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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

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Rome, 20–29 June 2006

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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The IPCS is a joint venture of the United Nations Environment Programme, the International Labour Organization and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met in Rome from 20 to 29 June 2006. The meeting was opened by Mr Alexander Müller, Acting Assistant Director-General, Food and Agriculture Organization (FAO), on behalf of the Directors-General of FAO and the acting Director-General of the World Health Organization (WHO). Mr Müller informed the Committee of the recent decisions taken by the FAO Conference to reform FAO to better meet the demands of Member countries for improved efficiency in the achievement of the objectives of the organization. Consequent to the decisions taken, the Food and Nutrition Division, which hosted the FAO JECFA Secretariat, had been renamed the Nutrition and Consumer Protection Division, and moved to the Agriculture, Biosecurity, Nutrition and Consumer Protection Department, in line with the farm-to-table approach to issues of food safety and quality. Mr Müller emphasized that expert scientific advice is one of the cornerstones in the process, as it ensures that food safety and quality measures and standards are based on scientific principles and provide the necessary advice for the adequate human health protection. He also highlighted the fact that the work of JECFA and other international expert bodies providing scientific advice remains a high priority for FAO.

Referring to the tasks of the Committee at its present meeting, Mr Müller made particular mention of the ongoing work of the Committee to refine the principles and procedure for the exposure assessment of flavouring agents for future assessments. Mr Müller emphasized that the recommendations from the Committee would be highly valuable in the continued work of the Codex Alimentarius Commission and for countries around the world, especially developing countries.

Mr Müller informed the Committee that the present meeting marked the fiftieth anniversary of the establishment of the Committee, and that FAO and WHO had commissioned JECFA medals in silver and bronze to commemorate that important event and to acknowledge the contribution of the experts in the continued provision of international scientific advice. He informed the Committee that a silver medal would be awarded to members, expert advisors to the Joint FAO/WHO JECFA Secretariat and to former JECFA Secretaries who had participated in ten meetings or more, and that a bronze medal would be awarded to those who had participated in five to nine meetings. Mr Müller invited the participants to celebrate the anniversary by attending a ceremony at which the medals were to be awarded, to be held later that day.

1.1 Declaration of interests

The Secretariat informed the Committee that all experts participating in the sixty-seventh meeting of JECFA had completed declaration-of-interest forms, and that no significant conflicts had been identified. The following potential conflicts were discussed by the Committee. Dr Susan Barlow declared an interest for annatto. The employer of Dr Ian Munro receives part of its revenues from consulting on the safety assessment of certain food additives. That company, but not Dr Munro personally, had been involved in work on lycopene dossiers. The research unit of Dr Philippe Verger received funding from the fishing industry for a project related to methylmercury (assessment of the impact of risk management measures). These participants did not take part in the discussions on the respective subjects.

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 66 previous meetings of the Committee (Annex 1). The present meeting was convened on the basis of a recommendation made at the sixty-fifth meeting (Annex 1, reference *178*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants, in particular, additional considerations on the assessment of dietary exposure to flavouring agents (section 2);
— to undertake toxicological evaluations of certain food additives and contaminants (sections 3, 4 and Annex 2);
— to review and prepare specifications for certain food additives (section 3 and Annex 2).

2.1 Modification of the agenda

The food additives acetylated oxidized starch, DL-malic acid and its calcium and sodium salts, maltitol and zeaxanthin were added to the agenda, for revision of specifications.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, 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*, and *178*), 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 and contaminants.

2.2.1 *Additional method for assessing dietary exposure to flavouring agents*

Introduction

JECFA employs the maximized survey-derived intake (MSDI) method as a surrogate measure of dietary exposure for use in the Procedure for the Safety Evaluation of Flavouring Agents. The MSDI is a per-capita estimate based on the reported amount of the flavouring agent disappearing into the food supply per year in specific regions (currently Europe and the United States of America (USA); data from Japan were anticipated in the future) and on the assumption that 10% of the population would consume the foods containing the flavour. This exposure estimate is used according to the Procedure for the Safety Evaluation of Flavouring Agents and compared with the thresholds of toxicological concern (TTC) in a decision-tree approach.

The Committee considered issues related to the dietary exposure of flavouring agents at its forth-fourth, forty-sixth, forty-ninth, fifty-fifth and sixty-third meetings (Annex 1, references *116*, *122*, *139*, *149* and *173*). The estimation of dietary exposures based on annual production data was considered to be a practical and realistic approach. Further consideration was recommended for flavouring agents for which there were high anticipated average use levels in foods, but low dietary exposures when calculated by the MSDI method. Such consideration was needed because some flavouring agents could be disseminated unevenly within the food supply, raising the possibility of high dietary exposures in individuals regularly consuming specific flavoured foods.

At its sixty-fifth meeting, the Committee considered how to improve the identification and assessment of flavouring agents for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods. At its sixty-fifth meeting, the Committee proposed that an ad-hoc Working Group be convened to further consider all relevant

aspects of the introduction of an additional screening method based on use levels, to complement the MSDI.

Having examined data for over 800 flavouring agents, the ad-hoc Working Group noted that MSDI values could be up to four orders of magnitude lower than dietary exposures derived using anticipated average use levels in foods. Analysis of the safety implications showed that in the majority of cases the differences between estimates would not have affected the conclusions reached by the Committee on those flavours, because of the increasing margin of safety at low poundages (and low MSDI estimates) compared with the relevant TTC values used in the Procedure. The ad-hoc Working Group explored various options and proposed an additional method of dietary exposure assessment to address the questions raised by previous Committees.

Proposed additional method to assess dietary exposure

It was proposed that at the next meeting at which flavouring agents were to be considered, the Committee would evaluate those agents according to the Procedure. The Committee recommended that an additional method to assess dietary exposure should be tested at that meeting. Dietary exposures for selected flavouring agents would be estimated using a method based on use levels. The additional method would be based on flavour-industry recommended use levels for each flavouring agent in food categories, in combination with standard portion sizes (see Annex 4). For flavouring agents with usages in multiple food categories, only the food category contributing the highest potential dietary exposure would be considered. This dietary exposure is taken to represent that of a regular consumer of a flavoured food, who is loyal to a brand containing the specific flavour of interest. Such an estimate, based on daily consumption and using a single standard portion size, is likely to provide a conservative assessment of long-term average dietary exposure for consumers with a high-percentile intake of flavouring agents. The additional analyses would be performed before that meeting.

The ramifications of any differences between the MSDI and the dietary exposure estimated by the additional method would be examined by the Committee. Any discrepancies would be considered in detail and recommendations on the need for, and nature of, any possible future changes to the Procedure would be proposed after such detailed consideration.

The Committee recognized that the production of such use-level data is a major undertaking and therefore consideration of the additional

method should focus on selected flavouring agents that would provide useful information on its utility.

Prioritization

The Committee proposed to focus on a limited number of flavouring agents with poundages at the lower and upper ends of the distribution. The analyses should provide information to address the comments of the Committee made at previous meetings.

(a) Flavouring agents with poundages of less than 10 kg per year

The Committee noted that although the discrepancies between different methods to estimate dietary exposure were greatest at low reported poundages, there is no clear cut-off value that can be used to define a "low-poundage" flavouring agent. An annual production volume of less than 10 kg in each specific region was selected as a value to identify flavouring agents that might have limited food applications and for which there might be greater uncertainty about their dissemination within the food supply.

(b) Flavouring agents with poundages that result in MSDI values of more than one third of the relevant TTC value

The MSDI is a population-based estimate of dietary exposure and may not adequately represent the dietary exposures of consumers with brand loyalty to a particular flavoured food. Because consumption at high percentiles (approximately 90th) of widely distributed foodstuffs approximates to three times the average dietary consumption, the relationship can be applied to "high-poundage" flavouring agents. Therefore the additional method to estimate dietary exposure should be applied to flavouring agents with poundages that result in MSDI values of one third or more of the relevant TTC value for that flavouring agent.

(c) Naturally-occurring flavouring agents

Flavouring agents that are known to occur naturally in the food supply in quantities that are more than tenfold the total amount used for flavouring purposes could be excluded from the initial analysis.

Request for data

On request, the Committee had received information from the industry on use levels for three flavouring agents currently in commerce. The information included the number of formulations containing the specific flavouring agent, the approximate range of use levels for the flavouring agent within the formulation, the food types containing

the formulation, the range of levels of the formulation in each food type, and the resulting anticipated average use levels in the food type. The Committee concluded that such information would provide a suitable basis for the additional estimations of dietary exposure.

The Committee requested this type of information for:

— flavouring agents with poundages of less than 10 kg per year in every region;[1] and
— flavouring agents with poundages that result in MSDI values that are greater than one third of the relevant TTC value.[2]

In order to facilitate the preparation of dossiers and of the additional information requested herein, the food categories and standard portion sizes (listed in Annex 4) should be transmitted to appropriate parties who would submit dossiers on flavouring agents to the Committee.

2.2.2 *Surveys of production of flavouring agents*

The Committee was informed that new surveys of production of flavouring agents for use in food had recently been undertaken by flavour industry associations in the European Union (EU), Japan and the USA, and that the results of the surveys would be available to support the Committee's future evaluations of flavouring agents and to update previous evaluations. The Committee welcomed this development, which would help to address recommendations, made at the forty-sixth and forty-ninth meetings, concerning the need for periodic updating of the poundage data and extended geographical coverage. The Committee asked that the survey methods be described in detail when data from the new surveys are submitted for the first time, so that the Committee could fully assess the coverage of the surveys and any uncertainties in the results.

2.3 Food additive specifications

2.3.1 *Combined Compendium of Food Additive Specifications, Volumes 1–4*

The Secretariat informed the Committee of the publication of the first three volumes of the up-to-date *Combined Compendium of Food Additive Specifications*. The new combined compendium had been

[1] Should a large number of flavouring agents meet this criterion, the Committee considered that data on the 100 flavouring agents with the lowest poundages would be sufficient to provide information suitable for assessing the new method.

[2] Data on use levels for previously evaluated flavouring agents could be requested by the JECFA Secretariat for this exercise, if there are few examples meeting this criterion among the flavouring agents to be evaluated by the Committee.

published by FAO as the first in a new series of FAO JECFA Monographs (Annex 1, reference *180*). It consists of four volumes, of which three volumes contain food additive specifications and the fourth contains the analytical methods, test procedures and laboratory solutions required and referenced in food additive specifications. One new feature of the compendium is the inclusion of information on acceptable daily intakes (ADIs) established by the Committee. The publication replaces FAO Food and Nutrition Paper 52 and 13 addenda and the FAO Food and Nutrition Paper 5, revision 2. Volume 4 of the publication was made available to the Committee in draft form and was used as a working document.

The Committee also received a presentation by an FAO staff member about the updated and searchable on-line database containing all current specifications monographs, which is available on the FAO JECFA web site. This database provides query pages and background information in five languages — English, Spanish, French, Arabic and Chinese (see http://www.fao.org/ag/agn/jecfa-additives/search/html?lang=en).

2.3.2 *Issues arising from the preparation of Volume 4 of the Combined Compendium of Food Additive Specifications*

The Committee was informed by the Secretariat of questions related to analytical methods and specifications that had arisen in connection with the preparation of Volume 4 of the *Combined Compendium of Food Additive Specifications*, containing analytical methods, test procedures and laboratory solutions used by and referenced in the specifications for food additives. The items were discussed and the following conclusions were reached:

- An analytical method that is described in one specification only would not be included in Volume 4. In the future, for individual specifications monographs that are subject to review, the Committee recommended that if a method were relevant to more than one monograph the method would not be included in the specifications monograph, but would be published separately, with reference to Volume 4.
- Analytical methods using paper chromatography are no longer commonly used and alternative methods should therefore be identified. The Committee recommended that such alternative analytical methods for synthetic colours should be placed on the agenda of a future meeting.
- The Committee noted inconsistencies in purity criteria among the specifications monographs for food additives produced using ethylene oxide. Specifications for the substances should include limits

for ethylene oxide and ethylene chlorohydrins in addition to the limit for 1,4-dioxane. Volume 4 contains a method for the analysis of 1,4-dioxane and ethylene oxide.

— At its present meeting, the Committee decided to harmonize the specifications for DL-malic acid, calcium DL-malate, sodium hydrogen DL-malate and sodium DL-malate with respect to the limits of the impurities fumaric acid and maleic acid. The relevant analytical method for the determination of those impurities is included in Volume 4 (see section 3.2.4).
— With respect to microbiological test methods, the Committee noted that the specifications monograph for lysozyme hydrochloride contained a reference to a method not included in Volume 4. At its present meeting, the Committee elaborated a method for the isolation and detection of *Staphylococcus aureus*. This method should be included in Volume 4 before publication.
— In line with a previous recommendation on hexanes made by the Committee at its sixty-fifth meeting, the Committee at its present meeting concluded that a review of all specifications for alkane hydrocarbon solvents, including hexanes and light petroleum, was needed.

2.3.3 *General Specifications and Considerations for Enzyme Preparations Used in Food Processing*

The General Specifications and Considerations for Enzyme Preparations Used in Food Processing were last revised by the Committee at its fifty-seventh meeting (Annex 1, reference *154*) and published in the *Compendium of Food Additive Specifications* (Annex 1, reference *156*). At its sixty-fifth meeting (Annex 1, reference *178*), the Committee recommended that the document be updated.

The General Specifications and Considerations for Enzyme Preparations Used in Food Processing were revised by the Committee at its present meeting (see Annex 5). General information on the classification and nomenclature of enzymes was updated and recommendations for naming enzymes in JECFA specifications monographs, including enzymes from microorganisms containing recombinant DNA, were included.

The description of an enzyme preparation was expanded to include formulation ingredients as well as the constituents of the source organism and compounds originating from the manufacturing process, which, in some instances, may be carried over to the final enzyme preparation. The discussion on active enzymes present in enzyme preparations and their characterization was expanded.

The general information on microbial sources was updated to address the use of fungal species with the potential to produce low levels of certain mycotoxins under fermentation conditions conducive to mycotoxin synthesis. A statement was added that enzyme preparations derived from such fungal species should not contain toxicologically significant levels of mycotoxins that could be produced by those species.

The paragraph on safety assessment was modified by including a statement that evaluation of the enzyme component should include considerations of its potential to cause an allergic reaction.

The list of references to international documents pertaining to foods and food ingredients from plants and microorganisms containing recombinant DNA was updated.

2.3.4 *Withdrawal of specifications*

Butyl p*-hydroxybenzoate (butyl paraben)*

The reproductive toxicity of the parabens appears to increase with increasing length of the alkyl chain, and there are specific data showing adverse reproductive effects in male rats of butyl paraben. In view of this and the fact that butyl paraben was not included in the group ADI for parabens, the Committee concluded that the specifications for this substance should be withdrawn.

Ethylene oxide

The Committee's attention was drawn to the continued existence of a specifications monograph for ethylene oxide used as a food additive, despite the fact that this substance has never been used as a food additive as such. In view of the known hazards of ethylene oxide, the Committee decided to withdraw the specification.

2.3.5 *Harmonization of terms*

The Committee was informed that a project to harmonize the terminology used by JECFA and the Codex Committee for Food Additives and Contaminants (CCFAC) to describe the functional uses of food additives had been approved by the Codex Alimentarius Commission at its Twenty-eighth Session (*2*). A proposed list of the terms used by both JECFA and CCFAC was submitted to the Codex Alimentarius Commission in May 2006. The Committee agreed that this list, once adopted by the Codex Alimentarius Commission, would be used by JECFA in specifications monographs for food additives at future meetings (see Annex 6).

2.3.6 *Food additives in nanoparticulate form*

Some chemical substances may be manufactured or formulated as very small particles described as "nanoparticles". The term "nanoparticle" is generally taken to refer to materials with a particle size of less than 100 nm. Particles of this small size can exhibit chemical and physical properties that are significantly different from those of larger particles of the same substance, and their toxicological properties may also differ.

To date, the Committee's evaluations of food additives have not taken account of possible differences between nanoparticles and other formulations. In cases where the chemical or physical properties of nanoparticles are different from those of the conventional food additive, it is possible that the nanoparticulate form will not meet the definition of the substance that was evaluated, as set out in the specifications monograph. In general, the Committee wished to affirm that neither the specifications nor the ADIs for food additives that have been evaluated in other forms are intended to apply to nanoparticulate materials.

3. Specific food additives

The Committee evaluated two food additives for the first time and re-evaluated three others. Six food additives were only considered for revision of specifications. Information on the safety evaluations and specifications is summarized in Annex 2. Details of further toxicological studies and other information required for certain substances are summarized in Annex 3.

3.1 Safety evaluations

3.1.1 *Annatto extracts*

Explanation

Annatto extracts were evaluated by the Committee at its thirteenth, eighteenth, twenty-sixth, forty-sixth, fifty-third and sixty-first meetings (Annex 1, references *19*, *35*, *59–61*, *122, 143* and *166*).

At its eighteenth meeting, the Committee considered the results of long-term and short-term tests in experimental animals fed an annatto extract containing 0.2–2.6% pigment expressed as bixin. A long-term study in rats provided the basis for evaluation; the no-observed-effect level (NOEL) in this study was 0.5% in the diet, the highest dose tested, equivalent to 250 mg/kg bw. A temporary ADI for this annatto extract was established at 0–1.25 mg/kg bw.

The Committee re-evaluated annatto extracts at its twenty-sixth meeting, when the results of the requested studies of metabolism became available. Studies of mutagenicity, additional long-term (1-year) studies in the rat, and observations of the effects of annatto extract in humans were also considered. The metabolism studies were conducted on three different extracts — a vegetable oil solution, a vegetable oil suspension (containing mainly bixin pigment) and a water-soluble extract (mainly norbixin) — alone and in admixture. No evidence was found for the accumulation of annatto pigments in the tissues of rats fed with at low dietary concentrations (20–220 mg/kg bw per day) with annatto extracts containing up to 2.3% bixin/norbixin mixture for 1 year, and clearance from the plasma was rapid.

The NOEL in the original long-term study in rats was identified as 0.5% in the diet, equivalent to 250 mg/kg bw, and the ADI for these annatto extracts was set at 0–0.065 mg/kg bw expressed as bixin. At that time, the Committee considered the highest concentration of bixin in the material tested (i.e. 2.6%) and established an ADI on the basis of the content of bixin.

At its forty-sixth meeting, the Committee revised the specifications for annatto extracts and redesignated them according to their methods of manufacture into two general types: oil- or alkali-extracted products, and solvent-extracted products. The ADI was not changed at that meeting. At its fifty-third meeting, the Committee assessed intake of annatto extracts and concluded that the intake of annatto extracts would exceed the ADI for bixin if all foods contained annatto extracts at the maximum levels proposed in the Codex Alimentarius Commission draft General Standard for Food Additives (GSFA) (*3*). Intake assessments based on national permitted levels led to the conclusion that the ADI for bixin was unlikely to be exceeded as a result of the use of annatto extracts.

Table 1 describes the designation of the extracts.

At its sixty-first meeting, the Committee established temporary ADIs for annatto extracts B, C, E and F. As insufficient data on the potential toxicity of annatto D or annatto G were available, no ADIs could be established for those extracts.

At that meeting, additional information was requested to clarify the role that the non-pigment components of the extract play in the expression of the qualitative and quantitative differences in toxicity between the various extracts. In addition, the Committee requested data on the reproductive toxicity of an extract, such as annatto F, that contains norbixin.

Table 1
Designation of annatto extracts

Annatto extract description[a]	Alternative designation[b]	Pigment content (%)[c]		Specified pigment content[d] (%)
		Bixin	Norbixin	
Solvent-extracted bixin	Annatto B	89.2 (92)	1.6 (1.7)	≤85% pigment (as bixin) ≤2% norbixin
Solvent-extracted norbixin	Annatto C	NR	(91.6)	≤85% pigment (as norbixin) (includes Na^+ and K^+ salts)
Oil-processed bixin	Annatto D	10.2	0.18	≤10% pigment (as bixin)
Aqueous processed bixin	Annatto E	25.4 (26)	1.1 (4.2)	≤25% pigment (as bixin) ≤7% norbixin
Alkali-processed norbixin (acid precipitated)	Annatto F	NA NA	41.5 (38.4)	≤35% norbixin
Alkali-processed norbixin (not acid precipitated)	Annatto G	NA	17.1	≤15% norbixin

NA: Not applicable; NR: Not reported.
[a] Description used by the Committee at its present meeting.
[b] Designation used by the Committee at its sixty-first meeting.
[c] Analytical data on the bixin/norbixin content of various extracts. Values in parentheses are for extracts tested in 90-day studies.
[d] Specified by the Committee at its present meeting

At the present meeting, most of those data were available and were evaluated, and a re-evaluation of the overall database was performed.

Toxicological data

Mass balance studies have characterized the components of the annatto extracts to the extent of greater than 95%, including non-pigment material, except for oil-processed bixin for which no new analytical data were provided.

A study of developmental toxicity in rats fed an annatto extract with a norbixin content of 41.5% at doses of up to 160 mg/kg bw per day (equal to 68 mg/kg bw per day expressed as norbixin) confirmed the absence of developmental toxicity at this, the highest dose tested.

In its previous evaluations, the Committee had concluded that annatto extracts are not carcinogenic. This conclusion was based on the results of tests with annatto preparations containing low concentrations of bixin. In a study of the initiation/promotion of liver carcinogenesis, solvent-extracted norbixin did not increase the incidence of preneoplastic lesions. A recent study showed that annatto extract

(5% bixin) at dietary concentrations of up to 1000 mg/kg had no influence on the development of preneoplastic glutathione-*S*-transferase (GST-P)-positive foci in livers of male rats treated with diethylnitrosamine, nor on DNA fragmentation in the livers using the comet assay. Together with the results of the tests for genotoxicity and the absence of proliferative lesions in the short-term tests for toxicity, those data support the earlier conclusion made by the Committee, that annatto extracts are not carcinogenic.

Dietary exposure assessment

During its sixty-first meeting, the Committee performed an assessment of dietary exposure based on typical use levels (provided by industry) of extracts expressed as bixin and norbixin. Combining those levels with various average levels of food consumption resulted in dietary exposures ranging from 0.03 to 0.4 mg/day. Combining the use levels reported by industry with 97.5th percentiles of consumption by United Kingdom (UK) consumers of foods potentially containing annatto resulted in a dietary exposure of 1.5 mg/day of total bixin plus norbixin.

No additional data were provided for this meeting, therefore exposure scenarios were performed on the basis of the previous dietary exposure to pigments, assuming a body weight of 60 kg.

Evaluation

At its present meeting, the Committee re-evaluated the 90-day studies of toxicity available for four of the extracts for which compositional data were provided. The results of those studies are summarized in Table 2.

In re-evaluating the studies of toxicity with solvent-extracted bixin (92% bixin) and solvent-extracted norbixin (91.6% norbixin) in the

Table 2
Results of 90-day studies of toxicity with annatto extracts

Annatto extract	Pigment in extract tested (%)		Extract NOEL[a] (mg/kg bw)	
	Bixin	Norbixin	Male	Female
Solvent-extracted bixin	92	1.7	1311	1446
Solvent-extracted norbixin	NR	91.6	69	76
Aqueous processed bixin	26	4.2	734	801
Alkali-processed norbixin (acidprecipitated)	NA	38.4	79	86

NA: Not applicable; NR: Not reported.
[a] As determined by the Committee at its sixty-first meeting.

light of the additional compositional data, the Committee considered that ADIs could be allocated to those pigments on the basis of the studies conducted on the extracts summarized in Table 2.

The Committee established an ADI for bixin of 0–12 mg/kg bw on the basis of the NOEL of 1311 mg/kg bw per day from a 90-day study in male rats fed an extract containing 92% bixin, corrected for pigment content and applying a safety factor of 100.

The Committee established a group ADI for norbixin and its sodium and potassium salts of 0–0.6 mg/kg bw (expressed as norbixin) on the basis of the NOEL of 69 mg/kg bw per day from a 90-day study in male rats fed an extract containing 91.6% norbixin, corrected for pigment content and applying a safety factor of 100.

The Committee further evaluated compositional data on aqueous processed bixin and alkali-processed norbixin (acid-precipitated), together with toxicological data on annatto extracts for which NOELs had been identified in 90-day studies of toxicity. It concluded that the use of these annatto extracts as sources of bixin or norbixin would not raise safety concerns, provided that they complied with the relevant specifications. Accordingly, the ADIs given above could be applied to bixin and norbixin derived from those annatto extracts. The Committee noted that the pigment in alkali-processed norbixin (not acid-precipitated) consists of sodium or potassium salts of norbixin and that compositional data on this extract, complying with the specifications, did not raise safety concerns. Consequently, the Committee concluded that the group ADI for norbixin and its sodium and potassium salts could be applied to norbixin salts from this source.

As no NOEL could be identified for oil-processed bixin and no compositional data were available, the Committee decided that the above evaluation could not be applied to this extract.

If all the pigment ingested were bixin, the estimated dietary exposure of 1.5 mg/day would result in an intake of bixin of 26 μg/kg bw per day, corresponding to approximately 0.2% of the ADI (0–12 mg/kg bw). Similarly, if all the pigment were norbixin, the estimated dietary exposure of 1.5 mg/day would result in an intake of norbixin of 26 μg/kg bw per day, corresponding to approximately 4% of the ADI (0–0.6 mg/kg bw).

All previously established ADIs and temporary ADIs for bixin and annatto extracts were withdrawn.

The tentative specifications for all annatto extracts were revised and the tentative designations removed, with the exception of the specifi-

cation for annatto extract (oil-processed bixin), which was maintained as tentative because the requested information on chemical characterization of the non-colouring-matter components of commercial products was not provided. The tentative specification for annatto extract (oil-processed bixin) would be withdrawn if the requested information is not received by the Committee before the end of 2008.

The Chemical and Technical Assessment prepared by the Committee at its sixty-first meeting was updated.

An addendum to the toxicological monograph was prepared.

3.1.2 *Lycopene (synthetic)*

Explanation

At the request of CCFAC at its Thirty-seventh Session (*4*), the Committee at its present meeting evaluated lycopene to be used as a food additive. Lycopene is a naturally-occurring pigment found in vegetables (especially tomatoes), fruits, algae and fungi. It can also be synthesized chemically. The Committee had previously evaluated lycopene (both natural and synthetic) to be used as a food colour at its eighth, eighteenth, and twenty-first meetings (Annex 1, references *8*, *35* and *44*). The lack of adequate information available at those meetings precluded the Committee from developing specifications and establishing an ADI for lycopene to be used as a food colour. Under consideration at the present meeting were synthetic lycopene (the subject of this item) and lycopene from the fungus *Blakeslea trispora* (see section 3.1.3).

Lycopene (synthetic) is a red crystalline powder containing at least 96% total lycopene, of which not less than 70% is all-*trans*-lycopene and the remainder is predominantly 5-*cis*-lycopene. Synthetic lycopene is produced by the Wittig condensation of intermediates and may contain low concentrations of reaction by-products, such as triphenyl phosphine oxide (TPPO; not more than 0.01%) and apo-12≥-lycopenal (not more than 0.15%). Owing to its insolubility in water and susceptibility to oxidative degradation in the presence of light and oxygen, only formulated material is marketed for use in food. Lycopene crystals are formulated as suspensions in edible oils or as water-dispersible powders, and are stabilized with antioxidants. The other substances present in the marketed formulations (such as sucrose, corn starch, gelatin, corn oil, ascorbyl palmitate and a-tocopherol) are common food ingredients and do not raise safety concerns.

Toxicological data

The Committee considered the results of a large number of studies of pharmacokinetics and metabolism, acute toxicity, short- and long-term studies of toxicity, and studies of carcinogenicity, genotoxicity and reproductive toxicity with lycopene. Most of those studies had been performed with formulations of synthetic lycopene complying with the specifications as prepared at the present meeting, and met appropriate standards for study protocol and conduct.

In rats given a single oral dose of a formulation containing 10% radiolabelled synthetic lycopene, lycopene was rapidly but poorly absorbed. Owing to the poor absorption (less than 10% of the administered dose), concentrations of radioactivity in organs and tissues were low, with highest concentrations being found in the liver, and lower concentrations in the spleen, adipose tissue and adrenals. In rats, repeated oral doses of formulations containing 10% synthetic lycopene and of lycopene from tomato concentrate also resulted in the accumulation of lycopene in the liver (with higher concentrations in females than in males), and to a lesser extent in spleen and adipose tissue. This accumulation in the liver was associated with pigment deposits in hepatocytes, both with synthetic lycopene and with lycopene from tomato concentrate, although higher doses of the latter were necessary to induce the same level of effect. In the rat body, the isomeric ratio changed to favour *cis* isomers, the percentage of *cis* isomers of lycopene being higher in plasma and most tissues, including liver, than in the test material. *Trans*- to *cis*-isomerization was also observed in dogs. Studies in dogs and monkeys confirmed that the highest concentrations of lycopene accumulate in the liver.

In humans, absorption of formulated synthetic lycopene was comparable to absorption of lycopene contained in tomato-based products. Like in laboratory species, the systemic availability of lycopene in humans is generally low, but can be increased in the presence of dietary fat. The most abundant isomers in human plasma are all-*trans*-lycopene and 5-*cis*-lycopene, with all the *cis* isomers contributing to more than 50% of total lycopene. This isomer ratio differs from that of synthetic lycopene and lycopene in food, indicating that conversions take place after ingestion, as was also shown in laboratory species.

Little is known about the metabolism or degradation of lycopene in mammals. It is not converted to vitamin A. In rats, non-characterized polar metabolites are present in tissues and excreta. In humans, the proposed metabolic pathway involves oxidation of lycopene to lycopene 5,6-oxide, which subsequently undergoes cyclization and

enzymatic reduction to form an epimeric mixture of 2,6-cyclolycopene-1,2-diol.

When administered orally as a formulation containing 10% synthetic lycopene, the median lethal dose (LD_{50}) for lycopene was more than 500 mg/kg bw in rats.

The toxicity of synthetic lycopene was evaluated using the results of short-term studies in which rats were given one of several 10% formulations, either in the diet for 4 or 14 weeks, or by gavage for 3 months. Synthetic lycopene was well tolerated in those studies. A reddish discoloration of the faeces was observed in the feeding and the gavage studies, owing to excretion of the red-staining test substance. The gavage study also showed a red discoloration of contents of the gastrointestinal tract, and the feeding studies showed an orange-reddish discoloration of the liver and adipose tissue. The observed discoloration in the liver was associated with orange-brown pigment deposits in the hepatocytes, with female rats being more affected than males. There was, however, no histopathological evidence of liver damage. The Committee considered that the changes observed in the short-term studies of toxicity did not represent adverse effects. The NOELs for lycopene were 1000, 500 and 300 mg/kg bw per day for the 4-week, 14-week and 3-month study, respectively, corresponding to the highest doses tested in those studies.

Observations made in short-term studies of toxicity in dogs were consistent with the findings in rats. When administered in capsules at a dose of 30 mg/kg bw per day for 28 days or 100 mg/kg bw per day for 192 days, synthetic lycopene caused only a red discoloration of the faeces and liver, respectively, with pigment being detectable in the latter, without associated hepatocellular alterations.

In a long-term study of toxicity, rats received diet mixed with a beadlet formulation containing 10% synthetic lycopene at target doses of 0 (untreated control), 0 (beadlet control), 10, 50, or 250 mg/kg bw per day for 52 weeks, followed by a recovery period of 13 weeks for some of the animals. Treatment-related findings were confined to discoloured faeces/red staining at the lowest, intermediate and highest dose, red contents in the stomach and caecum and yellow connective tissue in the abdominal cavity at the intermediate and highest dose, and (particularly in female rats at all doses) golden brown pigment deposits in the liver. The pigment deposits were still observed after recovery, albeit to a lesser degree. There was no apparent sign of liver dysfunction but, in contrast to the findings in the short-term studies of toxicity, the liver pigmentation in hepatocytes and histiocytes was associated with a greater incidence and severity of

basophilic foci in females at the intermediate and highest dose than in females at the lowest dose or in the control groups. The histopathological alterations were considered to be treatment-related.

In a study of carcinogenicity in which diets were mixed with the same beadlet formulation containing 10% synthetic lycopene, rats received synthetic lycopene at target doses of 0 (untreated control), 0 (beadlet control), 2, 10, or 50 mg/kg bw per day for 104 weeks. Again, treatment resulted in a red discoloration of the faeces, red contents in the gastrointestinal tract, and yellow connective tissue at the intermediate and/or highest dose, golden brown pigment deposits in the liver (at all doses), as well as pigmentation in kidneys (females at the highest dose) and mesenteric and mandibular lymph nodes (at all doses). Liver pigmentation was observed in females (in hepatocytes and histiocytes) and, to a lesser degree, in males (in histiocytes). 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 dose, albeit without a consistent dose–response relationship. There was no apparent sign of liver dysfunction. 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 mainly observed at the intermediate and highest dose were considered to be treatment-related.

Synthetic lycopene has been tested in vitro for its capacity to induce reverse mutations in *Salmonella typhimurium* and *Escherichia coli*, gene mutations in mouse lymphoma L1578Y $Tk^{+/-}$ cells, and chromosomal aberrations in Chinese hamster V79 cells and human lymphocytes. It has also been tested in vivo for its ability to induce micronucleus formation in bone marrow and peripheral blood cells of mice and unscheduled DNA synthesis in rat hepatocytes. In those studies, several formulations containing 10% synthetic lycopene were tested, and the outcomes were predominantly negative. In contrast, when oxidatively degraded, unformulated synthetic lycopene was tested for capacity to induce gene mutations in *S. typhimurium*, the outcome was positive. On the basis of those data and the results of the study of carcinogenicity in rats, the Committee concluded that synthetic lycopene, when formulated and, as such protected against oxidative processes, has no genotoxic or carcinogenic potential.

In a two-generation study of reproductive toxicity, rats received a diet mixed with a formulation containing 10% synthetic lycopene at target

doses of 0, 50, 150, or 500 mg/kg bw per day. In the parental generation, apart from red-coloured faeces and yellow-orange staining of fur/skin/fat/abdominal organs attributable to the colour of lycopene, treatment with lycopene was only associated with marginal effects on body weight and food consumption (F_1 generation only). Mating performance and fertility, and survival and growth of the pups were not affected by treatment with lycopene. The NOELs for parental, reproductive and offspring toxicity were all 500 mg/kg bw per day, the highest dose tested.

The developmental toxicity of synthetic lycopene was evaluated via studies in which one of several 10% formulations was administered orally to rats (via diet and via gavage) and rabbits (via gavage) at up to maximum practical doses. Administration via the diet was tolerated better than was administration of large volumes of the highly viscous test substance via gavage. In all studies, dams showed red discoloured faeces, and in the gavage studies the contents of the gastrointestinal tract were red. Synthetic lycopene did not affect reproductive or fetal parameters in the studies in rats and rabbits, nor did it increase the overall number of external, visceral and skeletal abnormalities and variations. Given the absence of significant toxicological findings, the NOELs for both maternal and developmental toxicity were 500 and 300 mg/kg bw per day in the feeding and gavage studies in rats, respectively, and 400 and 200 mg/kg bw per day in the gavage studies in rabbits, corresponding to the highest doses tested in those studies.

In reports in the literature, most 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 yellow-orange skin discoloration and/or gastrointestinal discomfort after prolonged high intakes of lycopene-rich food and supplements, those effects being reversible upon cessation of lycopene ingestion.

Since most of the available toxicological studies have been performed with formulations of synthetic lycopene complying with the specifications, the safety of any impurities/reaction by-products present (if any) has been implicitly tested at their maximum permissible levels. Additional toxicological data available on apo-12≥-lycopenal and TPPO did not raise safety concerns.

Dietary exposure assessment

Lycopene is a normal constituent of the human diet owing to its presence in a number of vegetables and fruits. Dietary intakes

of lycopene range from 1 to 10 mg/person per day, based on published estimates from eight countries. Additional exposure to lycopene would result from its proposed uses in a variety of food types, including flavoured dairy beverages, yogurts, candies, cereals, soups, salad dressings, sauces, fruit and vegetable juices, sports drinks, carbonated beverages, and cereal and energy bars. An estimate of high exposure (greater than 95th percentile), which includes intake from fruits and vegetables, is 30 mg/person per day. This estimate is based on food intake data from a number of national surveys, combined with proposed maximum levels for use of lycopene in food. This estimate is conservatively high in that it is assumed that lycopene would be present in all foods within a food type, at the maximum use level.

Evaluation

After ingestion, synthetic lycopene is considered to be equivalent to naturally-occurring dietary lycopene. Being a normal constituent of the human diet, with a background intake ranging from 1 to 10 mg/person per day, lycopene has a long history of consumption. Available data indicate that dietary lycopene is generally well tolerated in humans. After prolonged high intakes of lycopene-rich food and supplements, effects limited to yellow-orange skin discoloration and/or gastrointestinal discomfort have been reported. In the available toxicological studies, histopathological alterations of liver foci were observed in rats with synthetic lycopene at doses of greater than or equal to 50 mg/kg bw per day for 1 year and 10 mg/kg bw per day for 2 years. The significance of those treatment-related alterations for humans is unclear, given that there was no apparent sign of liver dysfunction and that they were without a consistent dose–response relationship. Moreover, although hepatocellular foci are commonly found at a high incidence in the ageing rat, they are extremely rare in humans. Only in parts of the world where, for example, hepatitis is endemic, low incidences of hepatocellular foci are found. Although foci can be precursors of liver neoplasia in rats, the Committee noted that treatment with synthetic lycopene did not cause progression of the foci to neoplasia in the 2-year study of carcinogenicity. The Committee also noted that many substances that are known to induce liver foci in rodents do not have a similar effect in humans. Taking all this into account, the Committee concluded that the observed histopathological alterations of liver foci in rats do not raise a safety concern for humans.

The Committee established an ADI of 0–0.5 mg/kg bw for synthetic lycopene based on the highest dose of 50 mg/kg bw per day tested in

the 104-week study in rats (at which no adverse effects relevant to humans were induced), and a safety factor of 100. This ADI was made into a group ADI to include lycopene from *Blakeslea trispora*, which was also under consideration at the present meeting and which was considered to be toxicologically equivalent to chemically synthesized lycopene. The estimate of high exposure (greater than 95th percentile) of 30 mg/person per day, equivalent to 0.5 mg/kg bw per day, which includes background exposure plus additional exposure from food additive uses, is compatible with the ADI.

A toxicological monograph and a Chemical and Technical Assessment were prepared, and new specifications were established.

3.1.3 *Lycopene from* Blakeslea trispora

Explanation

At the request of CCFAC at its Thirty-seventh Session (*4*), the Committee at its present meeting evaluated lycopene to be used as a food additive. Lycopene is a naturally-occurring pigment found in vegetables (especially tomatoes), fruits, algae and fungi. It can also be synthesized chemically. The Committee had previously evaluated lycopene (both natural and synthetic) to be used as a food colour at its eighth, eighteenth, and twenty-first meetings (Annex 1, references *8*, *35* and *44*). The lack of adequate information at those meetings precluded the Committee from developing specifications and establishing an ADI for lycopene to be used as a food colour. Under consideration at the present meeting were lycopene from the fungus *Blakeslea trispora* (the subject of this item) and synthetic lycopene (see section 3.1.2).

Lycopene from *B. trispora* is obtained by cofermentation of the (+) and (–) sexual mating types of the fungus. It is an intermediate in the biosynthesis of β-carotene from *B. trispora*, the safety of which was evaluated by the Committee at its fifty-seventh meeting (Annex 1, reference *154*). The Committee concluded at that meeting that the source organism *B. trispora* is neither pathogenic nor toxigenic, and that the production process and composition of β-carotene from *B. trispora* do not raise safety concerns.

Lycopene is extracted from the biomass of *B. trispora* and purified by crystallization and filtration, using the solvents isobutyl acetate and isopropanol. The process by which lycopene is produced from *B. trispora* is nearly identical to that used to manufacture β-carotene from *B. trispora*, the only difference being the addition of imidazole to the fermentation broth to inhibit the formation of β- and γ-carotene from lycopene.

Lycopene from *B. trispora* is a red crystalline powder that contains at least 95% total lycopene (of which at least 90% is all-*trans*-lycopene) and up to 5% other carotenoids. The extraction solvents isopropanol and isobutyl acetate may be present in the final product at concentrations of less than 0.1% and 1%, respectively. Owing to its insolubility in water and susceptibility to oxidative degradation in the presence of light and oxygen, only formulated material is marketed for use in food. Lycopene crystals from *B. trispora* are formulated as suspensions in edible oils or as water-dispersible powders, and are stabilized with antioxidants. The other substances present in the marketed formulations (such as sunflower seed oil and α-tocopherol) are common food ingredients and do not raise safety concerns.

Toxicological data

The Committee considered the results of short-term studies of toxicity and studies of genotoxicity that had been performed with formulations of lycopene from *B. trispora* complying with the specifications as prepared at the present meeting, and that met appropriate standards for study protocol and conduct.

In a short-term study of toxicity, rats received diets mixed with a suspension of 20% (w/w) lycopene in sunflower seed oil, resulting in dietary concentrations of lycopene of 0, 0.25, 0.50, or 1.0%, equal to approximately 0, 150, 300, and 600 mg/kg bw per day respectively, for 90 days. Lycopene from *B. trispora* was well tolerated, and there were no adverse effects. The only treatment-related finding was a red discoloration of the contents of the gastrointestinal tract, caused by ingestion of the red-staining test substance. The NOEL for lycopene was approximately 600 mg/kg bw per day, the highest dose tested.

Lycopene from *B. trispora* has been tested in vitro for its capacity to induce reverse mutations in *S. typhimurium* and *E. coli* and chromosomal aberrations in human lymphocytes. In those studies, lycopene was formulated as 20% cold water-dispersible product. Lycopene gave negative results in both studies.

No studies of acute toxicity, long-term studies of toxicity or studies of reproductive and developmental toxicity have been conducted with lycopene from *B. trispora*. No data were available on the bioavailability of formulated lycopene from *B. trispora*, but it is expected that after ingestion lycopene from *B. trispora* is equivalent to natural dietary lycopene, because the other components in the final formulations are also present in food.

The Committee also considered a number of published studies of pharmacokinetics and metabolism, tolerance, acute toxicity, geno-

toxicity, and short-term studies of toxicity with lycopene derived from other natural sources. The materials tested in those studies (e.g. tomato-derived (oleoresin) extracts, tomato paste, tomato juice) did not comply with the food-additive specifications for lycopene from *B. trispora*, and several studies were not aimed at examining adverse health effects. Nonetheless, the Committee was able to conclude that there is evidence for a similar kinetic profile indicating low absorption of orally administered lycopene in laboratory species and humans, that little is known about the metabolism of lycopene and that, taken as a whole, the results are consistent with low toxicity, show no evidence for genotoxicity, and generally reveal no adverse effects in humans after administration of dietary lycopene. There is also evidence for a common feature in the alteration of the isomeric ratio to favour *cis* isomers after consumption of lycopene, given that all-*trans*-lycopene is less abundant in plasma of humans and animals than it is in lycopene in foods. This is also likely to be the case for lycopene from *B. trispora*.

On the basis of the observed phenomenon of *trans*- to *cis*-isomerization after ingestion, the Committee concluded that differences in *trans* and *cis* isomer ratio of lycopene from *B. trispora* and other lycopenes (whether from other natural sources or chemically synthesized) are not toxicologically relevant. The Committee thus considered lycopene from *B. trispora* to be toxicologically equivalent to chemically synthesized lycopene.

Dietary exposure assessment

Lycopene is a normal constituent of the human diet owing to its presence in a number of vegetables and fruits. Dietary intakes of lycopene range from 1 to 10 mg/person per day, based on published estimates from eight countries. Additional exposure to lycopene would result from its proposed uses in a variety of food types, including flavoured dairy beverages, yogurts, candies, cereals, soups, salad dressings, sauces, fruit and vegetable juices, sports drinks, carbonated beverages, and cereal and energy bars. An estimate of high exposure (greater than 95th percentile), which includes intake from fruits and vegetables, is 30 mg/person per day. This estimate is based on food intake data from a number of national surveys, combined with proposed maximum levels for use of lycopene in food. This estimate is conservatively high in that it is assumed that lycopene would be present in all foods within a food type, at the maximum use level.

Evaluation

Lycopene from *B. trispora* is considered to be toxicologically equivalent to chemically synthesized lycopene, for which an ADI of

0–0.5 mg/kg bw was established by the Committee at its present meeting. This was given further credence by the negative results obtained for lycopene from *B. trispora* in two tests for genotoxicity, and the absence of adverse effects in a short-term study of toxicity considered at the present meeting. The ADI for synthetic lycopene was therefore made into a group ADI of 0–0.5 mg/kg bw to include lycopene from *B. trispora*.

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

3.1.4 *Natamycin (exposure assessment)*

Explanation

Natamycin is an antibiotic that is used for the surface treatment of semi-hard and semi-soft cheese and dry, cured sausages. Natamycin was evaluated by the Committee at its twelfth, twentieth and fifty-seventh meetings (Annex 1, references *17*, *41*, and *154*). An ADI of 0–0.3 mg/kg bw was established by the Committee at its twentieth meeting. At its fifty-seventh meeting, the Committee confirmed the previous ADI and noted that the estimated intakes of natamycin based on maximum levels of use in cheese and processed meat do not exceed the ADI.

At its Thirty-seventh session (*4*), CCFAC asked the Committee to perform a new exposure assessment to include novel proposed uses for natamycin. The Committee received information on methods for the application of natamycin to food, in particular, cheese; namely, by dipping, spraying an aqueous solution, or dusting a dry mixture onto the surface. Such treatments can be applied either before or after slicing. Natamycin can also be added to plastic film used to coat the cheese.

Because natamycin is used for surface treatment, the Codex maximum levels for this additive are expressed in mg/dm^2. In cured meat products and cheese, the maximum levels are 1 and 2 mg/dm^2, respectively, with absence of natamycin beyond a depth of 5 mm. Based on those figures, and assuming a density of 1 g/cm^1 for both meat and cheese, the highest concentrations of natamycin could be 20 and 40 mg/kg^3 for meat and cheese respectively in the outer 5 mm of the surface. These concentrations are used in the following dietary exposure assessment for all meat and cheese as eaten. This corresponds to a worst-case scenario, assuming that all the food consumed was taken

[1] A concentration of 2 mg/50 cm^3 (10 cm × 10 cm × 0.5 cm) corresponds to 40 mg/kg, assuming a density of 1 g/cm^3.

from the surface of the whole piece of cheese or meat (less than 5 mm deep) or that all the food consumed was treated after slicing or shredding. These concentrations are the same as those used by the Committee at its fifty-seventh meeting.

The Committee at its present meeting also received refined estimates for consumption of cured meat products and cheese and therefore updated its previous dietary exposure assessment.

Dietary exposure assessment

Owing to the fact that this additive is intended for surface treatment, the budget method is not applicable. Therefore the Committee performed a dietary exposure assessment based on (a) per capita estimates of food consumption and (b) individual food consumption data.

(a) Per-capita dietary exposure, based on GEMS/Food Consumption Cluster Diets[1]

The Global Environment Monitoring System — Food Contamination Monitoring and Assessment Programme (GEMS/Food) Consumption Cluster Diets represent the amount of food available per capita for 440 foods for each of 13 clusters. For the purpose of the current assessment, only the four clusters with the highest consumption of cheese and meat were considered. It was assumed that all meat and cheese contained natamycin, and that all the meat and cheese eaten was treated with natamycin at the maximum authorized concentration (cheese, 40 mg/kg; meat products, 20 mg/kg). Finally, it was also assumed that all the food eaten was taken less than 5 mm from the surface of the whole piece of cheese or meat.

Despite such factors of overestimation, the sum of the highest exposure to natamycin from meat and cheese would result in an overall dietary exposure of less than 0.1 mg/kg bw per day, assuming a body weight of 60 kg (Table 3).

(b) Refined estimate of dietary exposure, based on individual food consumption data

The sponsor provided results based on food consumption surveys from the UK and Germany (Table 4), with a refinement of the food categories likely to contain natamycin and a focus on children (who are more likely to have higher levels of exposure because their body weights are lower than those of adults).

[1] For more details on the GEMS/Food Consumption Cluster Diets, see: http://www.who.int/foodsafety/publications/chem/regional_diets/en/.

Table 3
Estimated per-capita dietary exposure to natamycin, based on the GEMS/Food Consumption Cluster Diets

Dietary exposure	GEMS/Food Consumption Cluster							
	Cluster b (mainly Mediterranean countries)		Cluster e (mainly western and eastern Europe)		Cluster f (mainly northern Europe)		Cluster m (mainly North America, certain countries in South America, and Australia and New Zealand)	
Food category	Cheese	Meat	Cheese	Meat	Cheese	Meat	Cheese	Meat
Use level (mg/kg)	40	20	40	20	40	20	40	20
Food intake (g/day)	23	64	44	118	34	130	36	223
Natamycin exposure per capita (mg/kg bw per day perperson)	0.015	0.02	0.03	0.04	0.02	0.04	0.02	0.07

GEMS/Food, Global Environment Monitoring System — Food Contamination Monitoring and Assessment Programme

Table 4
Estimated dietary exposure to natamycin, based on individual food consumption data

Country	Food category	Use level (mg/kg)	Children at the 97.5th percentile		Adults at the 97.5th percentile	
			Food intake (g/day)	Dietary exposure (mg/kg bw per (g/day) day)	Food intake	Dietary exposure[a] (mg/kg bw per day)
UK	Cheese[b]	40	28	0.08[c]	62	0.04
UK	Cured meat comminuted[d]	20	30	0.04[c]	19	0.006
Germany	Cheese	40	40	0.1[e]	74[f]	0.05
Germany	Cured meatcomminuted	20	43	0.05[e]	64[f]	0.02

UK: United Kingdom
[a] Based on a body weight of 60kg.
[b] All cheese other than cream cheese and including that used in recipes.
[c] Pre-school children aged 18–54 months.
[d] Including products such as salamis and other dried sausages.
[e] Children aged 4–10 years, assuming a body weight of 15kg
[f] This estimate included all subjects aged more than 10 years.

In conclusion, the data as a whole, including estimations based on GEMS/Food Consumption Cluster Diets and calculations for consumers with a high intake and children, confirm the results of the assessment made by the Committee at its fifty-seventh meeting and show that the current ADI of 0–0.3 mg/kg bw is unlikely to be exceeded.

3.1.5 *Propyl paraben*

Explanation

The parabens (methyl-, ethyl-, and propyl *p*-hydroxybenzoate) having a functional use as preservatives in food were evaluated by the Committee at its sixth, ninth, tenth and seventeenth meetings (Annex 1, references *6*, *11*, *13* and *32*). At its seventeenth meeting, the Committee established a group ADI of 0–10 mg/kg bw (expressed as the sum of methyl-, ethyl-, and propyl esters of *p*-hydroxybenzoic acid). Additional information subsequently became available concerning estrogenic and reproductive effects of the parabens, which led the European Food Safety Authority to exclude propyl paraben from the group ADI for the parabens. At its Thirty-seventh Session in 2005 (*4*), CCFAC placed propyl paraben on the priority list for toxicological re-evaluation by JECFA.

Toxicological data

Data on endocrine and reproductive effects are available from studies in vitro and in vivo with various parabens, including the three parabens used in food, and on their common metabolite, *p*-hydroxybenzoic acid. They show that the likelihood of such effects is related to the length of the alkyl chain, with occurrence and potency increasing with increasing chain length. The three parabens used as food additives (methyl-, ethyl- and propyl *p*-hydroxybenzoate) are those with the shortest chain length.

The parabens have been shown to exhibit weak estrogenic activity in a number of test systems in vitro. They are able to bind to the estrogen receptors ERα and ERβ and to stimulate proliferation in estrogen-dependent mammalian cell lines. In these test systems, estrogenic potency increases with increasing length and branching of the alkyl chain in the following order: methyl < ethyl < propyl < butyl < isopropyl < isobutyl < benzyl < heptyl < 2-ethylhexyl *p*-hydroxybenzoate. For example, in assays screening for estrogenic activity in recombinant yeast (using yeast cells transfected with the human ERα gene), the relative potency of 17-β-estradiol (E2) was around 3 million-fold that of methyl *p*-hydroxybenzoate; and that of E2 was 150 000–200 000-fold that of ethyl *p*-hydroxybenzoate. The relative potency of

E2 was 30 000-fold and 10 000-fold that of the propyl and butyl esters, respectively. One study has reported that the common metabolite of the parabens, *p*-hydroxybenzoic acid, shows estrogenic activity by several measures in estrogen-dependent mammalian cell lines, with relative binding affinity to the estrogen receptor being 500 000 times lower than that of E2. Two other studies on *p*-hydroxybenzoic acid have reported that it is inactive in vitro. The Committee considered that the relevance for human health, if any, of very weak estrogenic activity in vitro is unclear at present.

The estrogenic activity of the parabens and their common metabolite, *p*-hydroxybenzoic acid, has been tested in vivo in uterotrophic assays in immature or ovariectomized mice or rats treated by oral, subcutaneous or topical dermal administration. While methyl, ethyl and propyl parabens showed uterotrophic activity after dosing by the subcutaneous route, none of those were active in the uterotrophic assay when given orally by gavage at doses of up to 800 mg/kg bw per day for the methyl paraben, up to 1000 mg/kg bw per day for the ethyl paraben and up to 100 mg/kg bw per day for the propyl paraben. For *p*-hydroxybenzoic acid, one study reported an uterotrophic effect in mice after subcutaneous administration, but this was not confirmed in a subsequent study in which it was given orally or subcutaneously at higher doses than in the first study.

Several studies have investigated the effects of parabens on male reproductive parameters in rodents. Juvenile rats given diets containing propyl paraben at doses equivalent to about 10, 100 or 1000 mg/kg bw per day for 4 weeks showed dose-related reductions in epididymal sperm reserves and sperm concentrations at the intermediate and highest doses, reductions in daily sperm production in the testis and reductions in serum concentrations of testosterone in all treated groups. In a similar study, in which diets containing butyl paraben at the same doses were given for 8 weeks, similar effects were observed but they were more marked than those with propyl paraben and, in addition, epididymal and seminal vesicle weights were reduced. Similar effects on sperm counts and serum concentrations of testosterone were observed in juvenile mice given butyl paraben at dietary doses of 15–1500 mg/kg bw per day for 10 weeks. In contrast to butyl and propyl parabens, neither methyl paraben nor ethyl paraben showed any effects on male reproductive organs, sperm parameters or sex hormones in juvenile rats given dietary doses of up to 1000 mg/kg bw per day for 8 weeks. There are insufficient data to conclude whether the effects observed with parabens of higher alkyl chain length in males are mediated via an estrogenic, anti-androgenic or some other mechanism.

Dietary exposure assessment

No specific information on the intake of propyl paraben was available to the Committee. Estimates of total dietary intake of parabens by consumers have been calculated, using the respective use levels from the USA and the EU and assuming an average adult body weight of 60 kg. In the USA, average to 90th-percentile intakes range from 3.7 to 7.8 mg/kg bw per day. In the EU, average to 95th-percentile intakes range from 1.2 to 5.3 mg/kg bw per day. The estimates are highly conservative, being based on the assumption that parabens are used in all possible foods at the highest maximum permitted levels.

Evaluation

The Committee concluded that, in view of the adverse effects in male rats, propyl paraben (propyl *p*-hydroxybenzoate) should be excluded from the group ADI for the parabens used in food. This conclusion was reached on the grounds that the group ADI was originally set on a NOEL of 1000 mg/kg bw per day for a different toxicological endpoint — growth depression — taken from the range of studies then available for the methyl, ethyl and propyl parabens. Propyl paraben has shown adverse effects in tissues of reproductive organs in male rats at dietary doses of down to 10 mg/kg bw per day, which is within the range of the group ADI (0–10 mg/kg bw), with no NOEL yet identified.

The Committee maintained the group ADI of 0–10 mg/kg bw for the sum of methyl and ethyl esters of *p*-hydroxybenzoic acid.

An addendum to the toxicological monograph was prepared. The specifications for propyl paraben were withdrawn as a result of the exclusion of propyl paraben from the group ADI for parabens. Specifications for the other parabens were not considered at the present meeting.

3.2 Revision of specifications

3.2.1 *Acetylated oxidized starch*

The Committee was informed of an error in the current specifications for acetylated oxidized starch, that first appeared in the specifications monograph for modified starches in the FAO Food and Nutrition Paper 52 Addendum 9 in 2001 (Annex 1, reference *156*), and was republished in the *Combined Compendium of Food Additvie specifications in* 2005 (Annex 1, reference *180*). The Committee agreed to correct the specified carboxyl value from 1.1% to 1.3% and requested that the Joint FAO Secretary note the corrigendum in the FAO JECFA Monographs.

3.2.2 *Carob bean gum*

The Committee was requested by CCFAC at its Thirty-seventh Session (*4*) to review the specifications monograph entitled "Carob bean gum" and noted that, as written, it covers two grades of product. It was therefore decided to prepare two specifications monographs. The monograph entitled "Carob bean gum" concerns the milled endosperm product. The second monograph entitled "Carob bean gum, clarified", concerns the clarified form. Both monographs were designated as tentative. For carob bean gum, data are required on gum content, solubility in water and an improved method for measuring residual solvents. For carob bean gum, clarified, synonyms and a range of other information are required. The tentative specifications monographs would be withdrawn unless the required information was received before the end of 2007.

3.2.3 *Guar gum*

The Committee was requested by CCFAC at its Thirty-seventh Session (*4*) to review the specifications monograph entitled "Guar gum" and noted that, as written, it covers two grades of product. It was therefore decided to prepare two specifications monographs. The monograph entitled "Guar gum" concerns the milled endosperm product. The second monograph, entitled "Guar gum, clarified", concerns the clarified form. Both monographs were designated as tentative. For guar gum, data are required on gum content and an improved method for measuring residual solvents. For guar gum, clarified, synonyms and a range of other information are required. The tentative specifications monographs would be withdrawn unless the required information was received before the end of 2007.

3.2.4 *DL-Malic acid and its calcium and sodium salts*

The Committee noted that the draft Volume 4 of FAO JECFA Monographs 1 contains a high-performance liquid chromatography (HPLC) method for the determination of fumaric acid and maleic acid, which replaces an earlier, outdated, polarographic method. However, the current specifications monographs for DL-malic acid and sodium DL-malate included the outdated polarographic method. The Committee therefore decided to delete the polarographic method from those monographs and include a reference to Volume 4 and the HPLC method. In addition, the Committee included a limit for fumaric acid in the specifications monographs for calcium DL-malate and sodium hydrogen DL-malate in order to align the four specifications monographs on malic acid derivatives (calcium

DL-malate, DL-malic acid, sodium hydrogen DL-malate and sodium DL-malate).

The functional uses of DL-malic acid and sodium DL-malate as flavouring agents were deleted, as was the functional use of calcium DL-malate as a seasoning agent, because the Committee was aware that those compounds were not used as flavouring agents. The limits for sulfated ash, contained in specifications monographs for DL-malic acid and sodium DL-malic acid, were also deleted.

3.2.5 *Maltitol*

When the specifications for heavy metals (as lead), other metals and arsenic in sweeteners, were reviewed by the Committee at its fifth-seventh meeting in 2001 (Annex 1, reference *154*), maltitol was inadvertently omitted. The Committee agreed with the Secretariat's proposal to bring the maltitol specification into line with other polyols, with regard to metals, in the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*).

3.2.6 *Titanium dioxide*

In response to a request from CCFAC at its Thirty-seventh Session (*4*), the Committee revised the specifications monograph for titanium dioxide prepared by the Committee at its sixth-third meeting by:

— Including mention of the "chloride process" in the definition, in addition to the "sulfate process," as an alternative means for manufacturing titanium dioxide; and
— Noting in the description that the colour of the additive can be a "slightly coloured" powder, as well as a white powder.

The Committee also lowered the maximum limit for arsenic to 1 mg/kg, replaced the method of assay with a newer method that does not require use of a mercury salt for the analysis, and made editorial changes to the texts of other analytical methods. A Chemical and Technical Assessment was prepared.

3.2.7 *Zeaxanthin (synthetic)*

In response to a request from CCFAC at its Thirty-seventh Session (*4*), the Committee revised the specifications monograph for zeaxanthin (synthetic) by:

— Including the statement on solubility to read "sparingly soluble in chloroform, practically insoluble in water and ethanol"; and
— Revising the sum of 12≥-apo-zeaxanthinal, diatoxanthin, and parasiloxanthin to 1.1%.

In addition, the analytical method for determining triphenylphosphine oxide was transferred from the specifications monograph to Volume 4 of the *Combined Compendium of Food Additives Specifications*, as this method is described in more than one specifications monograph. The method of assay was improved in terms of clarity. The Chemical and Technical Assessment for zeaxanthin (synthetic) and zeaxanthin-rich extract prepared by the Committee at its sixth-third meeting was updated.

4. Contaminants

4.1 Aluminium (from all sources, including food additives)

Explanation

Various aluminium compounds had been evaluated by the Committee at its thirteenth, twenty-first, twenty-sixth, twenty-ninth, thirtieth and thirty-third meetings (Annex 1, references *20*, *44*, *59*, *70*, *73* and *83*). At the thirteenth meeting, an ADI "not specified" was established for sodium alumino-silicate and aluminium calcium silicate (Annex 1, reference *20*). At its thirtieth meeting, the Committee noted concerns about a lack of precise information on the aluminium content of the diet and a need for additional safety data. The Committee set a temporary ADI of 0–0.6 mg/kg bw expressed as aluminium for all aluminium salts added to food, and recommended that aluminium in all its forms should be reviewed at a future meeting.

In the evaluation made by the Committee at its thirty-third meeting, emphasis was placed on estimates of consumer exposure, absorption and distribution of dietary aluminium and possible neurotoxicity, particularly the relationship between exposure to aluminium and Alzheimer disease. The Committee set a provisional tolerable weekly intake (PTWI) of 0–7.0 mg/kg bw for aluminium, including food additive uses. This was based upon a study in which no treatment-related effects were seen in beagle dogs given diets containing sodium aluminium phosphate (acidic) at a concentration of 3% for 189 days, equivalent to approximately 110 mg/kg bw aluminium. A consolidated monograph was produced (Annex 1, reference *84*).

Aluminium was re-evaluated by the Committee at its present meeting, as requested by CCFAC at its Thirty-seventh Session (*4*). The Committee was asked to consider all data relevant to the evaluation of the toxicity and intake of aluminium (including bioavailability) used in food additives and from other sources, including sodium aluminium phosphate. CCFAC asked that the exposure assessment cover all compounds included in the Codex GSFA.

Two documents were particularly important in the evaluation made by the Committee at its present meeting: the International Programme on Chemical Safety (IPCS) Environmental Health Criteria document on aluminium (*5*) and a report of the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) on a water pollution incident that occurred in Cornwall, England in 1988 (*6*). The Committee used those assessments as the starting point for its evaluation and also evaluated other data in the scientific literature relating to aluminium compounds. No original toxicological data on aluminium-containing food additives were submitted.

Absorption, distribution, metabolism and excretion

Assessment of the bioavailability of aluminium compounds is confounded by limitations in the analytical methodology, particularly for older studies, by concurrent exposure to modifying factors and by dose-dependency. Speciation appears to be an important factor in absorption and it is widely assumed that soluble aluminium compounds, such as the chloride and lactate salts, are more bioavailable than insoluble compounds, such as aluminium hydroxide or silicates. Studies in laboratory animals and in human volunteers generally show that absorption of aluminium is less than 1%. However, because of the differences in methodology, it is not possible to draw precise conclusions on the rate and extent of absorption of different aluminium compounds. Concurrent intake of organic anions (particularly citrate) increases the absorption of aluminium, while other food components, such as silicates and phosphate, may reduce the absorption of aluminium.

Studies reviewed by the Committee at its thirty-third meeting showed no detectable aluminium in the urine of normal subjects given aluminium hydroxide gel (2.5 g/day expressed as elemental aluminium (Al), equivalent to 42 mg/kg bw per day assuming body weights of 60 kg) for 28 days. In contrast, faecal excretion of aluminium in patients with chronic renal disease given aluminium hydroxide (1.5–3.5 g/day expressed as Al, equivalent to 25–57 mg/kg bw per day, assuming body weights of 60 kg) for 20–32 days indicated a daily absorption of 100–568 mg of Al. Slight increases in concentrations of aluminium in plasma were reported over the study period.

Oral dosing of rats with aluminium compounds has been shown to result in increased concentrations of aluminium in blood, bone, brain, liver and kidney. Studies with ^{26}Al administered intravenously to a small number of human volunteers indicate a biological half-life of

about 7 years (in one individual) and interindividual variation in clearance patterns.

Aluminium compounds have been reported to interfere with the absorption of essential minerals such as calcium and phosphate, although the extent to which this occurs at dietary exposure levels is unclear.

Toxicological data

The available studies were from the published literature and were not designed to assess the safety of food additives. Most were conducted to investigate specific effects or mechanisms of action, and many do not provide information on the dose–response relationship. Some do not make clear whether the stated dose relates to elemental aluminium or to the aluminium compound tested. A further complication is that many studies do not appear to have taken into account the basal aluminium content of the animal feed before addition of the test material. Some studies refer to basal aluminium content in the region of 7 mg/kg, which would not add significantly to the doses of aluminium under investigation. However, it has been reported that there are diverse concentrations ranging from 60 to 8300 mg/kg feed and that substantial brand-to-brand and lot-to-lot variation occurs. For chow containing Al at a concentration of 200 mg/kg, applying the default JECFA conversion factors indicates doses of Al equivalent to 30 mg/kg bw for mice and 20 mg/kg bw for rats.

The toxicological data are influenced by the solubility, and hence the bioavailability, of the tested aluminium compounds, and the dose–response relationship will be influenced by the Al content of the basal animal feed.

Recent studies have identified effects of aluminium compounds at doses lower than those reviewed previously by the Committee. Studies in rats, rabbits and monkeys have indicated effects on enzyme activity and other parameters associated with oxidative damage and calcium homeostasis in short-term studies with aluminium at oral doses in the region of 10–17 mg/kg bw per day. Those studies involved administration at a single dose and did not take into account the aluminium content of the diet. The functional relevance of the observations is unclear and since the total exposure is unknown, they are not suitable for the dose–response analysis.

Mild histopathological changes were identified in the kidney and liver of rats given aluminium sulfate by gavage at a dose of 17 mg/kg bw per day, expressed as Al, for 21 days. Rats given drinking-water containing aluminium chloride at a dose of 5 or 20 mg/kg bw per day,

expressed as Al, for 6 months showed non-dose-dependent decreases in body weight and changes in haematological parameters and acetylcholine-associated enzymes in the brain. Histopathological changes were observed in the kidney and brain at doses of 20 mg/kg bw per day, expressed as Al, in the latter study. Such effects had not been observed in other studies and total exposure was unknown since the aluminium content of the diet was not taken into account.

Beagle dogs given diets containing sodium aluminium phosphate (basic) for 6 months showed decreased food intake and body weight and histopathological changes in the testes, liver and kidneys in the males at the highest Al concentration tested, 1922 mg/kg of diet, equal to 75 mg/kg bw per day. No effects were seen in female dogs at this dietary concentration, equal to 80 mg/kg bw per day, expressed as Al. The NOEL in this study was a dietary concentration of 702 mg/kg, equal to 27 mg/kg bw per day, expressed as Al. This study is similar to that providing the basis for the previously established PTWI, which used sodium aluminium phosphate (acidic). The Committee noted that there was no explanation for the observed sex difference, and limitations in the reporting made interpretation of this study difficult.

Special studies have highlighted a potential for effects on reproduction, on the nervous system and on bone. Few of those studies are adequate to serve as a basis for the determination of no-effect levels, as they were designed to address specific aspects, and only a very limited range of toxicological end-points were examined.

Soluble aluminium compounds have demonstrated reproductive toxicity, with lowest-observed-effect levels (LOELs) in the region of 13–200 mg/kg bw per day, expressed as Al, for reproductive and developmental effects with aluminium nitrate. None of those studies identified NOELs. The lowest LOELs were obtained in studies in which aluminium compounds were administered by gavage; taking into account the aluminium content of the diet, the total dose may have been in the region of 20 mg/kg bw per day or more, expressed as Al.

Neurotoxicity potential has received particular attention because of a speculated association of aluminium with Alzheimer disease. Many of the studies in laboratory animals have been conducted using parenteral administration and are of uncertain relevance for dietary exposure because of the limited bioavailability of aluminium compounds likely to be present in food. In contrast to studies with other routes of administration, the available data from studies using oral administration do not demonstrate definite neuropathological effects. Some studies indicate that certain aluminium compounds, especially

the more soluble forms, have the potential to cause neurobehavioural effects at doses in the region of 50 to 200 mg/kg bw per day, expressed as Al, administered in the diet. The studies indicating the lowest LOELs took account of the basal diet content of aluminium and one of those studies also indicated a NOEL of 10 mg/kg bw per day, expressed as Al.

The previously established PTWI of 0–7.0 mg/kg bw for aluminium was based upon a study in which no treatment-related effects were seen in beagle dogs given diets containing sodium aluminium phosphate (acidic) at a dietary concentration of 3% for 189 days, equivalent to approximately 110 mg/kg bw aluminium.

The new data reviewed at the present meeting indicated that soluble forms of aluminium may cause reproductive and developmental effects at a dose lower than that used to establish the previous PTWI. Although insoluble aluminium compounds may be less bioavailable, the evidence that other dietary components, such as citrate, can increase uptake of insoluble aluminium suggests that data from studies with soluble forms of aluminium can be used as a basis for deriving the PTWI.

Observations in humans

The previous evaluation of aluminium made by the Committee at its thirty-third meeting did not include epidemiology studies. Since then a number of epidemiology studies had been conducted, with most focusing on the potential association of oral exposure to aluminium in water, food or antacids with Alzheimer disease and cognitive impairment. Some epidemiology studies of aluminium in water suggested an association of consumption of aluminium in water with Alzheimer disease, but such an association was not confirmed in others. None of the studies accounted for ingestion of aluminium in foods, a potentially important confounding factor. The studies relied on concentrations of aluminium in the residential water supply as a measure of exposure, with the one exception of a study that also assessed ingestion of bottled water.

There was minimal information from the epidemiology literature about the association between intake of aluminium in food and neurological conditions, and the current information from a pilot case–control study evaluating Alzheimer disease was considered to be preliminary. The epidemiology studies of the use of antacids did not capture dose information and did not demonstrate an association with neurological conditions. In the literature there have been a few case reports of adults, infants and a child with normal kidney

function who experienced skeletal changes attributable to frequent use of aluminium-containing antacids considered to induce phosphate depletion.

In summary, no pivotal epidemiology studies were available for the risk assessment.

Exposure to aluminium from the diet and other sources

Only consumer exposure to aluminium in the diet and via other routes or commodities were considered by the Committee; occupational exposure was not taken into account. Dietary sources of exposure include natural dietary sources, drinking-water, migration from food-contact material and food additives. When dietary exposure was expressed on a kg body weight basis, a standard body weight of 60 kg for an adult was considered by the Committee, unless otherwise specified.

Soil composition has a significant influence on the Al content of the food chain. The solubility of Al compounds may increase when acid rain decreases the pH of the soil; as a consequence, Al content increases in surface water, plants and animals. Most foods contain Al at concentrations of less than 5 mg/kg. It is estimated that quantities of about 1–10 mg/day per person generally derive from natural dietary sources of aluminium, corresponding to up to 0.16 mg/kg bw per day, expressed as Al. The concentration of dissolved Al in untreated water at near pH 7 is typically 1–50 μg/l, but this can increase to 1000 μg/l in acidic water. Exposure through this source is therefore up to 2 mg/day, corresponding to 0.03 mg/kg bw per day based on the consumption of 2 l of water per day. Al may also be present in drinking-water owing to the use of Al salts as flocculants in the treatment of surface waters. The concentration of Al in finished water is usually less than 0.2 mg/l. Based on a daily consumption of 2 l per day, dietary exposure to Al from treated drinking-water may be up to 0.4 mg/day, corresponding to 0.007 mg/kg bw per day.

Al is utilized extensively in structural materials used in food-contact materials, including kitchen utensils. Al can be released into the foodstuff in the presence of an acidic medium. Conservative assessments suggest that mean potential dietary exposure through this source may be up to 7 mg/day. Such dietary exposure corresponds to 0.1 mg/kg bw per day.

The current and draft provisions made for aluminium compounds in the Codex GSFA are reported in Table 5. Some Al-containing additives are listed only in the current versions of Table 1 and 2 of the Codex GSFA, and for those additives reference is made to the PTWI

Table 5
Aluminium compounds used as food additives present in the current and draft GSFA

Name	Function	Applications	Levels of use (expressed as Al)	INS No.	JECFA evaluation[a]
SALP, acidic & basic	Acidity regulator, emulsifier in processed cheeses,raising agent in bakery products, stabilizer, thickener	Baking powder, flours, bakery products, cheese, cocoa powders, desserts, bakery wares, confectionery, mixes for soups and sauces, concentrates for water-based flavoured drinks	Up to 35 000 mg/kg in processed cheese and 45 000 mg/kg in flours	541(i), 541(ii)	PTWI for aluminium powder (GSFA Tables 1 and 2)
Aluminium ammonium sulfate	Firming agent, raising agent, stabilizer	Bakery products (including ordinary bakery products), egg products, herbs and spices, soya-bean products, snacks, processed fish, processed vegetables, candied fruit	Up to 10 000 mg/kg in bakery products GMP in starch and soya-bean products	523	PTWI for aluminium powder (GSFA Tables 1 and 2)
Sodium aluminium silicate	Anti-caking agent	Salt and salt substitutes, sugar, grain Permitted for use in food in general	Up to 20 000 mg/kg in salt GMP in grain and food in general	554	ADI "not specified"
Calcium aluminium silicate	Anti-caking agent	Salt and salt substitutes, sugar, Grape wines, grain Permitted for use in food in general	Up to 20 000 mg/kg in salt GMP in grain, grape wine and food in general	556	ADI "not specified" (GSFA Tables 1, 2 and 3)
Aluminium silicate	Anti-caking agent	Salt and salt substitutes Grain, herbs and spices Permitted for use in food in general	Up to 10 000 mg/kg in salt GMP in grain, herbs and spices and in food in general	559	ADI "not specified" (GSFA Tables 1, 2 and 3)

ADI: acceptable daily intake; GMP: Good manufacturing practice; GSFA: General Standard for Food Additives; SALP: Sodium aluminium phosphate
[a] As reported in current and draft (*3*) GSFA

for aluminium established in 1988 by JECFA. It is the case for aluminium ammonium sulfate and sodium aluminium phosphate (SALP) — acidic and basic. Those aluminium compounds may be used according to good manufacturing practice (GMP) in a large number of products and at maximum levels in other products. The Committee noted that maximum levels are generally expressed as Al (e.g. 35 000 mg/kg expressed as Al, for sodium aluminium phosphate used in processed cheese) but that in some cases the reporting basis is not specified (up to 10 000 mg/kg in bakery products containing aluminium ammonium sulfate).

The Committee also noted that some food additives containing Al are listed in Tables 1, 2 and 3 of the current and draft Codex GSFA. In Table 3, reference is made to an ADI "not specified", and sodium aluminium silicate, calcium aluminium silicate and aluminium silicate are allowed at concentrations consistent with GMP in food in general. Specifications for other aluminium compounds are available in the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*), but no provision had yet been made for them in Codex GSFA. This is the case for aluminium lakes of colouring matters, aluminium sulfate, aluminium powder and potassium aluminium sulfate. Other aluminium compounds are used in a number of countries but are not reported in the Codex GSFA nor in the *Combined Compendium of Food Additive Specifications*. This was the case for aluminium oxide and potassium aluminium silicate.

The Committee was provided with an exposure assessment based on annual sales of SALP in Europe suggesting that the average exposure in the general population is about 0.1 mg/kg bw per day, corresponding to less than 0.01 mg/kg bw per day expressed as Al, based on the fact that tetrahydrate SALP acidic has an Al content of 8.5%. The Committee was also provided with disappearance data from the USA for a number of aluminium compounds used as food additives. Overall, aluminium present in SALP, basic and acidic; aluminium sodium sulfate; sodium aluminium silicate and aluminium lakes intended for human consumption sold in the USA in 2003 and 2004 would provide 9 mg of Al per capita per year, corresponding to 0.0004 mg/kg bw per day. Other data provided to the Committee suggest that there is a large range of exposure among consumers. A survey conducted in 1979 suggests that 5% of adults in the USA were exposed to more than 1.5 mg/kg bw per day, expressed as Al, from food additives.

Additional data were available to estimate exposure in the population of interest i.e. regular consumers of products containing food additives containing aluminium. In the USA, although aluminium-

containing additives were found to be present in only a limited number of foods, some processed foods have a very high Al content: processed cheese, 300 mg/kg; home-made corn bread, 400 mg/kg (owing to the use of Al-containing leavening agents); muffins, 130 mg/kg; baking powder, 2300 mg/kg; and table salt, 164 mg/kg. In Germany, the processed foods found to have the highest Al content were biscuits (22 mg/kg) and soft cheese (8–16 mg/kg). In the 2000 UK Total Diet Study, the miscellaneous cereals group was reported to have the highest mean concentration of Al (19 mg/kg). In the 1992–1993 Chinese Total Diet Study, cereal products were also found to have the highest Al content (50 mg/kg) owing to the use of leavening agents containing Al. The potentially high Al content of cereal products and, in particular, of ordinary baked goods may be of special importance in a number of countries where they constitute staple food and may therefore be consumed regularly in large quantities by a significant proportion of the population.

Total dietary exposure to Al from all sources has been estimated through duplicate diet studies performed in adults in a number of countries. Mean values varied between 3 and 13 mg/day. The highest single reported value was 100 mg/day. In a multicentre study, exposure at the 75th percentile ranged from 3 to 26 mg/day, according to country. Data reported in Germany suggest that the amount of Al in the diet decreased by about half between 1988 and 1996.

A number of market-basket studies have also been performed, allowing estimation of exposure in different population groups based on mean content of Al in food groups, and on mean consumption. Exposure for consumers with a high consumption of cereal products or in regular consumers of products that contain higher-than-mean concentrations of Al will therefore be higher than estimated in those studies. In the adult population, mean exposure to Al estimated by model diet or market basket varied from 2 mg/day in the most recent French survey to more than 40 mg/day in China.

The highest mean exposure to Al per kg bw was found in young children: 0.16 mg/kg bw per day in the 1.5–4.5 years age group in the UK, based on measured body weight; approximately 0.5 mg /kg bw per day in the USA in children aged 2 years, considering a standard body weight of 12 kg; approximately 1 mg/kg bw per day in China in age groups 2–7 years and 8–12 years, considering as standard body weight 16.5 kg and 29.4 kg, respectively.

Values for high levels of exposure, estimated on the basis of high levels of consumption, were available for UK children aged 1.5–4.5 years (0.33 mg/kg bw per day).

The issue of bioavailability was considered by the Committee, but available data were not sufficient to correct the exposure assessment on the basis of bioavailability. Aluminium contained in some food additives such as silicates may have a low bioavailability, but the main sources of exposure are sulfates and phosphates used in cereal products. A diet high in fruit and fruit-based products could lead to higher bioavailability owing to the increased absorption of aluminium in the presence of citric acid. Citric acid is one of the main organic acids present in fruit and may also be added to fruit-based products and to cheese.

The Al content of milk and formulae was considered when estimating exposure for infants. The Al content of human and cows' milk was found to be negligible (less than 0.05 mg/l), while cows' milk-based and soya-based formulae were found to contain high levels of Al, leading to concentrations of 0.01–0.4 and 0.4–6 mg/l, respectively, in the ready-to-drink product. The Committee estimated dietary exposure to aluminium based on the highest of those values in an infant aged 3 months weighing an average of 6 kg, considering as 1 l of reconstituted formula per day as consumption at the 95th percentile. Expressed on a kg body weight basis, dietary exposure to Al was estimated to be up to 1 mg/kg bw per day and 0.06 mg/kg bw per day in infants fed soya-based formulae and milk-based formulae respectively. In the case of infants fed human or cows' milk, high consumption would lead to Al exposures of less than 0.01 mg/kg bw per day.

Sources of exposure to Al other than in the diet that were considered by the Committee were air, cosmetic and toiletry products and medicines. Al from air, in industrial areas, contributes up to 0.04 mg/day and therefore constitutes a minor source of exposure. Estimates of dermal absorption of aluminium chlorohydrate used as an active ingredient of antiperspirant suggest that only about 4 μg of Al is absorbed from a single use on both underarms. Some medical applications of aluminium may lead to long-term exposure: aluminium hydroxides in antacids, phosphate-binders and buffered analgesics. If taken as directed, the daily intake of Al from antacids could be as much as 5 g, while Al-buffered aspirin used for rheumatoid arthritis could contribute 0.7 g of aluminium per day.

In conclusion, the present assessment confirms previous evaluations made by the Committee in which dietary exposure, particularly through foods containing aluminium compounds used as food additives, was found to represent the major route of aluminium exposure for the general population, excluding persons who regularly ingest aluminium-containing drugs.

Evaluation

The Committee concluded that aluminium compounds have the potential to affect the reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI and therefore the PTWI should be revised. However, the available studies have many limitations and are not adequate for defining the dose–response relationships. The Committee therefore based its evaluation on the combined evidence from several studies. The relevance of studies involving administration of aluminium compounds by gavage was unclear because the toxicokinetics after gavage were expected to differ from toxicokinetics after dietary administration, and the gavage studies generally did not report total aluminium exposure including basal levels in the feed. The studies conducted with dietary administration of aluminium compounds were considered most appropriate for the evaluation. The lowest LOELs for aluminium in a range of different dietary studies in mice, rats and dogs were in the region of 50–75 mg/kg bw per day expressed as Al.

The Committee applied an uncertainty factor of 100 to the lower end of this range of LOELs (50 mg/kg bw per day, expressed as Al) to allow for inter- and intraspecies differences. There are deficiencies in the database, notably the absence of NOELs in the majority of the studies evaluated and the absence of long-term studies on the relevant toxicological end-points. The deficiencies are counterbalanced by the probable lower bioavailability of the less soluble aluminium species present in food. Overall, an additional uncertainty factor of three was considered to be appropriate. The Committee confirmed that the resulting health-based guidance value should be expressed as a PTWI, because of the potential for bioaccumulation. The Committee established a PTWI for Al of 1 mg/kg bw, which applies to all aluminium compounds in food, including additives. The previously established ADIs and PTWI for aluminium compounds were withdrawn.

The potential range of exposure from dietary sources is summarized in Table 6.

The Committee noted that the PTWI is likely to be exceeded to a large extent by some population groups, particularly children, who regularly consume foods that include aluminium-containing additives. The Committee also noted that dietary exposure to aluminium is expected to be very high for infants fed on soya-based formula.

Further data on the bioavailability of different aluminium-containing food additives are required.

Table 6
Estimated ranges of mean exposure of the adult population to aluminium from different dietary sources

Mean exposure	Natural dietary sources	Water (assuming a consumption of 2 l/day)	Food-contact materials	Overall diet, including additives
Expressed as Al in mg/week	7–70	<0.7 (typical untreated water) 1.4–2.8 (water treated with aluminium salts) 14 (acidic untreated water)	0–49[a]	14–280
Expressed as percentage of PTWI (assuming a body weight of 60 kg)	2–120	1–20	<80[a]	20–500

[a] Theoretical exposure using conservative assumptions

There is a need for an appropriate study of developmental toxicity and a multigeneration study incorporating neurobehavioural endpoints, to be conducted on a relevant aluminium compound(s).

Studies to identify the forms of aluminium present in soya formulae, and their bioavailability, are needed before an evaluation of the potential risk for infants fed on soya formulae can be considered.

An addendum to the toxicological monograph was prepared.

The ten existing specifications monographs for food additives containing aluminium were not reviewed at this meeting. They were (INS numbers): Aluminium ammonium sulfate (523), Aluminium lakes of colouring matters, Aluminium potassium sulfate (522), Aluminium powder (173), Aluminium silicate (559), Aluminium sulfate (anhydrous) (520), Calcium aluminium silicate (556), Sodium aluminium phosphate, acidic (541(i)), Sodium aluminium phosphate, basic (541(ii)) and Sodium aluminosilicate (554).

Recommendations to Codex

The Committee recommended that provisions for aluminium-containing additives included in the Codex GSFA should be compatible with the newly established PTWI for aluminium compounds of 1 mg/kg bw expressed as Al. The Committee noted in particular that provisions for such additives used at levels consistent with GMP in staple foods may lead to high exposure in the general population and in particular in children.

4.2 Choropropanols

4.2.1 *3-Chloro-1,2-propanediol*

Explanation

3-Chloro-1,2-propanediol is formed when chloride ions react with lipid components in foods under a variety of conditions, including food processing, cooking, and storage. The compound has been found as a contaminant in various foods and food ingredients, most notably in acid-hydrolysed vegetable protein (acid-HVP) and soy sauces.[1] 3-Chloro-1,2-propanediol was first evaluated by the Committee at its forty-first meeting (Annex 1, reference *107*). The Committee concluded that it is an undesirable contaminant in food and expressed the opinion that its concentration in acid-HVP should be reduced as far as technically achievable.

3-Chloro-1,2-propanediol was re-evaluated by the Committee at its fifty-seventh meeting (Annex 1, reference *154*). Short- and long-term studies in rodents showed that 3-chloro-1,2-propanediol is nephrotoxic in both sexes and also affects the male reproductive tract and male fertility. At that meeting, the Committee considered that the kidney was the main target organ and tubule hyperplasia in the kidney the most sensitive end-point for deriving a tolerable intake. This effect was seen in a long-term study of toxicity and carcinogenicity in male and female Fischer 344 rats given drinking-water containing 3-chloro-1,2-propanediol. The Committee concluded that 1.1 mg/kg bw per day, the lowest dose, was a LOEL and that this was close to a NOEL. The Committee established a provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg bw for 3-chloro-1,2-propanediol on the basis of this LOEL, using a safety factor of 500. This factor was considered adequate to allow for the absence of a clear NOEL and to account for the effects on male fertility and for inadequacies in the studies of reproductive toxicity. Data available to the Committee at that time indicated that the estimated mean intake of 3-chloro-1,2-propanediol for consumers of soy sauce would be at or above this PMTDI.

The present re-evaluation was conducted in response to a request from CCFAC at its Thirty-seventh Session (*4*) for JECFA to review and summarize all new data on the toxicology and occurrence of 3-chloro-1,2-propanediol. In particular, the Committee was requested to carry out an exposure assessment for 3-chloro-1,2-propanediol

[1] The term "soy sauce" is used to encompass liquid seasonings made from soya beans by a range of methods including acid-hydrolysis and traditional fermentation, possibly with the addition of acid-HVP. In some countries, the term "soy sauce" is reserved solely for fermented products.

based on the contributions from all food groups in the diet (not only soy sauce), with particular consideration to groups that might have higher levels of exposure.

Toxicological data

At its present meeting, the Committee evaluated two new short-term studies on the reproductive effects of 3-chloro-1,2-propanediol in rats.

In the first study, effects on fertility and sperm parameters were examined in male rats given 3-chloro-1,2-propanediol by oral gavage at doses ranging from 0.01 to 5 mg/kg bw per day for 28 days. The NOEL for effects on fertility was 1 mg/kg bw per day, in accordance with the results of earlier studies. With respect to the findings on sperm count, the nature of the dose–response relationship was unusual and was not in conformity, quantitatively, with results from earlier studies. The Committee considered that the data on sperm motility did not show any effect of treatment; the proportion of motile sperm in all treated groups was within 10% of the control value. On the basis of these considerations, the Committee concluded that this study should not be used as the pivotal study for risk assessment.

In the second new study it was shown that administration of 3-chloro-1,2-propanediol at doses of up to 25 mg/kg bw per day by gavage to pregnant rats on days 11 to 18 of gestation did not affect testicular organogenesis in the fetuses.

In a new study of neurotoxicity, rats given repeated oral doses of 3-chloro-1,2-propanediol at doses of up to 30 mg/kg bw per day for 11 weeks did not show neuromotor deficits. Previous studies in rats and mice had indicated that high daily doses (mice, 25–100 mg/kg bw; rats, 50–100 mg/kg bw) given intraperitoneally were associated with dose-related lesions of the central nervous system.

Occurrence

Acid-HVPs are widely used in seasonings and as ingredients in processed savoury food products. They are used to flavour a variety of foods, including many processed and prepared foods, such as sauces, soups, snacks, gravy mixes, bouillon cubes. As a result of those uses, 3-chloro-1,2-propanediol had been identified in many foods and food ingredients, most notably in acid-HVP and soy sauces.

Recent studies have demonstrated that 3-chloro-1,2-propanediol may also be formed in other processed foods, particularly in meat products (salami and beef burgers), dairy products (processed cheese and

cheese alternatives), a range of cereal products subjected to heat treatments such as baking, roasting or toasting (toasted biscuits, doughnuts, malt and malt extract), and some other foods.

Data on the occurrence of 3-chloro-1,2-propanediol in food were provided by 14 countries and by the International Hydrolysed Protein Council. Data on 3-chloro-1,2-propanediol in soy sauces and related products for an additional country were available from the published literature.

The average concentration of 3-chloro-1,2-propanediol present in soy sauce and soy sauce-related products was much higher (8 mg/kg, with a range of 0.01 to 44.1 mg/kg) than that present in any other food or food ingredient (less than 0.3 mg/kg). Data from Japan showed that soy sauce produced by traditional fermentation contains insignificant average amounts of 3-chloro-1,2-propanediol (0.003 mg/kg) compared with soy sauce made with acid-HVP (1.8 mg/kg).

Fatty acid esters of monochloropropanols have recently been identified in a range of processed and unprocessed foods. To date, only a limited number of analyses have been reported, but the amount of esterified 3-chloro-1,2-propanediol in many of the samples is higher than the amount of free (non-esterified) monochloropropanol in the same samples. The significance of the presence of esterified 3-chloro-1,2-propanediol in food has yet to be determined.

Dietary exposure assessment

National dietary intake data for 3-chloro-1,2-propanediol were provided for 10 countries (Denmark, Finland, France, Germany, Ireland, the Netherlands, Norway, Sweden, UK, Thailand). The national intakes were calculated by linking data on individual consumption and body weight from national food consumption surveys with mean occurrence data obtained from food contamination surveys. The estimated average intakes from a wide range of foods, including soy sauce and soy sauce-related products, ranged from 0.02 to 0.7 μg/kg bw per day in the general population. For consumers at a high percentile (95th), including young children, the estimated intakes ranged from 0.06 to 2.3 μg/kg bw per day.

Combining the average contamination levels for soy sauce produced by traditional fermentation or with acid-HVP (from the Japanese submission) with a daily consumption figure of soy sauce of 30 g (per-capita consumption for Japan and 95th percentile of consumption from Australia) resulted in values for dietary exposures of 0.0015 and 0.90 μg/kg bw per day, respectively, assuming a body weight of 60 kg.

Evaluation

As no new pivotal toxicological studies had become available, the Committee retained the previously established PMTDI of 2 μg/kg bw for 3-chloro-1,2-propanediol.

The Committee concluded that, based on national estimates from a wide range of foods, including soy sauce and soy-sauce related products, an intake of 3-chloro-1,2-propanediol of 0.7 μg/kg bw per day could be taken to represent the average for the general population, and that an intake of 2.3 μg/kg bw per day could be taken to represent high consumers. In the intake estimates for average to high intake, young children are also included.

When the estimated exposures are expressed as a percentage of the current PMTDI, the results at the national level ranged from 1% to 35% for average exposure in the general population. For consumers at the high percentile (95th), the estimated intakes ranged from 3% to 85% and up to 115% in young children. The estimates are based on concentrations of 3-chloro-1,2-propanediol derived before any remedial action had been taken by government or industry.

Because the distribution of 3-chloro-1,2-propanediol concentrations in soy sauce contains a number of highly contaminated samples, regular consumption of a certain brand or specific type of product could result in intakes greater than the PMTDI by such consumers. The Committee noted that reduction in the concentration of 3-chloro-1,2-propanediol in soy sauce made with acid-HVP could substantially reduce the intake of this contaminant by certain consumers of this condiment.

Recommendation

The Committee noted that it has been reported that fatty acid esters of 3-chloro-1,2-propanediol are present in foods, but there were insufficient data to enable either their intake or toxicological significance to be evaluated. The Committee recommended that studies be undertaken to address this question.

An addendum to the toxicological monograph was prepared.

4.2.2 *1,3-Dichloro-2-propanol*

Explanation

1,3-Dichloro-2-propanol is formed when chloride ions react with lipid components in foods under a variety of conditions, including food processing, cooking, and storage. The compound has been found as a contaminant in various foods and food ingredients, most notably in acid-hydrolysed vegetable protein (acid-HVP) and soy sauces.[5] This

compound was first evaluated by the Committee at its forty-first meeting (Annex 1, reference *107*), when it concluded that it is an undesirable contaminant in food and expressed the opinion that its concentration in acid-HVP should be reduced as far as technically achievable.

1,3-Dichloro-2-propanol was re-evaluated by the Committee at its fifty-seventh meeting (Annex 1, reference *154*). Although only a few studies of kinetics and metabolism and few short- and long-term studies of toxicity and of reproductive toxicity were available for evaluation, they clearly indicated that 1,3-dichloro-2-propanol was hepatotoxic and nephrotoxic, induced a variety of tumours in various organs in rats, and was genotoxic in vitro. The Committee therefore concluded that it would be inappropriate to estimate a tolerable intake of 1,3-dichloro-2-propanol. The Committee noted that the dose that caused tumours in rats (19 mg/kg bw per day) was about 20 000 times greater than the highest estimated intake of 1,3-dichloro-2-propanol by consumers of soy sauce (1 μg/kg bw per day), and that the available evidence suggested that in soy sauces 1,3-dichloro-2-propanol was associated with high concentrations of 3-chloro-1,2-propanediol, concentrations of the latter being approximately 50 times higher than those of 1,3-dichloro-2-propanol. Therefore, in the opinion of the Committee, regulatory control of the latter would obviate the need for specific controls on 1,3-dichloro-2-propanol.

The present re-evaluation was conducted in response to a request from CCFAC at its Thirty-seventh Session (*4*) that JECFA review and summarize all new data on the toxicology (including new studies of genotoxicity in vivo) and occurrence of 1,3-dichloro-2-propanol. In particular, the Committee was asked to carry out an exposure assessment to readdress 1,3-dichloro-2-propanol as a separate issue from 3-chloro-1,2-propanediol.

Toxicological data

At its present meeting, the Committee reviewed two new studies of genotoxicity, a test for micronucleus formation in rat bone marrow in vivo and an assay for unscheduled DNA synthesis in rat hepatocytes in vivo/in vitro, which met appropriate standards for study protocol and conduct. In those assays, 1,3-dichloro-2-propanol yielded negative results in the tissues assessed. However, toxicity was not demonstrated in the tissues and hence the level of exposure is unclear. No other new data were available.

In the light of the limitations of the negative results for genotoxicity in vivo, the Committee reconsidered the results from the long-term

study of carcinogenicity previously evaluated at its fifty-seventh meeting (Annex 1, reference *154*). In that study, rats were given drinking-water containing 1,3-dichloro-2-propanol at a dose of 0, 2.1, 6.3, or 19 mg/kg bw per day in males and 0, 3.4, 9.6, or 30 mg/kg bw per day in females for 104 weeks. Increased incidences of tumours were demonstrated in both sexes at the two higher doses tested. No increase in tumour incidence was seen at the lowest doses tested, 2.1 and 3.4 mg/kg bw per day for male and female rats, respectively. Treatment-related increases in tumour incidence (adenomas and carcinomas) occurred in liver, kidney (males only), the tongue, and thyroid gland. Certain of the tumours (i.e. liver and kidney) might have arisen by non-genotoxic processes, but no clear mode of action was established. Moreover no mode of action was evident for the increased incidence of tongue papillomas and carcinomas in both sexes of rats at the highest dose. In spite of the negative results for genotoxicity in vivo in the tissues assessed (i.e. bone marrow and liver), the Committee could not exclude a genotoxic basis for the neoplastic findings, because of the absence of persuasive negative genotoxicity data in the target organs for carcinogenicity, and the findings that 1,3-dichloro-2-propanol caused point mutations in bacteria and mammalian cells in culture and caused multi-organ carcinogenicity in both sexes. The Committee therefore confirmed that 1,3-dichloro-2-propanol should be regarded as a genotoxic and carcinogenic compound and performed dose–response modelling of the carcinogenicity data from the long-term study in rats to calculate the margin of exposure, according to the recommendations of the Committee at its sixty-first meeting (Annex 1, reference *166*).

The Committee calculated benchmark doses for 10% extra risk of tumours (BMD_{10}) and 95% lower confidence limit for the benchmark dose ($BMDL_{10}$) values for the incidences of treatment-related tumours at each site for each sex. Extra risk is defined as the additional incidence divided by the tumour-free fraction of the population in the controls. Also, because of the presumed common genotoxic mode of action, the incidences of animals with treatment-related tumours were modelled for each sex. Consistent results were obtained from use of several models for all datasets modelled. The $BMDL_{10}$ values for the individual treatment-related tumours ranged from 7.2 to 19.1 mg/kg bw per day and for the incidence data for tumour bearing animals from 3.3 to 7.7 mg/kg bw per day, as shown in Table 7.

Occurrence

Data on 1,3-dichloro-2-propanol analysed in food were obtained from several countries. 1,3-Dichloro-2-propanol was only found at quanti-

Table 7
BMD10[a] and BMDL10[b] values obtained from fitting models to incidence data for all treatment-related tumours and for individual tumour locations in male and female rats treated with drinking water containing 1,3-dichloro-2-propanol for 104 weeks

Treatment-affected sites and tumour types	Range of BMD_{10} values (mg/kg bw per day)	Range of $BMDL_{10}$ values (mg/kg bw per day)
Males		
Tumour-bearing animals/all treatment-associated sites	5.4–7.5	3.3–6.1
Renal adenoma and carcinoma	11.1–12.2	7.2–7.7
Hepatocellular adenoma and carcinoma	14.4–16.0	10.3–12.3
Tongue papilloma and carcinoma	12.4–17.9	8.7–11.6
Females		
Tumour-bearing animals/all treatment-associated sites	8.5–10.3	6.6–7.7
Hepatocellular adenoma and carcinoma	11.2–14.6	9.1–10.1
Tongue papilloma and carcinoma	17.1–22.8	11.5–19.1

[a] BMD_{10}: benchmark dose for 10% extra risk of tumours.
[b] $BMDL_{10}$: 95% lower confidence limit for the benchmark dose. Extra risk is defined as the additional in1 cidence divided by the tumour-free fraction of the population in the controls.

fiable levels in samples of soy sauce, in samples of ingredients such as acid-HVPs and malt products, in samples of minced beef (dry-fried, raw or cooked), pork ham, sausage meat (raw or cooked) and in samples of fish fillet (battered and fried).

Average levels in samples of soy sauce-based products ranged from 0.09 mg/kg for soy oyster sauce to 0.6 mg/kg for soy mushroom sauce. Average levels were 0.024 mg/kg in samples of fish product, 0.034 mg/kg in samples of meat products and 0.022 mg/kg in samples of malt products.

1,3-Dichloro-2-propanol was detected only in samples that also contained 3-chloro-1,2-propanediol, except in samples of meat and meat products where 1,3-dichloro-2-propanol was detected in the presence (18 samples) and in the absence (32 samples) of detected levels of 3-chloro-1,2-propanediol. In meat products, the concentrations of 1,3-dichloro-2-propanol are generally higher than those of 3-chloro-1,2-propanediol.

The Committee noted that 1,3-dichloro-2-propanol is found in samples of soy sauce and soy sauce-based products when the concentrations of 3-chloro-1,2-propanediol exceed 0.4 mg/kg. Based on limited data, there appears to be a linear relationship between

the concentrations of 1,3-dichloro-2-propanol and 3-chloro-1,2-propanediol, but there was considerable scatter in the data at low concentrations and there was some variation between different types of products. Additional occurrence data would be needed to confirm the relationships, before they could be used to predict the concentrations of 1,3-dichloro-2-propanol based on the concentrations of 3-chloro-1,2-propanediol.

Dietary exposure assessment

National estimates of dietary intake of 1,3-dichloropropanol was provided by Australia, and estimates for EU member states were assessed by the Committee based on available occurrence data provided both by EU member states and Australia. Intakes were calculated by linking individual consumption data with mean occurrence data, using the actual body weight of the consumer as reported in consumption surveys.

Intake estimates from various food sources including soy sauce and soy-sauce products at the national level ranged from 0.008 to 0.051 μg/kg bw per day for the average in the general population. For consumers at a high percentile (95th), including young children, intake estimates ranged from 0.025 to 0.136 μg/kg bw per day.

Meat products were the main contributor in all national estimates, ranging from 45% to 99% depending on the country diet. Soy sauce and soy sauce-based products contributed up to 30% in all national estimates. Other food groups contributed up to 10% of the total intake.

The Committee concluded that based on national estimates, an intake of 0.051 μg/kg bw per day of 1,3-dichloro-2-propanol could be taken to represent the average for the general population and that an intake of 1,3-dichloro-2-propanol of 0.136 μg/kg bw per day could be taken to represent high consumers. In the intake estimates for average to high intake, young children are also included.

Evaluation

The available evidence suggests that 1,3-dichloro-2-propanol occurs at lower levels than 3-chloro-1,2-propanediol in soy sauce and related products, and also in food ingredients containing acid-HVP. However, in meat products the concentrations of 1,3-dichloro-2-propanol are generally higher than those of 3-chloro-1,2-propanediol.

The Committee concluded that the critical effect of 1,3-dichloro-2-propanol is carcinogenicity. The substance yielded negative results in

two new studies of genotoxicity, a test for micronucleus formation in bone marrow in vivo and an assay for unscheduled DNA synthesis in vivo/in vitro in rat hepatocytes, but limitations in those studies and positive findings in tests for genotoxicity in vitro as well as lack of knowledge on the modes of action operative at the various tumour locations led the Committee to the conclusion that a genotoxic mode of action could not be excluded. Accordingly, the cancer dose–response data were analysed by dose–response modelling, and the Committee used eight different models to calculate BMD_{10} and $BMDL_{10}$ values. $BMDL_{10}$ values for the individual tumours ranged from 7.2 to 19.1 mg/kg bw per day and for incidence data on tumour-bearing animals for all treatment-affected locations from 3.3 to 7.7 mg/kg bw per day.

The Committee concluded that a representative mean intake for the general population of 1,3-dichloro-2-propanol of 0.051 μg/kg bw per day and an estimated high-level intake (young children included) of 0.136 μg/kg bw per day could be used in the evaluation. Comparison of the mean and high-levels intakes with the lowest $BMDL_{10}$ of 3.3 mg/kg bw per day, which was the $BMDL_{10}$ for incidence data on tumour-bearing animals for all treatment-affected locations, indicates margins of exposure of approximately 65 000 and 24 000, respectively. Based on those margins of exposure, the Committee concluded that the estimated intakes of 1,3-dichloro-2-propanol were of low concern for human health.

4.3 Methylmercury

Explanation

Methylmercury was evaluated by the Committee at its sixteenth, twenty-second, thirty-third, fifty-third and sixty-first meetings (Annex 1, references *30*, *47*, *83*, *143* and *166*). At its sixty-first meeting, the Committee established a new PTWI of 1.6 μg/kg bw, after considering information that had become available since its fifty-third meeting. This information included the results of studies performed in laboratory animals and humans, and epidemiological studies of the possible effects of prenatal exposure to methylmercury on child neurodevelopment. Neurodevelopment was considered to be the most sensitive health outcome and development in utero the most sensitive period of exposure. Calculation of the PTWI was based on an average BMDL/NOEL of 14 mg/kg (14 μg/g) for concentrations of mercury in maternal hair in the studies of neurodevelopmental effects in cohorts of children from the Faroe Islands and the Seychelles. The concentration of mercury in maternal hair was calculated to be equivalent to a maternal blood methylmercury concentration of

0.056 mg/l (56 μg/l), which was calculated to arise from a daily intake of methylmercury of 1.5 μg/kg bw. The PTWI was derived by dividing this intake by a total uncertainty factor of 6.4 to give a value of 1.6 μg/kg bw. The PTWI established in 2003 was considered to be sufficient to protect the developing embryo and fetus, the most sensitive subgroup of the population. The new value of 1.6 μg/kg bw was a revision of the previous PTWI of 3.3 μg/kg bw, and the latter value should be considered as withdrawn.

After the establishment of this new PTWI, based on maternal–fetal exposure, CCFAC at its Thirty-seventh Session in 2005 (*4*) considered a discussion paper on guideline levels for methylmercury in fish. CCFAC noted that JECFA usually sets a single health-based guidance value for the whole population, which is protective for the most sensitive part of the population; however, in the case of guidance values based on developmental end-points, this may be overly conservative for some parts of the population. CCFAC further commented that in specific cases JECFA might consider setting separate values for subgroups of the population. This request to clarify the PTWI for methylmercury in this context was considered by JECFA at its present meeting, taking into account relevant earlier and recent studies. The following issues were addressed:

— Clarification of the relevance of the PTWI of 1.6 μg/kg bw for different subgroups of the population;
— Assessment of the scientific evidence on the relevance of direct exposure to methylmercury to neurodevelopment in infants and young children;
— The impact of current guideline levels for methylmercury in fish on exposure and risk.

Toxicological data

(a) Vulnerability of the embryo and fetus

The Committee noted that the new toxicokinetic, toxicological and epidemiological studies available since the last evaluation in 2003 further confirmed the embryo and fetus as the most vulnerable life-stage with respect to the adverse effects of methylmercury. The new data do not suggest the need for revision of the previously established PTWI of 1.6 μg/kg bw, with respect to maternal intakes and this life-stage.

(b) Vulnerability of the infant and child

In reviewing the available studies relevant to risk assessment for infants and young children exposed after birth via human milk and via

the diet in general, the Committee noted that few studies have attempted to separate the potential effects of postnatal exposure to methylmercury from the known neurodevelopmental effects of prenatal exposure.

There is clear evidence from the concentrations of mercury in human milk and in the blood of infants that, compared with exposure in utero, postnatal exposure to methylmercury is considerably lower in infants who are breastfed and, similarly, postnatal exposure is lower in those that are formula-fed. The Faroe Islands study reported earlier developmental milestones in breastfed compared with formula-fed infants and lack of any independent association between breastfeeding and neurological deficits at age 7 years. The study authors suggested that breastfeeding is beneficial even in a population with a relatively high prenatal exposure to methylmercury because of maternal consumption of fish and whale. This suggestion is compatible with other extensive data showing that breastfeeding per se offers benefits for cognitive development.

It is clear from the earlier major poisoning incidents in Japan and Iraq that methylmercury did cause neurotoxicity when exposure of children was limited to the postnatal period. However, the incidents do not give much insight into the question of whether children may be more vulnerable than adults to exposure at low levels, since in most cases there was prenatal as well as postnatal exposure to methylmercury and the exposures were very high. Similarly, while monkeys exposed to methylmercury from birth to early adulthood (age 7 years), but not exposed in utero, showed deficits in fine motor control (clumsiness) beginning in middle age and restrictions in visual fields during old age, the exposure levels in those studies, at 50 μg/kg bw per day, were high relative to dietary exposures in humans. Data from the Faroe Islands have suggested a subtle but measurable effect of postnatal exposure on latency in a single interpeak interval in brainstem auditory evoked potentials measured at age 14 years. The health significance of this observation, if any, remains unclear.

Knowledge of human brain development raises the theoretical possibility of continuing vulnerability to neurodevelopmental effects from postnatal exposure to methylmercury, but there is no clear evidence on this. For example, the influence of exposure to methylmercury on synaptogenesis, which continues well into adolescence in humans, is not known. However, in rats given methylmercury as a single, high, oral dose at 8 mg/kg bw administered by gavage during the late fetal period, synaptogenesis had been shown to be affected. Similarly, both neuronal myelination and remodelling of the cortex of the brain occur

postnatally in humans and have a protracted time course, continuing through adolescence until about age 17 years, but again there was no evidence as to whether exposures to methylmercury at low levels might affect these potentially vulnerable processes.

In summary, there are insufficient data from the studies previously reviewed by the Committee and the more recent studies reviewed at the present meeting to draw conclusions regarding the vulnerability of infants and children to methylmercury. It is clear that they are not more vulnerable than the embryo and fetus, but the information available to date does not enable any firm conclusions to be drawn on whether infants and children, including adolescents, are more, or less, vulnerable than adults.

(b) Vulnerability of adults

For adults, the previously established PTWI of 3.3 μg/kg bw, which was revised in 2003, was regarded by the Committee in 1988 at its thirty-third meeting (Annex 1, reference *83*) as adequate to take account of neurotoxicity, excluding developmental neurotoxicity; the Committee at its present meeting considered that this remained the case. Concerning other health aspects, the Committee gave further consideration to previous and more recent studies on methylmercury exposure and cardiovascular findings and concluded that the weight of evidence at the current time did not indicate an increased risk of adverse cardiovascular events. The Committee also noted that fish consumption in general is associated with cardiovascular benefits.

Impact of current guideline levels for methylmercury in fish on exposure and risk

The Committee evaluated the impact of current Codex guideline levels for methylmercury in fish (predatory fish, 1.0 mg/kg; non-predatory fish, 0.5 mg/kg) on exposure and risk. Submissions were received from France, Japan, and the UK, and additional information on the distribution of mercury and methylmercury in various fish species was obtained from the USA. Additionally, two recent publications concerning risk management options for the control of exposure to methylmercury were considered by the Committee.

Previous Committees have noted that excluding foodstuffs containing a contaminant at a concentration that is at the high end of a lognormal distribution of concentrations is not an effective method for reducing overall exposure to that contaminant in the general population. Large proportions of foodstuffs must be excluded from the market before the average exposure to the contaminant is significantly reduced. The

data from France, Japan, the UK and the USA reviewed at this meeting support this conclusion for methylmercury in fish. In each of those countries, the total market — and hence the total distribution of methylmercury in seafood — is dominated by species that do not contain a high concentration of mercury. If it were the case that seafood consumers randomly chose from the total market over their lifetime, their mean level of exposure to methylmercury in seafood would not be substantially reduced by excluding fish containing methylmercury at concentrations greater than the guideline levels of 1.0 mg/kg for predatory fish and 0.5 mg/kg for non-predatory fish, and the numbers of individuals exposed to methylmercury at intakes greater than the PTWI would not be lowered significantly.

For individual consumers whose preferred choice of fish comprises species that are known to accumulate methylmercury at higher concentrations, exclusion from their diets of all fish found to exceed the guideline levels may significantly limit their total exposure to methylmercury. The information submitted by France, the UK and the USA showed that excluding fish samples found to contain methylmercury at concentrations greater than the current Codex guideline levels would reduce the mean concentration of methylmercury in those species by 30–100% in fish available on the market. This would, however, be at the cost of removing the majority of samples of those species from the market. The French analysis suggests that the impact of those exclusions on an individual's intake of methylmercury may not be great, as the percentage of women exceeding the PTWI for methylmercury would only be reduced significantly if all fish containing methylmercury at concentrations greater than 0.5 mg/kg (one half of the guideline level for predatory species) were removed from their diets, while the percentage of children aged 3–10 years with exposures greater than the PTWI would still not be significantly reduced.

In other populations (e.g. Japan, where the mean consumption of seafood in the population is higher than that in France, the UK or the USA), exclusion from the population diet of all fish exceeding the Codex guideline levels may have a greater impact on the percentage of individuals with exposures greater than the PTWI. It was not possible from the data submitted by Japan to determine the percentage of samples in the Japanese market that exceeded the current Codex guideline levels for each marine species, and therefore, not possible to estimate the extent or significance of any reduction in exposure to methylmercury resulting from the removal of such fish from the market. The species containing the highest concentrations of methylmercury are not consumed by large percentages of the

Japanese population, suggesting that guideline levels would not be very effective in reducing the overall number of vulnerable individuals in the population who would have exposures greater than the PTWI.

Evaluation

At its present meeting, the Committee made it clear that the previous PTWI of 3.3 μg/kg bw had, in fact, been withdrawn in 2003. The Committee confirmed the existing PTWI of 1.6 μg/kg bw, set in 2003, based on the most sensitive toxicological end-point (developmental neurotoxicity) in the most susceptible species (humans). However, the Committee noted that life-stages other than the embryo and fetus might be less sensitive to the adverse effects of methylmercury.

In the case of adults, the Committee considered that intakes of up to about two times higher than the existing PTWI of 1.6 μg/kg bw would not pose any risk of neurotoxicity in adults, although in the case of women of childbearing age, it should be borne in mind that intake should not exceed the PTWI, in order to protect the embryo and fetus.

Concerning infants and children aged up to about 17 years, the data did not allow firm conclusions to be drawn regarding their sensitivity compared with that of adults. While it was clear that they are not more sensitive than the embryo or fetus, they might be more sensitive than adults because significant development of the brain continues in infancy and childhood. Therefore, the Committee could not identify a level of intake higher than the existing PTWI that would not pose a risk of developmental neurotoxicity for infants and children.

The Committee had previously noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets. The present Committee recommended that the known benefits of fish consumption need to be taken into consideration in any advice aimed at different subpopulations. Risk managers might wish to consider whether specific advice should be given concerning children and adults, after weighing the potential risks and benefits. The Committee was unable to offer any further advice in this regard since it is not within its remit to examine the beneficial aspects of fish consumption. The Committee also noted that the relative benefits of fish consumption will vary from situation to situation, depending on, for instance, the species of fish consumed and the relative nutritional importance of fish in the diet.

The Committee concluded that the setting of guideline levels for methylmercury in fish may not be an effective way of reducing expo-

sure for the general population. The Committee noted that advice targeted at population subgroups that might be at risk from methylmercury exposure could provide an effective method for lowering the number of individuals with exposures greater than the PTWI.

An addendum to the toxicological monograph was prepared.

5. Future work

- The Committee recommended that an additional method to assess dietary exposure (based on flavour-industry recommended use levels for each flavouring agent in food categories, in combination with standard portion sizes) should be tested at the next meeting at which flavouring agents were to be considered.
- The Committee recommended that any analytical method relevant to more than one specifications monograph should not be included in the individual monographs, but be published separately in annexes to the FAO JECFA Monographs, and included in the on-line version of that publication.
- The Committee recommended that methods alternative to paper chromatography for synthetic colours should be placed on the agenda of a future meeting.
- The Committee recommended that additives made using ethylene oxide should be re-evaluated at a future meeting, including the limits for ethylene oxide, ethylene chlorohydrins and 1,4-dioxane.
- The Committee endorsed the recommendation made at the sixty-fifth meeting that hexanes be re-evaluated and that other alkane hydrocarbon solvents, such as light petroleum, should also be included.

6. Recommendations

1. In view of increasing interest in the commercial production of nanoparticulate materials, the Committee recommended to FAO and WHO that a special consultation should be convened to consider approaches to the safety evalaution of such materials in food.
2. The Committee recommended to the Codex Alimentarius Commission that provisions for aluminium-containing additives included in the Codex GSFA should be compatible with the newly established PTWI for Al of 1 mg/kg bw. The Committee noted in particular that provisions for such additives used at levels consis-

tent with GMP in staple foods may lead to high exposure in the general population and in particular in children.

3. The Committee recommended that studies be undertaken to determine the intake and toxicological significance of fatty acid esters of 3-chloro-1,2-propanediol, reported to be present in foods.
4. The Committee had previously noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets. The present Committee recommended that the known benefits of fish consumption need to be taken into consideration in any advice aimed at different subpopulations. Risk managers might wish to consider whether specific advice should be given concerning children and adults, after weighing the potential risks and benefits.

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Annex 1
Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

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Annex 2
Toxicological recommendations and information on specifications

Food additives and ingredients evaluated toxicologically or assessed for dietary exposure

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Annatto extracts	R	ADI for bixin: 0–12 mg/kg bw Applicable to the following annatto extracts, provided they comply with the respective specifications: — solvent-extracted bixin (≥ 85% bixin, ≤ 2.5% norbixin) — aqueous processed bixin (≥ 25% bixin, ≤ 7% norbixin) Does not apply to oil-processed bixin (≥10% bixin) Group ADI for norbixin and its sodium and potassium salts: 0–0.6 (expressed as norbixin) Applicable to the following annattoextracts, provided they comply withthe respective specifications: — solvent-extracted norbixin (≥ 85% norbixin) — alkali-processed norbixin, acid-precipitated (≥ 35% norbixin) and not acid precipitated (≥ 15% norbixin) In re-evaluating the studies of toxicity with solvent-extracted bixin (92% bixin) and solvent-extracted norbixin (91.6% norbixin) and in light of the additional compositional data, the Committee considered that ADIs could be allocated to these pigments, on the basis of studies conducted on the extracts. The Committee established an ADI for bixin of 0–12 mg/kg bw based on the NOEL of 1311 mg/kg bw per day from a 90-day study in male rats fed an extract containing 92% bixin, corrected for pigment content and applying a safety factor of 100 The Committee established a group ADI for norbixin and its sodium and potassium salts of 0–0.6 mg/kg bw (expressed as norbixin) on the basis of the NOEL of 69 mg/kg bw per day from a 90-day study in male rats fed an extract containing 91.6% norbixin, corrected for pigment content and applying a safety factor of 100. On the basis of compositional data and

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
		toxicological data on aqueous processed bixin and alkali-processed norbixin (acid precipitated), the Committee concluded that the use of these annatto extracts as sources ofbixin or norbixin would not raise safety concerns, provided that they complied with the relevant specifications. Accordingly, the ADIs given above could be applied to bixin and norbixin derived from these annatto extracts The Committee noted that the pigment in alkali-processed norbixin (not acid-precipitated) consists of sodium or potassium salts of norbixin and that compositional data on this extract, complying with the specifications, did not raises safety concerns. Consequently, the Committee concluded that the group ADI for norbixin and its sodium and potassium salts is applicable to norbixin salts from this source. As no NOEL could be identified for oil-processed bixin and no compositional data were available, the Committee decided that the above evaluation could not be applied to this extract. Assuming all annatto-derived pigment were bixin, the estimated intake would amount to approximately 0.2% of the ADI (0–12 mg/kg bw). Assuming all annatto derived pigment were norbixin, the estimated intake would amount to approximately 4% of the ADI (0– 0.6 mg/kg bw). Specifications were established for all extracts covered by the established ADIs, and tentative specifications were established for oil-processed bixin.
Lycopene (synthetic)	N	The Committee established an ADI of 0–0.5 mg/kg bw for synthetic lycopene based on the highest dose of 50 mg/kg bw per day tested in the 104-week study in rats (at which no adverse effects relevant to humans were induced) and a safety factor of 100. This ADI was made into a groupADI to include lycopene from *Blakeslea trispora*, which was also under consideration at the present meeting and was considered to be toxicologically equivalent to chemically synthesized lycopene. The estimate of high exposure (>95th percentile) of 30 mg/person per day, equivalent to 0.5 mg/kg bw per day, which includes background exposure plus additional exposure from food additive uses, is compatible with the ADI.

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Lycopene from *Blakeslea trispora*	N	Lycopene from *Blakeslea trispora* is considered to be toxicologically equivalent to chemically synthesized lycopene, for which an ADI of 0–0.5 mg/kg bw was established. This was given further credence by the negative results obtained for lycopene from *B. trispora* in two tests for genotoxicity, and the absence of adverse effects in a short-term toxicity study considered at the present meeting. The ADI for synthetic lycopene was therefore made into a group ADI of 0–0.5 mg/kg bw to include lycopene from *B. trispora*. The exposure estimate is the same as for synthetic lycopene.
Natamycin (also known as pimaricin) exposure assessment)		The data as a whole, including estimations based on GEMS/Food Consumption Cluster Diets and calculations for consumers with a high intake and children, confirm the results of the assessment made by the Committee at its fifty-seventh meeting and show that the current ADI of 0–0.3 mg/kg bw is unlikely to be exceeded.
Propyl paraben (also known as propyl para-hydroxybenzoate)	W	In view of the adverse effects in male rats, propyl paraben (propyl *p*-hydroxybenzoate) should be excluded from the group ADI for the parabens used in food. This conclusion was reached on the grounds that the group ADI was originally set on a NOEL of 1000 mg/kg bw per day for a different toxicological end-point — growth depression — taken from the range of studies then available for the methyl, ethyl and propyl parabens. Propyl paraben has shown adverse effects in tissues of reproductive organs in male rats at dietary doses of down to 10 mg/kg bw per day, which is within the range of the group ADI (0–10 mg/kg bw), with no NOEL yet identified. The specifications for propyl paraben were withdrawn. The group ADI of 0–10 mg/kg bw for the sum of methyl and ethyl esters of *p*-hydroxybenzoic acid was maintained.

GEMS: Global Environment Monitoring System — Food Contamination Monitoring and Assessment Programme; NOEL: no-observed-effect level.

[a] N: new specifications prepared; R: existing specifications revised; W: specifications withdrawn.

Food additives considered for specifications only

Food Additive	Specifications[a]
Acetylated oxidized starch	R
Annatto extracts (oil-processed bixin)	R, T
Butyl *p*-hydroxybenzoate (butyl paraben)	W
Carob bean gum	R, T
Carob bean gum (clarified)	N, T
Ethylene oxide	W
Guar gum	R, T
Guar gum (clarified)	N, T
DL-Malic acid and its calcium and sodium salts	R
Maltitol	R
Titanium dioxide	R
Zeaxanthin (synthetic)	R

[a] N: new specifications prepared; R: existing specifications revised; T: tentative specifications; W: specifications withdrawn.

Contaminants evaluated toxicologically

Contaminant	Tolerable intake and other toxicological recommendations
Aluminium (from all sources including food additives)	PTWI: 1 mg/kg bw expressed as Al The previously established ADIs and PTWI for aluminium compounds were withdrawn. The Committee concluded that aluminium compounds have the potential to affect the reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI and the PTWI was therefore revised. The available studies have many limitations and are not adequate for defining dose–response relationships. The Committee therefore based its evaluation on the combined evidence from several studies. The relevance of studies involving administration of aluminium compounds by gavage was unclear because the toxicokinetics after gavage were expected to differ from toxicokinetics after dietary administration, and these gavage studies generally did not report total aluminium exposure including basal levels in the feed. The studies conducted with dietary administration of aluminium compounds were considered most appropriate for the evaluation. The lowest LOELs for aluminium compounds in a range of different dietary studies in mice, rats and dogs were in the range of 50–75 mg/kg bw per day, expressed as Al. The Committee applied an uncertainty factor of 100 to the lower end of this range of LOELs (50 mg/kg bw per day expressed as Al) to allow for inter- and intraspecies differences. There are deficiencies in the

Contaminant	Tolerable intake and other toxicological recommendations
	database, notably the absence of NOELs in the majority of the studies evaluated and the absence of long-term studies on the relevant toxicological end-points. These deficiencies are counterbalanced by the probable lower bioavailability of the less soluble aluminium compounds present in food. Overall, it was considered appropriate to apply an additional uncertainty factor of three. The Committee confirmed that the resulting health-based guidance value should be expressed as a PTWI, because of the potential for bioaccumulation. The Committee noted that the PTWI is likely to be exceeded to a large extent by some population groups, particularly children, who regularly consume foods that include aluminium-containing additives. The Committee also noted that dietary exposure to Al is expected to be very high for infants fed on soya-based formula.
3-Chloro-1,2-propanediol	As no new pivotal toxicological studies had become available the Committee retained the previously established PMTDI of 2 μg/kg bw for 3-chloro-1,2-propanediol. Estimated exposures at the national level considered a wide range of foods, including soy sauce and soy-sauce related products, ranged from 1% to 35% of the PMTDI for average exposure in the general population. For the consumers at the high percentile (95th), the estimated intakes ranged from 3% to 85% and up to 115% of the PMTDI in young children. These estimates are based on concentrations of 3-chloro-1,2-propanediol derived before any remedial action had been taken by government or industry. The Committee noted that reduction in the concentration of 3-chloro-1,2-propanediol in soy sauce and related products made with acid-HVP could substantially reduce the intake of this contaminant by certain consumers of this condiment.
1,3-Dichloro-2-propanol	The Committee concluded that the critical effect of 1,3-dichloro-2-propanol is carcinogenicity. The substance yielded negative results in two new studies on genotoxicity in vivo, but limitations in these studies and positive findings in tests for genotoxicity in vitro as well as lack of knowledge on the modes of action operative at the various tumour locations led the Committee to the conclusion that a genotoxic mode of action could not be excluded. Accordingly, the cancer dose–

Contaminant	Tolerable intake and other toxicological recommendations
	response data were analysed by dose– response modelling to calculate BMD_{10} and $BMDL_{10}$ values. The Committee concluded that a representative mean intake for the general population of 1,3-dichloro-2-propanol of 0.051 μg/kg bw per day and an estimated high-level intake (young children included) of 0.136 μg/kg bw per day could be used in the evaluation. Comparison of these mean and high-levels intakes with the lowest $BMDL_{10}$ of 3.3 mg/kg bw per day, which was the $BMDL_{10}$ for incidence data on tumour-bearing animals for all treatment-affected locations, indicates margins of exposure of approximately 65 000 and 24 000, respectively. Based on these margins of exposure, the Committee concluded that the estimated intakes of 1,3-dichloro-2-propanol were of low concern for human health. The available evidence suggests that 1,3-dichloro-2-propanol occurs at lower concentrations than 3-chloro-1,2-propanediol in soy sauce and related products, and also in acid-HVP food ingredients. However, in meat products the concentrations of 1,3-dichloro-2-propanol are generally higher than the concentrations of 3-chloro-1,2-propanediol.
Methylmercury	The Committee made it clear that the previous PTWI of 3.3 μg/kg bw had, in fact, been withdrawn in 2003. The Committee confirmed the existing PTWI of 1.6 μg/kg bw, set in 2003, based on the most sensitive toxicological end-point (developmental neurotoxicity) in the most susceptible species (humans). However, the Committee noted that life-stages other than the embryo and fetus may be less sensitive to the adverse effects of methylmercury. In the case of adults, the Committee considered that intakes of up to about two times higher than the existing PTWI of 1.6 μg/kg bw would not pose any risk of neurotoxicity in adults, although in the case of women of childbearing age, it should be borne in mind that intake should not exceed the PTWI, in order to protect the embryo and fetus. Concerning infants and children aged up to about 17 years, the data do not allow firm conclusions to be drawn regarding their sensitivity compared to that of adults. While it is clear that they are not more sensitive than the embryo or fetus, they may be more sensitive than adults because significant development of the brain continues in infancy and childhood. Therefore, the Committee could not identify a level of intake

Contaminant	Tolerable intake and other toxicological recommendations
	higher than the existing PTWI that would not pose a risk of developmental neurotoxicity for infants and children. The Committee has previously noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets. The present Committee recommends that the known benefits of fish consumption need to be taken into consideration in any advice aimed at different subpopulations. Risk managers may wish to consider whether specific advice should be given concerning children and adults, after weighing the potential risks and benefits. The Committee concluded that the setting of guideline levels for methylmercury in fish may not be an effective way of reducing exposure for the general population. The Committee noted that advice targeted at population subgroups that may be at risk from methyl mercury exposure may provide an effective method for lowering the number of individuals with exposures greater than the PTWI.

ADI: acceptable daily intake; AI: elemental aluminium; LOEL: lowest-observed-effect level; NOEL: no-observed-effect level; PMTDI: provisionalPTWI: provisional maximum tolerable daily intake.

Annex 3
Further information required or desired

Annatto extracts (oil-processed bixin)

Information is required on the chemical characterization of the non-colouring matter components of commercial products. The tentative specifications monograph will be withdrawn unless the requested information is received before the end of 2008.

Carob bean gum

Data are required on gum content, solubility in water and an analytical method using capillary gas chromatography for measuring residual solvents for measuring residual solvents. For clarified carob bean gum, in addition to the information listed above for carob bean gum, information is requested on synonyms and a range of other information on purity. The tentative specifications monograph will be withdrawn unless the required information is received before the end of 2007.

Guar gum

Data are required on gum content and an analytical method using capillary gas chromatography for measuring residual solvents for measuring residual solvents. For clarified guar gum, in addition to the information listed above for guar gum, information is requested on synonyms and a range of other information on purity. The tentative specifications monograph will be withdrawn unless the required information is received before the end of 2007.

Aluminium

Further data on the bioavailability of different aluminium-containing food additives are required.

There is a need for an appropriate study of developmental toxicity and a multigeneration study incorporating neurobehavioural endpoints, to be conducted on a relevant aluminium compound(s).

Studies to identify the forms of aluminium present in soya formulae, and their bioavailability, are needed before an evaluation of the potential risk for infants fed on soya formulae can be considered.

3-Chloro-1,2-propanediol

The Committee noted that it has been reported that fatty acid esters of 3-chloro-1,2-propanediol are present in foods, but there were insufficient data to enable either their intake or toxicological significance to be evaluated. The Committee recommended that studies be undertaken to address this question.

Annex 4

Food categories and standard portion sizes to be used in the additional method for making estimates of dietary exposure for flavouring agents

Table 1 contains the food categories and the standard portion sizes (expressed as consumed) to be used in the additional method for making estimates of dietary exposure for flavouring agents. The complete classification can be found at: http://www.codexalimentarius.net/gsfaonline/foods/index.html. The portion sizes were derived from "Reference amounts customarily consumed per eating occasion" in Title 21 of the United States Code of Federal Regulations, Part 101.12(b) (http://www.cfsan.fda.gov/~lrd/CF101-12.HTML). If specific information were available to indicate that a flavouring agent would be used only in a more refined subcategory, an appropriate estimate of a portion size for that subcategory could be provided by the industry in place of the value for the broader category.

Table 1
Food categorization system for the General Standard for Food Additives (first sublevel only) with standard portion sizes

Food category	Standard portion sizes (g)
1. Dairy products, excluding products of category 2	
1.1 Milk and dairy-based drinks	200
1.2 Fermented and renneted milk products (plain), excluding food category 01.1.2 (dairy-based drinks)	200
1.3 Condensed milk and analogues	NF
1.4 Cream (plain) and the like	NF
1.5 Milk powder and cream powder and powder analogues (plain)	NF
1.6 Cheese and analogues	40
1.7 Dairy-based desserts (e.g. pudding, fruit or flavoured yoghurt)	125
1.8 Whey and whey products, excluding whey cheese	NF
2. Fats and oils and fat emulsions	
2.1 Fats and oils essentially free from water	15
2.2 Fat emulsions mainly of type water-in-oil	15
2.3 Fat emulsions mainly of type water-in-oil, including mixed and/or flavoured products based on fat emulsions	15
2.4 Fat-based desserts excluding dairy-based dessert products of category 01.7	50
3. Edible ices, including sherbet and sorbet	50

Food category	Standard portion sizes (g)
4. Fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes and aloe vera), seaweeds, and nuts and seeds	
4.1 Fruit	
4.1.2 Processed fruit	125
4.2 Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes and aloe vera), seaweeds, and nuts and seeds	
4.2.2 Processed vegetables and nuts and seeds	200
5. Confectionery	
5.1 Cocoa products and chocolate products, including imitations and chocolate substitutes	40
5.2 Confectionery including hard and soft candy and nougats etc. other than 5.1, 5.3 and 5.4,	30
5.3 Chewing gum	3
5.4 Decorations (e.g. for fine bakery wares), toppings (non-fruit) and sweet sauces	35
6. Cereals and cereal products derived from cereal grains, from roots and tubers, and pulses and legumes, excluding bakery wares of food category 07.0	
6.1 Whole, broken or flaked grain, including rice	NF
6.2 Flours and starches (including soybean powder)	NF
6.3 Breakfast cereals, including rolled oats	30
6.4 Pastas and noodles and like products (e.g. rice paper, rice vermicelli, soybean pasta and noodles)	200
6.5 Cereal and starch-based desserts (e.g. rice pudding, tapioca pudding)	200
6.6 Batters (e.g. for breading or batters for fish or poultry)	30
6.7 Pre-cooked or processed rice products, including rice cakes (Oriental type only)	200
6.8 Soybean products (excluding soybean products of food category 12.9 and fermented soybean products of food category 12.10)	100
7. Bakery wares	
7.1 Bread and ordinary bakery wares	50
7.2 Fine bakery wares (sweet, salty, savoury) and mixed	80
8. Meat and meat products, including poultry and game	
8.1 Fresh meat, poultry and game	NF
8.2 Processed meat, poultry and game products in whole pieces or cuts	100
8.3 Processed comminuted meat, poultry and game products	100
8.4 Edible casings (e.g. sausage casings)	NF
9. Fish and fish products, including molluscs, crustaceans and echinoderms	
9.1 Fresh fish and fish products, including molluscs, crustaceans and echinoderms	
9.1.1 Fresh fish	NF
9.1.2 Fresh molluscs, crustaceans and echinoderms	NF

Food category	Standard portion sizes (g)
9.2 Processed fish and fish products, including molluscs, crustaceans and echinoderms	100
9.3 Semi-preserved fish and fish products, including molluscs, crustaceans and echinoderms	100
9.4 Fully preserved. including canned or fermented fish and fish products, including molluscs, crustaceans and echinoderms	100
10. Eggs and egg products	
10.1 Fresh eggs	NF
10.2 Egg products	100
10.3 Preserved eggs, including alkaline. salted and canned eggs	100
10.4 Egg-based desserts (e.g. custard)	125
11. Sweeteners, including honey	
11.1 Refined and raw sugar	10
11.2 Brown sugar excluding products of food category 11.1.3	10
11.3 Sugar solutions and syrups, and (partially) inverted sugars, including molasses and treacle excluding products of food category 11.1.3	30
11.4 Other sugars and syrups (e.g. xylose, maple syrup, sugar toppings)	30
11.5 Honey	15
11.4 Table-top sweeteners, including those containing high-intensity sweeteners	15
12. Salts, spices, soups, sauces, salads, protein products (including soybean protein products) and fermented soybean products	
12.1 Salt and salt substitutes	NF
12.2 Herbs, spices, seasonings and condiments (e.g. seasoning for instant noodles)	1
12.3 Vinegars	15
12.4 Mustards	15
12.5 Soups and broths	200
12.6 Sauces and like products	30
12.7 Salads (e.g. macaroni salad, potato salad) and sandwich spreads excluding cocoa- and nut-based spreads of food categories	120/20*
12.8 Yeast and like products	NF
12.9 Protein products	15
12.10 Fermented soybean products	40
13. Foodstuffs intended for particular nutritional uses	
13.1 Infant formulae and follow-on formulae, and formulae for special medical purposes for infants	NC
13.2 Complementary foods for infants and young children	NC
13.3 Dietetic foods intended for special medical purposes	NC
13.4 Dietetic formulae for slimming purposes and weight reduction	NC
13.5 Dietetic foods other than 13.1–13.4	NC
13.6 Food supplements	5

Food category	Standard portion sizes (g)
14. Beverages, excluding dairy products	
14.1 Non-alcoholic ("soft") beverages	300
14.2 Alcoholic beverages, including alcohol-free and low-alcoholic counterparts	
14.2.1 Beer and malt beverages	300
14.2.3 Grape wines	150
14.2.5 Mead	
14.2.6 Spirituous beverages	30
15. Ready-to-eat savouries	
15.1 Snacks, potato-, cereal-, flour- or starch-based (from roots and tubers, pulses and legumes)	30
15.2 Processed nuts, including coated nuts and nut mixtures (with e.g. dried fruit)	30
15.3 Snacks — fish based	30
16 Composite foods (e.g. casseroles, meat pies, mincemeat) — foods that could not be placed in categories 1–15	NF

* 120 for salads and 20 for spreads.

NF, Not flavoured; appears in those categories that would not be expected to contain any flavouring agent.

NC, Not considered; appears in those categories which would not be considered in an assessment of dietary dietary exposure to flavourings.

Annex 5

General Specifications and Considerations for Enzyme Preparations Used in Food Processing

The following general specifications were prepared by the Committee at its sixty-seventh meeting (2006) for publication in FAO JECFA Monographs 3 (2006), superseding the general specifications prepared at the fifty-seventh meeting (Annex 1, reference *154*) and published in FAO JECFA Monographs 1 (Annex 1, reference *180*).

These specifications were originally prepared by the Committee at its twenty-fifth meeting (Annex 1, reference *56*) and published in FAO Food and Nutrition Papers No. 19 and No. 31/2 (Annex 1, references *58* and *69*). Subsequent revisions were made by the Committee at its thirty-fifth meeting and published in FAO Food and Nutrition Paper No. 52 (Annex 1, reference *103*). Additional amendments were made at the fifty-first meeting and published in FAO Food and Nutrition Paper No. 52 Add. 6 (Annex 1, reference *139*), and at the fifty-third meeting (Annex 1, reference *143*) and partially published in FAO Food and Nutrition Paper No. 52 Add. 7 (Annex 1, reference *145*).

Classification and nomenclature of enzymes

Enzymes are proteins that catalyse chemical reactions. The Enzyme Commission of the International Union of Biochemistry and Molecular Biology (formerly the International Union of Biochemistry) classified enzymes into six main classes: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases (*1*). Based on the type of reaction catalysed, enzymes are assigned to one of these classes and given an Enzyme Commission (EC) number, a systematic name, and a common name. Other names are also provided, if available. Enzymes used in food processing are often referred to by their common or traditional names such as protease, amylase, malt, or rennet. For enzymes derived from microorganisms, the name of the source microorganism is usually specified, for example, "α-amylase from *Bacillus subtilis*." For enzymes derived from microorganisms modified by using recombinant DNA techniques (referred to as recombinant-DNA microorganisms or genetically modified microorganisms), the names of both the enzyme source (donor organism) and the production microorganism are provided, for example, "α-amylase from *Bacillus licheniformis* expressed in *Bacillus subtilis*."

Enzyme preparations

Enzymes are used in food processing as enzyme preparations. An enzyme preparation contains an active enzyme (in some instances a blend of two or more enzymes) and intentionally added formulation ingredients such as diluents, stabilizing agents, and preserving agents. The formulation ingredients may include water, salt, sucrose, sorbitol, dextrin, cellulose, or other suitable compounds. Enzyme preparations may also contain constituents of the source organism (i.e. an animal, plant, or microbial material from which an enzyme was isolated) and compounds derived from the manufacturing process, for example, the residues of the fermentation broth. Depending on the application, an enzyme preparation may be formulated as a liquid, semi-liquid or dried product. The colour of an enzyme preparation may vary from colourless to dark brown. Some enzymes are immobilized on solid support materials.

Active components

1Enzyme preparations usually contain one principal enzyme that catalyses one specific reaction during food processing. For example, α-amylase catalyses the hydrolysis of 1,4-α-D-glucosidic linkages in starch and related polysaccharides. However, some enzyme preparations contain a mixture of enzymes that catalyse two or more different reactions in food. Each principal enzyme present in an enzyme preparation is characterized by its systematic name, common name, and EC number. The activity of each enzyme is measured using an appropriate assay and expressed in defined activity units per weight (or volume) of the preparation.

Source materials

Enzymes used in food processing are derived from animal, plant, and microbial sources. Animal tissues used for the preparation of enzymes should comply with meat inspection requirements and be handled in accordance with good hygienic practice.

Plant material and microorganisms used in the production of enzyme preparations should not leave any residues harmful to health in the processed finished food under normal conditions of use.

Microbial strains used in the production of enzyme preparations may be native strains or mutant strains derived from native strains by the processes of serial culture and selection or mutagenesis and selection or by the application of recombinant DNA technology. Although nonpathogenic and nontoxigenic microorganisms are normally used

in the production of enzymes used in food processing, several fungal species traditionally used as sources of enzymes are known to include strains capable of producing low levels of certain mycotoxins under fermentation conditions conducive to mycotoxin synthesis (*2–6*). Enzyme preparations derived from such fungal species should not contain toxicologically significant levels of mycotoxins that could be produced by these species.

Microbial production strains should be taxonomically and genetically characterized and identified by a strain number or other designation. The strain identity may be included in individual specifications, if appropriate. The strains should be maintained under conditions that ensure the absence of genetic drift and, when used in the production of enzyme preparations, should be subjected to methods and culture conditions that are applied consistently and reproducibly from batch to batch. Such conditions should prevent the introduction of microorganisms that could be the source of toxic and other undesirable substances. Culture media used for the growth of microbial sources should consist of components that leave no residues harmful to health in the processed finished food under normal conditions of use.

Enzyme preparations should be produced in accordance with good food manufacturing practice and cause no increase in the total microbial count in the treated food over the level considered to be acceptable for the respective food.

Substances used in processing and formulation

Substances used in processing and formulation of enzyme preparations should be suitable for their intended uses.

In the case of immobilized enzyme preparations, leakage of active enzymes, support materials, crosslinking agents and/or other substances used in immobilization should be kept within acceptable limits established in the individual specifications.

To distinguish the proportion of the enzyme preparation derived from the source material and manufacturing process from that contributed by intentionally added formulation ingredients, the content of total organic solids (TOS) is calculated as follows:

$$\% \text{ TOS} = 100 - (A + W + D)$$

where:

A = % ash, W = % water and D = % diluents and/or other formulation ingredients.

Purity

Lead:

Not more than 5 mg/kg

Determine using an atomic absorption spectroscopy/inductively coupled atomic-emission spectroscopy (AAS/ICP-AES) technique appropriate to the specified level. The selection of the sample size and the method of sample preparation may be based on the principles described in the Compendium of Food Additive Specifications, Volume 4.

Microbiological criteria:

Salmonella species: absent in 25 g of sample

Total coliforms: not more than 30 per gram

Escherichia coli: absent in 25 g of sample

Determine using procedures described in Volume 4.

Antimicrobial activity:

Absent in preparations from microbial sources.

Other considerations

Safety assessment of food enzyme preparations has been addressed in a number of publications and documents. Pariza & Foster (*2*) proposed a decision tree for determining the safety of microbial enzyme preparations. Pariza & Johnson (*7*) subsequently updated this decision tree and included information on enzyme preparations derived from recombinant-DNA microorganisms. The Scientific Committee on Food (*8*) issued guidelines for the presentation of data on food enzymes. The document includes a discussion on enzymes from genetically modified organisms including microorganisms, plants, and animals. Several international organizations, government agencies, and expert groups have also published discussion papers or guidelines that address safety assessment of food and food ingredients derived from recombinant-DNA plants and microorganisms (*9–19*). Certain information in these documents may be applicable to enzyme preparations derived from recombinant sources.

An overall safety assessment of each enzyme preparation intended for use in food processing should be performed. This assessment should include an evaluation of the safety of the production organism, the enzyme component, side activities, the manufacturing process, and the consideration of dietary exposure. Evaluation of the enzyme component should include considerations of its potential to cause an allergic reaction. For enzyme preparations from recombinant-DNA microorganisms, the following should also be considered:

1. The genetic material introduced into and remaining in the production microorganism should be characterized and evaluated for function and safety, including evidence that it does not contain genes encoding known virulence factors, protein toxins, and enzymes involved in the synthesis of mycotoxins or other toxic or undesirable substances.
2. Recombinant-DNA production microorganisms might contain genes encoding proteins that inactivate clinically useful antibiotics. Enzyme preparations derived from such microorganisms should contain neither antibiotic inactivating proteins at concentrations that would interfere with antibiotic treatment nor transformable DNA that could potentially contribute to the spread of antibiotic resistance.

References for Annex 5

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Annex 6

Table of functional classes, definitions and technological uses agreed by the Codex Committee on Food Additives and Contaminants at its Thirty-eighth Session

Functional classes For LABELLING	Definition	Sub-classes For TECHNOLOGICAL USE
1 Acidity Regulator	A food additive, which controls the acidity or alkalinity of a food	Acidity regulator, acid, acidifier, alkali, base, buffer, buffering agent, pH adjusting agent
2 Anticaking agent	A food additive, which reduces the tendency of components of food to adhere to one another	Anticaking agent, anti-stick agent, drying agent, dusting agent
3 Antifoaming agent	A food additive, which prevents or reduces foaming	Antifoaming agent, defoaming agent
4 Antioxidant	A food additive, which prolongs the shelf-life of foods by protecting against deterioration caused by oxidation	Antioxidant, antioxidant synergist, antibrowning agent
5 Bleaching agent	A food additive (non-flour use) used to decolourize food. Bleaching agents do not include pigments	Bleaching agent
6 Bulking agent	A food additive, which contributes to the bulk of a food without contributing significantly to its available energy value	Bulking agent, filler
7 Carbonating agent	A food additive used to provide carbonation in a food	Carbonating agent
8 [Carrier]	A food additive used to dissolve, dilute, disperse or otherwise physically modify a food additive or nutrient without altering its function (and without exerting any technicological effect itself) in order to facilitate its handling, application or use	Carrier, carrier solvent, nutrient carrier diluent for other food additives, encapsulating agent
9 Colour	A food additive, which adds or restores colour in a food	Colour, decorative pigment, surface colourant
10 Colour retention agent	A food additive, which stabilizes, retains or intensifies the colour of a food	Colour retention agent, colour fixative, colour Stabilizer, colour adjunct

Functional classes For LABELLING	Definition	Sub-classes For TECHNOLOGICAL USE
11 Emulsifier	A food additive, which forms or maintains a uniform emulsion of two or more phases in a food	Emulsifier, plasticizer, dispersing agent, surface active agent, crystallization inhibitor, density adjustment (flavouring oils in beverages), suspension agent, clouding agent
12 Emulsifying salt	A food additive, which, in the manufacture of processed food, rearranges proteins in order to prevent fat separation	Emulsifying salt, melding salt
13 Firming agent	A food additive, which makes or keeps tissues of fruit or vegetables firm and crisp, or interacts with gelling agents to produce or strengthen a gel	Firming agent
14 Flavour enhancer	A food additive, which enhances the existing taste and/or odour of a food	Flavour enhancer, flavour synergist
15 Flour treatment agent	A food additive, which is added to flour or dough to improve its baking quality or colour	Flour treatment agent, flour bleaching agent, flour improver, dough conditioner, dough strengthening agent
16 Foaming agent	A food additive, which makes it possible to form or maintain a uniform dispersion of a gaseous phase in a liquid or solid food	Foaming agent, whipping agent, aerating agent
17 Gelling agent	A food additive, which gives a food texture through formation of a gel	Gelling agent
18 Glazing agent	A food additive, which when applied to the external surface of a food, imparts a shiny appearance or provides a protective coating	Glazing agent, sealing agent, coating agent, surface-finishing gent, polishing agent, film-forming agent
19 Humectant	A food additive, which prevents food from drying out by counteracting the effect of a dry atmosphere	Humectant, moisture-retention agent, wetting agent
20 [Packaging gas]	A food additive gas, which is introduced into a container before, during or after filling with food	Packaging gas

Functional classes For LABELLING	Definition	Sub-classes For TECHNOLOGICAL USE
21 Preservative	A food additive, which prolongs the shelf-life of a food by protecting against deterioration caused by microorganisms	Preservative, antimicrobial preservative, antimycotic agent, bacteriophage control agent, fungistatic agent, antimould and antirope agent, antimicrobial synergist
22 Propellant	A food additive gas, which expels a food from a container	Propellant
23 Raising agent	A food additive or a combination of food dditives, which liberate(s) gas and thereby increase(s) the volume of a dough or batter	Raising agent
24 Sequestrant	A food additive, which controls the availability of a cation	Sequestrant
25 Stabilizer	A food additive, which makes it possible to maintain a uniform dispersion of two or more components	Stabilizer,foam stabilizer, colloidal stabilizer, emulsion stabilizer
26 Sweetener	A food additive (other than a mono- or disaccharide sugar), which imparts a sweet taste to a food	Sweetener, intense sweetener, bulk sweetener
27 Thickener	A food additive, which increases the viscosity ofa food	Thickener, bodying agent, binder, texturizing agent