietary exposures to SOE type I and type II combined for mean and high consumers, based on typical or maximum use levels, were well below the ADI of 0–30 mg/kg bw, with estimates ranging from 3% to 15% of the ADI.

The Committee emphasized that this evaluation is valid only for the material as specified. A toxicological monograph was prepared. New specifications and a Chemical and Technical Assessment were prepared for SOE type I and type II.

3.2 Revision of specifications

3.2.1 *Diacetyltartaric and fatty acid esters of glycerol*

Diacetyltartaric and fatty acid esters of glycerol (DATEM) were placed on the agenda of the present meeting for revision of specifications at the request of CCFA at its fortieth session (*7*). The Committee was informed that the existing procedure for determining free fatty acids was not appropriate for analysing the content of free fatty acids in DATEM, as it also captures other acids present in the product, thereby producing incorrect results. The Committee agreed to delete the criteria for free fatty acids and to replace them with the criteria for acid value. Minor editorial revisions were also made.

3.2.2 *Ethyl lauroyl arginate*

The Committee was requested to review the test method for L-arginine·HCl and ethyl arginate·2HCl in the specifications for ethyl lauroyl arginate. The existing specifications were revised at the current meeting.

3.2.3 *Glycerol ester of wood rosin*

At the present meeting, the Committee decided that the specifications for GEWR developed at its forty-sixth meeting (Annex 1, reference *122*) should be reconsidered in connection with the evaluation of the two new rosin esters, GEGR and GETOR.

The Committee noted that the existing specifications for GEWR contain a chromatographic method intended to distinguish among the rosin esters based on the identification of their resin alcohols, but recognized that both the chromatographic method and the sample chromatograms of the alcohols are quite old (mid-1980s). The Committee considered that it is likely that the method is outdated and that the chromatograms no longer represent products currently in commerce. The Committee received information that the original method has been updated since the specifications for GEWR were published, but did not receive the updated method. Data submitted on the resin acid composition of different batches of glycerol esters of rosins in commerce do not generally support the relative proportions of resin alcohols considered to be characteristic of the different rosin esters, as given in the gas chromatographic procedure in the monograph for GEWR.

The existing specifications for GEWR were revised to include a lower limit for lead and the sulfur test as an identity criterion to differentiate between GEWR and GETOR and to remove the purity test for hydroxyl number and the identification test "Gas chromatography of resin alcohols and glycerol". The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual rosin esters and their differentiation. This information should be submitted by the end of 2010.

3.2.4 *Nisin preparation*

Nisin preparation was on the agenda at the request of the fortieth session of CCFA (*7*) to clarify the existing specifications prepared by the Committee at its sixty-eighth meeting (Annex 1, reference *187*).

The Committee discussed the title of this monograph, because it is inconsistent with that used in the INS list, where it is given simply as "nisin". This is

the only food additive in the FAO JECFA monographs in which this descriptor is used, although there are many other food additives that could also be described as "preparations" (e.g. enzymes and some colours).

The Committee decided to rename the specifications monograph "nisin" and revised the existing specifications by modifying the definition to clarify that nisin A is the major polypeptide in nisin and revising the determination of sodium chloride in the method of assay.

3.2.5 *Nitrous oxide*

The Committee at its fifty-fifth meeting (Annex 1, reference *149*) prepared specifications for nitrous oxide and included an assay method based on measurement of volume of the gas using a manometer that is now obsolete. The Committee at its current meeting recognized that a specific method based on chromatography is required for the assay.

The specifications were revised. Assay, some identification and some purity criteria were revised to harmonize the specifications with other regional and national specifications. A gas chromatographic assay method employing a packed column was included. Identification and purity test methods were also revised to include simpler methods based on the detector tubes. The specifications were made tentative, as information on a capillary gas chromatographic assay method was required. This information should be submitted by the end of 2010.

3.2.6 *Pectins*

The Committee was made aware that an incorrect volume had been given in the method for "Galacturonic acid and degree of amidation" in the monograph in the Combined Compendium of Food Additive Specifications. The Committee agreed that a correction was needed, and the specifications were revised with two additional editorial changes.

3.2.7 *Starch sodium octenyl succinate*

Starch sodium octenyl succinate in the FAO JECFA monograph for modified starches includes a high-performance liquid chromatographic (HPLC) test method for residual octenyl succinic acid in which sodium octenyl succinate is used as a standard. The Committee had been informed that this standard is not commercially available. At the present meeting, a specifications monograph for OSA modified gum arabic was prepared. These specifications include the same HPLC method for quantification of residual octenyl succinic acid utilizing as a standard octenyl succinic acid anhydride, which is commercially available. The Committee concluded that this standard could also

be used in the method for residual OSA in the modified starches specifications monograph and revised the specifications accordingly.

3.2.8 *Tannic acid*

Tannic acid was placed on the agenda of the present meeting following a request for the revision of the method of assay described in the specifications. The Committee revised the method of assay, especially the procedure for calculating the amount of tannic acid. The existing specifications were editorially revised.

3.2.9 *Titanium dioxide*

The Committee at its sixty-seventh meeting (Annex 1, reference *184*) prepared specifications for titanium dioxide and included a method for the determination of aluminium oxide. The Committee at its current meeting recognized that the method needed minor revision with regard to certain reagents used. The specifications were revised to include an updated method for aluminium oxide.

3.2.10 *Triethyl citrate*

The Committee was made aware that the INS number in the triethyl citrate monograph, no. 1519, was incorrect. The Committee asked the Secretariat to correct the INS number to 1505 in the electronic version of the specification on the FAO JECFA web site.

4. Future work

- The Committee recommended that the specifications and toxicity of hexanes should be reconsidered at a future meeting in view of new data on the toxicity of *n*-hexane and the Committee's awareness that the composition of commercially available solvents containing *n*-hexane may not comply with the existing specifications.
- The Committee decided to update the General Specifications and Considerations for Enzymes Used in Food Processing to expand recommendations for microbiology and molecular biology information to be submitted in dossiers for enzymes from microorganisms (including those from GMMs) and to discuss toxicological and other safety studies for enzymes from all sources. The Committee recommended that the JECFA Secretariat establish a working group to update the current guidance document on enzymes for discussion at a future meeting.

5. Recommendation

1. To better assess chronic dietary exposure, the Committee recommends the use of food consumption data collected over a period of more than 1 day with an averaging of the amounts of food consumed per day. Moreover, the Committee recommends that food consumption data collected over a few days be adjusted by using food frequency questionnaires on a comparable population where these data are available.

Acknowledgement

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Annex 1

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

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

11. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases* (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases*. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.

13. *Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances* (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.

14. *Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non nutritive sweetening agents* (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.

15. *Toxicological evaluation of some flavouring substances and non nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.

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Annex 2

Acceptable daily intakes, other toxicological information and information on specifications

1. Food additives evaluated

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Branching glycosyltransferase from *Rhodothermus obamensis* expressed in *Bacillus subtilis*	N	The Committee allocated an **ADI "not specified"** for branching glycosyl-transferase from *Rhodothermus obamensis* expressed in *Bacillus subtilis* used in the specified applications and in accordance with Good Manufacturing Practice.
Cassia gum	N, T	The Committee allocated an **ADI "not specified"** for cassia gum that complies with the tentative specifications established at the current meeting, when used in the applications specified and in accordance with Good Manufacturing Practice. The Committee decided to make the specifications tentative pending submission of data on a suitable and validated method for determination of anthraquinones at a level of 0.5 mg/kg and below, by the end of 2010.
Cyclamic acid and its salts (dietary exposure assessment)		Of the four maximum use levels (250, 500, 750 and 1000 mg/kg) that the Committee considered at the request of CCFA for cyclamates in beverages covered by Codex GSFA Food Category 14.1.4, only the lowest level of 250 mg/kg was not likely to lead to dietary exposures exceeding the ADI for high consumers, including children. Moreover, it was noted that a maximum use level of 350 mg/kg also resulted in dietary exposures for high consumers, including children, that were less than the ADI.

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Cyclotetraglucose and cyclotetraglucose syrup	R (cyclotetraglucose syrup)	The Committee established an **ADI "not specified"** for cyclotetraglucose and cyclotetraglucose syrup. The specifications for cyclotetraglucose syrup were revised, and the tentative designation was removed.
Ferrous ammonium phosphate	N	The newly available information on the toxicity of iron did not indicate a need to revise the PMTDI of 0.8 mg/kg bw. Consideration of the toxicity of ammonium and phosphate did not indicate a need to revise the Committee's previous evaluations of these ions. The Committee concluded that ferrous ammonium phosphate is acceptable for use as a source of iron for dietary fortification, provided that the total intake of iron does not exceed the PMTDI. Products, including ferrous ammonium phosphate, that are intended to provide a source of additional iron should not be consumed by individuals with any type of iron storage disease, except under medical supervision.
Glycerol ester of gum rosin (GEGR)	N, T	The Committee decided to include GEGR in the ADI for GEWR of 0–25 mg/kg bw, thereby establishing a **group ADI of 0–25 mg/kg bw** for GEWR and GEGR. The specifications for GEGR were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual glycerol esters of rosins and their differentiation. This information should be submitted by the end of 2010.
Glycerol ester of tall oil rosin (GETOR)	N, T	The Committee concluded in principle that the data from GEWR could be used in the evaluation of GETOR; however, the Committee did not have adequate information on the composition of GETOR, considering that the source material and production processes are

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
		different, which may result in different by-products. The Committee decided that it could not evaluate GETOR without additional information on its composition in order to clarify the extent and significance of any differences relative to other glycerol esters of rosins. The specifications for GETOR were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual glycerol esters of rosins and their differentiation. The Committee also requested information on the identity of the sulfur compounds in the commercial products. This information should be submitted by the end of 2010.
Lycopene from all sources		The Committee decided to revise the group ADI established at the sixty-seventh meeting and replace it with a **group ADI "not specified"** for lycopene from all sources when used as a food colour. Hence, the previous group ADI of 0–0.5 mg/kg for lycopene has been withdrawn. The group ADI "not specified" applies to synthetic lycopene, lycopene derived from the fungus *Blakeslea trispora* and lycopene extract from tomato that comply with the specifications, when used in accordance with Good Manufacturing Practice.
Lycopene extract from tomato	N	The Committee established a **group ADI "not specified"** for synthetic lycopene, lycopene derived from the fungus *Blakeslea trispora* and lycopene extract from tomato, when used as a food colour, that comply with the specifications, and when used in accordance with Good Manufacturing Practice.
Mineral oil (low and medium viscosity) class II and class III		The Committee was informed that finalization of the requested studies has been delayed. The Committee decided to

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
		further **extend the temporary group ADI**, but noted that the temporary group ADI will be withdrawn at the end of 2011 if the data are not submitted by that time.
Octenyl succinic acid (OSA) modified gum arabic	N	The Committee decided to allocate a **temporary ADI "not specified"** for OSA modified gum arabic used in the applications specified and in accordance with Good Manufacturing Practice. The ADI is temporary pending submission of data by the end of 2011 showing hydrolysis of OSA modified gum arabic to confirm the validity of using gum arabic data in the evaluation of OSA modified gum arabic.
Sodium hydrogen sulfate	R	The Committee allocated an **ADI "not specified"** for sodium hydrogen sulfate, in line with the principles established for ionizable salts at its twenty-ninth meeting, when used in the applications specified and in accordance with Good Manufacturing Practice. Specifications were revised to include a new technological use.
Sucrose oligoesters (SOE) type I and type II	N	The Committee considered it appropriate to include SOE type I and type II in a **group ADI of 0–30 mg/kg bw** for sucrose esters of fatty acids, sucroglycerides and SOE type I and type II. The Committee emphasized that this evaluation is valid only for the material as specified.

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

[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 intake of 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.

2. Food additives considered for specifications only

Food additive	Specifications[a]
Diacetyltartaric and fatty acid esters of glycerol	R
Ethyl lauroyl arginate	R
Glycerol ester of wood rosin	R, T
Nisin preparation	R
Nitrous oxide	R, T
Pectins	R
Starch sodium octenyl succinate	R
Tannic acid	R
Titanium dioxide	R
Triethyl citrate	R

[a] R, existing specifications revised; T, tentative specifications.

Annex 3

Further information required or desired

Cassia gum

Information is required on a suitable and validated method for determination of anthraquinones in cassia gum at a level of 0.5 mg/kg and below. This information should be submitted by the end of 2010.

Glycerol ester of gum rosin

The Committee requested that it be provided with full reports of the two 90-day toxicity studies with GEGR in rats fed dietary concentrations of up to 1.0% to confirm the validity of the comparison of GEWR with GEGR.

The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual glycerol esters of rosins and their differentiation. This information should be submitted by the end of 2010.

Glycerol ester of tall oil rosin

The Committee did not have adequate information on the composition of GETOR, as the source material and production processes are different, which may result in different by-products. Therefore, the Committee decided that it could not evaluate GETOR without additional information on the composition of GETOR in order to clarify the extent and significance of any differences relative to other glycerol esters of rosins.

The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual glycerol esters of rosins and their differentiation. The Committee also requested information on the identity of the sulfur compounds in the commercial products. This information should be submitted by the end of 2010.

Glycerol ester of wood rosin

The specifications were made tentative pending the submission of infrared spectra that correspond to the commercially available products, data on the resin acid composition obtained with updated chromatographic techniques, and additional information on methods that enable the identification of the individual glycerol esters of rosins and their differentiation. This information should be submitted by the end of 2010.

Mineral oil (low and medium viscosity) class II and class III

The Committee at its current meeting was informed that studies are under way but that technical problems had been encountered that will delay the finalization of the requested studies. The Committee received confidential information on the studies and nature of the problems and, based on this, decided to further extend the temporary group ADI. The Committee noted that the temporary group ADI will be withdrawn at the end of 2011 if the data are not submitted by that time.

Nitrous oxide

The revised specifications were made tentative, as information on a capillary gas chromatographic assay method was required. This information should be submitted by the end of 2010.

Octenyl succinic acid modified gum arabic

The ADI is temporary pending submission of data by the end of 2011 showing hydrolysis of OSA modified gum arabic to confirm the validity of using gum arabic data in the evaluation of OSA modified gum arabic.

This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of various food additives, with a view to recommending acceptable daily intakes (ADIs) 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 and assessment of intake of food additives. A summary follows of the Committee's evaluations of technical, toxicological and intake data for certain food additives: branching glycosyltransferase from *Rhodothermus obamensis* expressed in *Bacillus subtilis*, cassia gum, cyclamic acid and its salts (dietary exposure assessment), cyclotetraglucose and cyclotetraglucose syrup, ferrous ammonium phosphate, glycerol ester of gum rosin, glycerol ester of tall oil rosin, lycopene from all sources, lycopene extract from tomato, mineral oil (low and medium viscosity) class II and class III, octenyl succinic acid modified gum arabic, sodium hydrogen sulfate and sucrose oligoesters type I and type II.

Specifications for the following food additives were revised: diacetyltartaric acid and fatty acid esters of glycerol, ethyl lauroyl arginate, glycerol ester of wood rosin, nisin preparation, nitrous oxide, pectins, starch sodium octenyl succinate, tannic acid, titanium dioxide and triethyl citrate.

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

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