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Fifty-fifth report of the
Joint FAO/WHO Expert Committee on
Food Additives

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

Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 46, 2001.

Specifications are issued separately by FAO under the title:

Compendium of food additives specifications, Addendum 8. FAO Food and Nutrition Paper, No. 52, Add. 8, 2000.

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 International Programme on Chemical Safety (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 met in Geneva from 6 to 15 June 2000. The meeting was opened by Mrs P.K. Singh, Executive Director, Sustainable Development and Healthy Environments, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Mrs Singh noted that Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), had been used by the Committee as a basis for consistent, credible evaluations during the past 13 years. However, in view of the tremendous scientific advances that had been made during that time and the increasing complexity and scope of the evaluations, FAO and WHO were considering the possibility of updating and consolidating the principles for the risk assessment of food additives and contaminants and of veterinary drug residues used by the Joint FAO/WHO Expert Committee on Food Additives and of pesticide residues used by the Joint FAO/WHO Meeting on Pesticide Residues.

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 fifty-four previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the fifty-third meeting (Annex 1, reference *143*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);
— to undertake toxicological evaluations of certain food additives, flavouring agents and contaminants (sections 3–5 and Annex 2);
— to assess the intake of specific food additives (section 6); and
— to review and prepare specifications for selected food additives and flavouring agents (sections 3 and 7 and Annex 2).

2.1 Modification of the agenda

Cross-linked sodium carboxymethyl cellulose and lycopene were removed from the agenda because no data were submitted. Paprika oleoresin was added to the agenda at the request of the Thirty-second Session of the Codex Committee on Food Additives and Contaminants (*2*), which had asked for clarification of the previous

evaluation. Microcrystalline wax was also added to the agenda for the review of the specifications.

Caustic sulfite caramel was evaluated under the name "caramel colour II", and cochineal extract, carmine and carminic acid were evaluated under the names "cochineal extract" and "carmines".

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, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated subsequently at meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107*, *116*, *122*, *131*, *137* and *143*), including the present one. Environmental Health Criteria, No. 70 (Annex 1, reference *76*) embraces the major observations, comments and recommendations on the safety assessment of food additives and contaminants contained, up to the time of its publication, in the reports of the Committee and other associated bodies. The Committee noted that the publication reaffirms the validity of recommendations that are still appropriate and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.2.1 *Principles governing the safety evaluation of flavouring agents*

α,β-Unsaturated compounds

Five α,β-unsaturated flavouring agents were considered by the Committee at its forty-ninth meeting (Annex 1, reference *131*), but their safety was not assessed at that time. Additional data on metabolism were considered necessary for the assessment of four α,β-unsaturated lactones (Nos 245, 246, 276 and 438), and the evaluation of *cis*-3- and *trans*-2-hexenyl propionate (No. 147) was postponed, pending consideration of other α,β-unsaturated carbonyl compounds. At its present meeting, the Committee considered data on furfural, cinnamaldehyde, structural analogues of cinnamaldehyde, pulegone and esters of the corresponding alcohols, which are predicted to be metabolized by formation of α,β-unsaturated carbonyls. The available data on the toxicity of these compounds showed a number of adverse effects at high doses in experimental animals, and no-observed-effect levels (NOELs) for these effects were identified. The presence of protective cellular processes, such as conjugation with glutathione, provides adequate detoxification capacity at the low doses associated with use of such compounds as flavouring agents. In

consequence, the Committee concluded that the presence of an α,β-unsaturated carbonyl group in a flavouring agent, or its formation during metabolism, would not preclude evaluation of that substance by the Procedure for the Safety Evaluation of Flavouring Agents.

Grouping of flavouring agents

The Committee recognized that a single flavouring agent could be a member of more than one group of such agents: for example, allyl 2-furoate was considered as a member of the group of allyl esters evaluated at the forty-sixth meeting (Annex 1, reference *122*), whereas five other esters of furoic acid were considered as members of the group of furfuryl alcohol and related agents evaluated at the present meeting. The Committee recognized that evaluations of combined intakes of a group of flavouring agents should take into account all relevant, structurally related agents, irrespective of the group in which they were evaluated.

Estimating intake of flavouring agents

The Committee considered use of the "per capita × 10"[1] method for estimating the intake of flavouring agents, as well as alternative procedures, such as the theoretical added maximum dietary intake and stochastic modelling methods, which are based on dietary surveys. The Committee concluded that its use of "per capita × 10" is appropriate currently. However, it recognized the potential usefulness of the other methods and noted that use of the "per capita × 10" method may, in some cases, result in an underestimate of the intake of persons with high levels of consumption of specific foods. The Committee was aware of research on methods to predict the intake of flavouring agents and concluded that data from such studies could be used to investigate the use of the "per capita × 10" method and alternative methods of intake assessment at future meetings of the Committee.

Correction factor for "poundage" data for flavouring agents

The Committee relies on "poundage" data provided by manufacturers and food producers to estimate intake of flavouring agents. Such data reflect the amounts of the substances that are used in foods. At previous meetings, the Committee used data that had been "corrected" for under-reporting by application of a factor of 0.6 (see Annex 1, reference *137*, page 50), an estimate of the fraction of the total amount of the material that was reported. The Committee

[1] This method is based on the assumption that 10% of the population consumes all of the flavouring agents used in foods. In the calculation, the reported annual poundage of a flavouring agent is converted to micrograms and then divided by 10% of the population (of either Europe or the USA) and by 365 days to arrive at a daily intake.

was aware that the poundage data reported from the USA for the flavouring agents evaluated at the present meeting had been corrected by a factor of 0.8. This factor was used because the investigators had found that approximately 87% of the poundage data on all flavouring agents had been reported in the most recent survey, completed in 1995 (*3*). A factor of 0.6 would continue to be applied to the reported data from Europe.

2.2.2 *Need for data*

In response to a request by the Thirty-first Session of the Codex Committee on Food Additives and Contaminants (*4*), three food additives were placed on the agenda of the present meeting of the Committee for consideration of their uses in the draft General Standard for Food Additives. The Committee was asked to consider the use of benzoyl peroxide in milk products, the use of nitrous oxide as a packaging gas, and the use of stearyl tartrate both as an emulsifier and as a flour treatment agent at a higher concentration than previously specified by the Committee. Although the specifications for these three substances were updated, no evidence for the use of stearyl tartrate could be found, and none of the substances could be evaluated toxicologically because no relevant information was provided.

While the Committee wishes to be responsive to the requests of the Codex Committee, it emphasized that it can evaluate substances only if relevant data on toxicology, intake and specifications are provided. The Committee therefore requested the Codex Committee on Food Additives and Contaminants to ensure that the necessary data are available before referring a substance for its consideration.

2.2.3 *Recommendations of the World Health Assembly*

The Committee noted that the Fifty-third World Health Assembly had requested the Director-General inter alia "to strengthen the expert advisory bodies that provide scientific guidance on food safety issues related to chemicals, and to maintain an updated databank of this scientific evidence to support Member States in making health-related decisions in these matters" (*5*). The Committee welcomed this recognition of the significance of its activities in assisting Member States to maintain and improve the safety of food supplies.

The Committee also noted the Assembly's request to the Director-General "to ensure that the procedures for designating experts and preparing scientific opinions are such as to guarantee

the transparency, excellence and independence of the opinions delivered" (*5*). The Committee will continue to strive to achieve the highest standards of excellence and independence that have enhanced the general acceptance of its opinions to date. Furthermore, the Committee recognized the importance of transparency in the selection of experts, its modus operandi, and descriptions of its evaluations.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *General specifications for enzyme preparations*

At its fifty-third meeting (Annex 1, reference *143*), the Committee revised Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*) to indicate that only non-toxicogenic and non-pathogenic strains may be used as source organisms in the production of enzyme preparations for use in food. The text has been published in FAO Food and Nutrition Paper, No. 52, Add. 7 (Annex 1, reference *145*).

The specifications for a number of enzyme preparations were considered at the present meeting, and specific wording was included in each case to require that only non-toxicogenic and non-pathogenic strains be used as source organisms. As this wording precludes, by definition, the production of toxins, specifications incorporating this wording will usually not require that specific limits be placed on potentially toxic by-products.

2.3.2 *Determination of low concentrations of metals*

The Committee continues to pay attention to improving its specifications for limits and methods of analysis for metals. At its present meeting, the Committee recognized that where concentrations of lead of 2 mg/kg or less have been specified in existing monographs, the recommended sample preparations and instrumental methods are not wholly satisfactory. The Committee therefore decided to discontinue use of the phrase "Prepare a sample solution as directed for organic compounds in the limit test and determine by atomic absorption spectroscopy", and to use instead the wording "Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the method described in "Instrumental methods" of FAO Food and Nutrition Paper, No. 5, Rev. 2" (Annex 1, reference *100*).

3. Specific food additives

The Committee evaluated two food additives for the first time and re-evaluated nine food additives already considered at previous meetings. In addition, the Committee evaluated a large number of flavouring agents using the Procedure for the Safety Assessment of Flavouring Agents (see section 4). Information on the evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and other information required for certain substances are given in Annex 3.

3.1 Flavouring agents

3.1.1 *Furfural*

Furfural was evaluated previously by the Committee at its thirty-ninth and fifty-first meetings (Annex 1, references *101* and *137*). An Acceptable Daily Intake (ADI) was not established at either meeting because of concern about the finding of tumours in male mice given furfural in corn oil by gavage and the fact that no NOEL was identified for hepatotoxicity in male rats. In a study in mice, the combined incidence of adenomas and carcinomas was increased in males at the highest dose tested (175 mg/kg of body weight per day).

In order to address the concern regarding the formation of liver tumours in mice, the Committee at its fifty-first meeting requested the results of studies of DNA binding or adduct formation in vivo to clarify whether furfural interacts with DNA in the liver of mice (Annex 1, reference *137*). While no specific studies of DNA binding were submitted, the results of an assay for unscheduled DNA synthesis in mice in vivo was reviewed by the Committee at its present meeting. This study, in which single doses of up to 350 mg/kg of body weight were given, was particularly relevant since it addressed potential DNA repair in the cells in which tumours arose, namely hepatocytes. The negative results obtained in this assay were considered by the Committee to provide evidence that the liver tumours observed in the long-term study in mice were unlikely to have occurred through a genotoxic mechanism. The Committee considered that the concerns raised previously with respect to the liver tumours in mice were adequately addressed by this study and that a study of DNA binding was unnecessary.

At its fifty-first meeting, the Committee also requested the results of a 90-day toxicity study in rats to identify a NOEL for hepatotoxicity. At its present meeting, the Committee reviewed the results of a 13-week study in rats in which microencapsulated furfural was administered in the diet. It noted that, in a complementary study, microen-

capsulated furfural was rapidly and completely released in an aqueous environment and therefore considered that this formulation was suitable for a feeding study. In the 13-week dietary study, minor hepatocellular alterations were observed in males, but not in females, at doses of 82 and 160 mg/kg of body weight per day. While these changes might be judged not to be adverse, the Committee took a conservative view, and considered the NOEL to be 53 mg/kg of body weight per day, at which dose there was no evidence of hepatic alterations. This result contrasts with those of the previous studies in rats, in which furfural was administered in corn oil by gavage. The Committee considered the NOEL obtained in the 13-week study to be valid because: (i) dietary administration is more appropriate than administration by gavage for compounds normally consumed in the diet; (ii) the peak tissue concentrations observed after administration of bolus doses by gavage are much higher than those seen after administration in the diet; (iii) microencapsulation prevents loss due to volatilization of compounds such as furfural; (iv) microencapsulated furfural is rapidly released in an aqueous environment; and (v) corn oil is known to produce morphological changes in the livers of mice and rats when administered by gavage over a long period.

The estimated daily intake of furfural from its use as a flavouring agent was determined from "poundage" data provided by the flavour industry (see page 22). On the basis of these data, the estimated daily intake was 9 μg/kg of body weight in Europe and 8 μg/kg of body weight in the USA. The Committee was aware that intake of furfural from its use as a flavouring agent accounts for only a minor fraction of the total dietary intake of this substance.

The metabolism of furfuryl alcohol, furfural and 10 derivatives of furfuryl alcohol, furfural and furoic acid was considered by the Committee at its present meeting as part of its evaluation of this group of flavouring agents (see section 4.2). The derivatives considered were furfuryl acetate, furfuryl propionate, furfuryl pentanoate, furfuryl octanoate, furfuryl 3-methylbutanoate, methyl 2-furoate, propyl 2-furoate, amyl 2-furoate, hexyl 2-furoate and octyl 2-furoate. Furfuryl alcohol, furfural and these derivatives are all metabolized to the same metabolite, furoic acid. Accordingly, the Committee decided to establish a group ADI of 0–0.5 mg/kg of body weight for furfural, furfuryl alcohol and these derivatives, based on the NOEL of 53 mg/kg of body weight per day in the 13-week study on furfural in rats and a safety factor of 100.

An addendum to the toxicological monograph was prepared. The specifications for furfural were revised (see section 7.2.3).

3.1.2 *Paprika oleoresin*

Paprika oleoresin was evaluated by the Committee at its fourteenth meeting (Annex 1, reference *22*), when no ADI was established because it was recognized that use of this material as a spice was self-limiting for technological and organoleptic reasons. At its Thirty-second Session (*2*), the Codex Committee on Food Additives and Contaminants requested clarification of this evaluation from the Committee. At its present meeting, the Committee did not evaluate the available data on paprika oleoresin, but reviewed the previous evaluation of this substance, which stated that "oleoresins of paprika ... are derived from a widely consumed natural foodstuff, and there were no data indicative of a toxic hazard. The use of the oleoresins as a spice was self-limiting and obviates the need for an ADI." At its present meeting, the Committee interpreted this statement to mean that the use of paprika oleoresin as a spice is acceptable. It was aware, however, that paprika oleoresin is also used as a food colour and drew attention to the fact that it has not been evaluated for this use.

A toxicological monograph was not prepared. The existing specifications were maintained.

3.2 Food colours

3.2.1 *Caramel colour II*

Caramel colour II (caustic sulfite caramel) differs from the other three classes of caramel colour (caramel colour I — plain caramel or caustic caramel; caramel colour III — ammonia caramel; caramel colour IV — sulfite ammonia caramel) in that it is manufactured using sulfite compounds rather than ammonium compounds. The processes used in the production of each of the four classes of caramel colour and their synonyms are described in the toxicological monograph prepared by the Committee at its twenty-ninth meeting (Annex 1, reference *72*).

The Committee was informed that caramel colour II is manufactured only in France and the USA. The volume of production of this substance represents less than 1% of the total volume of production of caramel colours. Caramel colour II is used mainly in distilled spirits (e.g. rum, whisky and brandy) and dietary intake of this compound depends primarily on the level of consumption of these alcoholic beverages. Caramel colour II may also be used in herbal infusions, extracts of meat and fish, coffee and vanilla, salted meats, sauces, bouillons, soups and tea beverages. The estimated dietary intake of caramel colour II in the USA, based on production data, is approximately 0.034 mg/kg of body weight per day. If it is assumed

that all the caramel colour II produced in the USA is consumed in distilled spirits, the intake would be 2.2 mg/kg of body weight per day for adult consumers of distilled spirits. The estimated dietary intake of caramel colour II in Australia, based on the average consumption of distilled spirits recorded in the 1995 National Nutrition Survey and on maximum levels of use of this colour, is 0.28 mg/kg of body weight per day. For consumers of distilled spirits at the 95th percentile of consumption, the estimated dietary intake is 0.91 mg/kg of body weight per day.

Caramel colours were evaluated by the Committee at its thirteenth, fifteenth and twenty-ninth meetings (Annex 1, references *19*, *26* and *70*). When evaluating the safety of caramel colours produced by the ammonium sulfite process at its twenty-fourth meeting (Annex 1, reference *53*), the Committee noted that no ADI had been allocated to caustic sulfite caramel colour (subsequently named "caramel colour II" at the twenty-ninth meeting). At its twenty-ninth meeting, the Committee concluded that caramel colour II is sufficiently different from the other classes of caramel colours to warrant a separate evaluation but that there were insufficient data to do so. No ADI was established.

The data summarized below were included in the toxicological monograph prepared by the Committee at its twenty-ninth meeting (Annex 1, reference *72*). The existing database consists of the results of a 90-day study in Fischer 344 rats given caramel colour II in their drinking-water to deliver doses of 4–16 g/kg of body weight per day and the results of several assays for genotoxicity. The principal observations in the toxicity study were: a dose-related decrease in body weight and reduced food consumption and fluid intake, mainly affecting the groups that received doses of 12 and 16 g/kg of body weight per day; slight, dose-related increases in absolute and relative kidney weights and full and empty caecum weights, with no evidence of significant histopathological changes; dose-related staining of the gastrointestinal tract and mesenteric lymph nodes, with deposits of yellow pigment observed microscopically in the caecal mucosa and mesenteric lymph nodes (only the highest-dose groups were examined). Negative results were obtained with caramel colour II in two assays for reverse mutation in *Salmonella typhimurium*, in an assay for chromosomal aberration in vitro, and in an assay for DNA repair in vitro. No new studies on caramel colour II were available for review by the Committee at its present meeting.

In reviewing the database on caramel colour II, the Committee concluded that the decreased body-weight gain and renal hypertrophy observed in rats in the 90-day study were the consequence of

the reduced consumption of food and fluids, which probably resulted from the treated drinking-water being unpalatable. The Committee considered that the pigmentation of mesenteric lymph nodes and enlargement of the caecum were not of toxicological significance and concluded that the NOEL was the highest dose tested, 16 g/kg of body weight per day.

The Committee established an ADI of 0–160 mg/kg of body weight per day for caramel colour II, based on the NOEL of 16 g/kg of body weight per day in the 90-day study in rats and a safety factor of 100.

A toxicological monograph was not prepared. A monograph summarizing the available data on intake was prepared. Caramel colour II is included in the existing specifications for caramel colours, which were revised with minor changes.

3.2.2 *Cochineal extract and carmines*

Cochineal extract is obtained from the dried bodies of female *Dactylopius coccus* Costa insects (cochineal). The extract is used directly in food and is also processed further to carmines. Specifications exist for cochineal extract and carmines, both of which contain carminic acid as the colouring principle. The Committee evaluated cochineal extract at its eighteenth and twenty-first meetings, but did not allocate an ADI at either meeting (Annex 1, references *35* and *44*). It evaluated carmines at its twenty-first, twenty-fifth and twenty-sixth meetings (Annex 1, references *44*, *56* and *59*). At its twenty-sixth meeting, the Committee allocated an ADI of 0–5 mg/kg of body weight for carmines, as ammonium carmine or the equivalent of calcium, potassium or sodium salts. At its present meeting, the Committee considered the potential allergenicity of cochineal extract, carmine and carminic acid (collectively referred to here as "cochineal colours") in response to a request from the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*4*). The ADI for carmines was not reconsidered and was retained at its present value.

At its fifty-third meeting (Annex 1, reference *143*), the Expert Committee considered the report of an ad hoc Panel on Food Allergens that had been convened to consider issues relating to the allergenicity of foodstuffs. The Panel had identified three criteria for adding foodstuffs to the list of common allergenic foods developed by the Codex Committee on Food Labelling, if found to be necessary. The Expert Committee, at its fifty-third meeting, concluded that these criteria form a suitable basis for addressing the allergenicity of food and food products. These criteria are as follows:

(i) the existence of a credible cause-and-effect relationship, based on a positive reaction to a double-blind placebo-controlled food challenge or unequivocal reports of a reaction with the typical features of a severe allergic or intolerance reaction;
(ii) the existence of reports of systemic reactions after exposure to the foodstuff; and
(iii) data on the prevalence of food allergies in children and adults, supported by appropriate clinical studies, in the general population of several countries; alternatively, data on the comparative prevalence of a specific food allergy in groups of patients in several countries could be used.

Adverse reactions to cochineal colours after occupational exposure, dermal contact or consumption of coloured food and drinks have been the subject of case reports. The reported effects were the consequence of allergic reactions, and the involvement of an immunologically mediated mechanism has been demonstrated. The nature of the adverse reactions, e.g. urticaria, rhinitis, diarrhoea and anaphylaxis, provides clear evidence that systemic reactions can follow exposure of a sensitized individual to cochineal colours. Some of the adverse reactions were severe and required emergency treatment. The weight of evidence suggests that proteins in the food colours are the allergenic species; however, the structures of the proteins and the role of protein-bound carminic acid in the allergic reaction are unknown. The Committee considered that the available data satisfied the first two criteria for the addition of a foodstuff to the Codex Committee's list of common allergenic foods.

The available data on allergic reactions to food and drinks containing cochineal colours are derived predominantly from case reports. Although tests on control groups of patients have been reported, in general these studies were not designed so as to allow estimation of the incidence or prevalence of allergy to cochineal colours in the general population. Additional data suggest that sensitization to cochineal colours is rare, but they did not allow estimation of even comparative prevalence rates between countries. The third criterion for the addition of a foodstuff to the Codex Committee's list of common allergenic foods was not therefore considered to be satisfied.

Cochineal colours are present in many foods and drinks. The quantity of the cochineal colours that provoked an adverse reaction in an individual was estimated in only one study. Because the occurrence and severity of an allergic reaction after ingestion of a specific amount of cochineal colours depends on the sensitivity of each atopic individual, the Committee concluded that estimates of the long-term

intake of these colours in a population were irrelevant to its deliberations.

The Committee concluded that cochineal extract, carmines, and, possibly, carminic acid in foods and beverages may initiate or provoke allergic reactions in some individuals. Because some of the adverse reactions are severe, it considered that appropriate information, for example noting the presence of cochineal colours in foods and beverages, should be provided to alert individuals who are allergic to these compounds.

An addendum to the toxicological monograph was prepared.

In response to a request from the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*4*), the Committee revised the specifications for cochineal extract to include a limit for residual ethanol. The Committee also reduced the limit on lead to 2 mg/kg, in line with its policy on lead and heavy metals. The Committee also revised the specifications for carmines by replacing the current limits for arsenic and heavy metals by a single limit for lead of 2 mg/kg.

3.3 Sweetening agents

3.3.1 *Aspartame–acesulfame salt*

Aspartame–acesulfame salt is intended for use as a replacement for aspartame and acesulfame potassium in applications where use of both substances is permitted. During manufacture, the potassium moiety of acesulfame potassium is replaced by aspartame to produce a salt composed of equimolar amounts of aspartame and acesulfame, in a 2:1 ratio by weight. The salt is more stable to decomposition under storage conditions or in powdered forms than is a simple mixture of aspartame and acesulfame potassium.

Aspartame and acesulfame potassium have both been evaluated previously by the Committee. Aspartame was evaluated at the twenty-fourth meeting (Annex 1, reference *53*), when the Committee allocated an ADI of 0–40 mg/kg of body weight. Acesulfame potassium was evaluated at the twenty-fifth, twenty-seventh and thirty-seventh meetings (Annex 1, references *56*, *62* and *94*). At the thirty-seventh meeting, the Committee established an ADI of 0–15 mg/kg of body weight, on the basis of a 2-year study in rats.

Data on the production of aspartame–acesulfame salt and on the properties that are relevant to an assessment of its safety were available. Aspartame–acesulfame salt dissociates rapidly and completely to its components in aqueous media or on contact with saliva or

gastric fluid, indicating that no new issues would be introduced into the evaluations of the safety of aspartame or acesulfame potassium. Consequently, the Committee concluded that the aspartame and acesulfame moieties of the salt would be covered by the ADIs for aspartame (0–40 mg/kg of body weight) and acesulfame potassium (0–15 mg/kg of body weight).

A toxicological monograph was not prepared. New specifications were prepared.

3.3.2 *D-Tagatose*

D-Tagatose is an epimer of D-fructose and is produced from D-galactose by isomerization under alkaline conditions in the presence of calcium. It is used as a sweetener, texturizer, stabilizer, humectant and formulation aid. D-Tagatose has not been evaluated previously by the Committee.

In a study in rats adapted to consumption of D-tagatose, 80–90% of an oral dose was absorbed.

The predicted daily intake of D-tagatose was determined on the basis of data on food consumption in the USA and the assumption that all foods in the categories being considered contain the additive at the maximum technological level. For the population of the USA, intake of this sugar from all proposed uses (except chewing-gum, dietary supplements and meal replacements) was predicted to be 9 g/day for consumers with mean intakes and 18 g/day for those with intakes at the 90th percentile. Intake from chewing-gum was predicted to be 4 g/day for consumers with mean intakes and 8 g/day for those with intakes at the 90th percentile. Similar results were obtained for the predicted intakes of young people aged 3–5 years, 6–12 years and 13–19 years. The estimated intakes of D-tagatose from dietary supplements and meal replacements were 3 g and 5 g per eating occasion, respectively. An analysis based on the same assumptions, combined with available data on food consumption from Australia and the European Union, showed that the predicted intake of D-tagatose would be similar in these regions.

D-Tagatose was tested in Sprague-Dawley rats in a series of short-term toxicity studies. The observed increases in liver weights and liver hypertrophy were found to be due, at least in part, to glycogen accumulation. The hepatic changes were partially reversed after exclusion of D-tagatose from the diet. Recovery from the induced liver hypertrophy took longer than recovery from glycogen accumulation. Data from short-term studies of the mechanism of glycogen accumulation suggest that the hepatic changes are due to

physiological changes in Sprague-Dawley rats and that Wistar rats are less sensitive to expression of these effects.

The precise metabolic pathway of D-tagatose that leads to gluconeogenesis has not been established. D-Tagatose is metabolized more slowly than fructose. A similar biochemical effect characterized by glycogen accumulation occurs in patients with hereditary fructose intolerance, and this reaction can increase the rates of purine breakdown and accumulation of uric acid. D-Tagatose is more effective than fructose in increasing the concentration of uric acid in serum.

In two studies of developmental toxicity in Sprague-Dawley rats, minimal effects were observed in dams, including reduced food consumption at doses greater than 12 g/kg of body weight per day and initial depression of weight gain, which returned to normal later in the study. A dose-related, statistically significant increase in liver weight was found, but histological examination of the livers revealed no abnormalities. No effects were found in either study on reproductive or developmental parameters.

The results of tests for genotoxicity in vitro and in vivo were consistently negative.

A number of studies of gastrointestinal effects have been conducted in healthy human volunteers and in patients with type 2 diabetes. Nausea and adverse gastrointestinal effects were reported in healthy adults given D-tagatose at high doses. Studies in which baseline serum concentrations of insulin and glucose were investigated showed no effect following administration of single or multiple doses, but a decreased glycaemic response was observed when D-tagatose was given before a glucose tolerance test.

Elevated serum uric acid concentrations were reported in three out of six studies in which this parameter was measured; in two of these studies, the values exceeded the normal range. In the three studies in which parameters indicative of liver function or hepatic changes were measured, no effects were observed.

On the basis of the available data, the Committee concluded that D-tagatose is not genotoxic, embryotoxic or teratogenic. The Committee noted that the increased liver weights and hepatocellular hypertrophy seen in Sprague-Dawley rats occurred concurrently with increased glycogen deposition; however, the reversal of increased glycogen storage after removal of D-tagatose from the feed occurred more rapidly than regression of the liver hypertrophy.

Although the gastrointestinal symptoms seen in adult humans with the expected daily intake of D-tagatose were minor, the Committee was concerned about the increased serum uric acid concentrations observed in a number of studies in humans following administration of either single or repeated doses of D-tagatose. Similar increases are seen with other sugars, such as fructose, but D-tagatose appears to be a more potent inducer of this effect. The Committee noted that the effect of D-tagatose has not been studied in people prone to high serum uric acid concentrations.

The Committee concluded that an ADI could not be allocated to D-tagatose because of concern about its potential to induce liver glycogen deposition and hypertrophy and to increase serum uric acid concentrations. Two studies in Sprague-Dawley and Wistar rats were submitted that might help to resolve the relevance of the induction of liver glycogen deposition and hypertrophy, but the reports were received in draft form and were not suitable for consideration at the present meeting. Before reviewing the compound again, the Committee would wish to evaluate the final reports of these studies and data to clarify the extent, mechanism and toxicological consequences of the increased serum uric acid concentrations observed in humans exposed to D-tagatose.

A toxicological monograph and new specifications were prepared.

3.4 Miscellaneous substances

3.4.1 *Benzoyl peroxide*

Benzoyl peroxide was evaluated for use as a bleaching agent in flour by the Committee at its seventh meeting (Annex 1, reference *7*), when it concluded that treatment of flour at concentrations of up to 40 mg/kg was acceptable. The Codex Committee's draft General Standard for Food Additives proposes a maximum concentration of 300 mg/kg for treatment of flours and starches, 1000 mg/kg for total ripened cheese and concentrations consistent with good manufacturing practice for whey and whey products. The present evaluation was conducted in response to a request by the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*4*) for the Expert Committee to evaluate the higher levels of use of benzoyl peroxide recommended for flour and starches and its additional uses in milk products.

At its seventh meeting, the Committee noted that when benzoyl peroxide is used as a bleaching agent in flour, it reacts with the oxidizable substances that are present and is converted to benzoic acid; any remaining traces of benzoyl peroxide are reduced still

further during baking due to reduction to benzoic acid. On this basis, the issues requiring consideration were the acceptability of small amounts of benzoic acid in bread, the possible effects of oxidative treatment on the nutritional value of flour, and the possible formation of harmful substances or anti-metabolites. A group ADI of 0–5 mg/kg of body weight for benzoic acid and its calcium, potassium and sodium salts, benzyl acetate, benzyl alcohol, benzaldehyde and benzyl benzoate was maintained at the forty-sixth meeting of the Committee (Annex 1, reference *122*).

The intake of benzoic acid derived from benzoyl peroxide was estimated on the basis of the maximum levels of use of benzoyl peroxide proposed in the draft General Standard for Food Additives and data on consumption of flours, starches and cheese products in the WHO Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food) regional diets, derived from food balance sheets. The mean intake of benzoic acid arising from the use of benzoyl peroxide was estimated to range from 20 to 120 mg/day. These values are likely to be overestimates.

The Committee noted that the intake of benzoic acid from foodstuffs treated with benzoyl peroxide should be considered together with intake from other dietary sources of benzoates in the group ADI of 0–5 mg/kg of body weight. When the Committee evaluated the intake of benzoates at its fifty-first meeting (Annex 1, reference *137*), it noted that the intake of some consumers may exceed the ADI, but the available data were insufficient to estimate the number of such consumers or the magnitude and duration of intakes above the ADI.

The Committee was informed that the Codex Committee on Food Additives and Contaminants had revised the maximum levels of benzoates proposed in the draft General Standard for Food Additives on the basis of the Expert Committee's evaluation of these substances at its fifty-first meeting. The Committee noted that the intake of benzoates derived from benzoyl peroxide should be included in future assessments of benzoate intake, although foodstuffs treated with benzoyl peroxide would not be labelled to indicate the presence of benzoate residues. In addition, the Committee noted that ingestion of benzoic acid has been associated with intolerance reactions.

At its present meeting, the Committee noted the importance of assessing the nutritional and toxicological implications of treatment of foods with benzoyl peroxide with respect to potential effects on

proteins, vitamins, antioxidants and physiologically important lipids. No information was available to the Committee that would assist such an assessment.

The Committee concluded that, in the absence of information about the nutritional and toxicological consequences of the proposed food uses of benzoyl peroxide and information on total benzoic acid intake in the context of all food additive uses, no conclusion could be drawn about the acceptability of the proposed uses.

A toxicological monograph was not prepared. The existing specifications for benzoyl peroxide were revised.

3.4.2 *Nitrous oxide*

Nitrous oxide was considered by the Committee at its twenty-second and twenty-ninth meetings (Annex 1, references *47* and *70*) for use as a propellant for food in aerosol containers. At its twenty-ninth meeting, the Committee concluded that use of nitrous oxide as a propellant for food was acceptable. An ADI was not established.

The present evaluation was conducted in response to a request by the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*4*) for the Expert Committee to evaluate the safety of the additional use of nitrous oxide as a packaging gas in modified atmospheric packaging.

No information on intake of nitrous oxide from its use as a packaging gas was available, although intake from this use is likely to be low. The Committee concluded that the use of nitrous oxide as a packaging gas could not be evaluated until such information became available.

A toxicological monograph was not prepared. The existing specifications were revised.

3.4.3 *Stearyl tartrate*

Stearyl tartrate was evaluated by the Committee at its ninth meeting (Annex 1, reference *11*) for use in strengthening dough before bread baking. At that time, the Committee considered that use of stearyl tartrate at concentrations of up to 500 mg/kg of flour was acceptable on the basis of data on its hydrolysis, metabolism and toxicity in experimental animals.

As higher levels of use and new uses were included in the draft General Standard for Food Additives, the Expert Committee was asked by the Codex Committee on Food Additives and Contaminants

(*4*) to re-evaluate stearyl tartrate at its present meeting. As no new data were submitted or were found in an extensive search of the literature, the Committee referred to the data reviewed at its ninth meeting (Annex 1, reference *11*). However, it was noted that the references on which the corresponding monograph was based were no longer available. The Committee concluded that either the original toxicological and metabolic studies should be made available or that new studies demonstrating hydrolysis in vivo should be submitted before the substance could be re-evaluated. The Committee also requires data on the intake of stearyl tartrate from all existing and proposed uses. The Committee noted that an ADI of 0–30 mg/kg of body weight had previously been established for L(+)-tartaric acid at its seventeenth meeting (Annex 1, reference *32*) and that the intake of stearyl tartrate relative to this ADI should be considered.

A toxicological monograph was not prepared. The existing specifications were revised.

3.4.4 *Trehalose*

Trehalose is a disaccharide that occurs naturally in insects, plants, fungi and bacteria. The major dietary source of naturally occurring trehalose is mushrooms. The commercial product is the dihydrate and is produced from liquefied starch by a multistep enzymatic process. Trehalose is used as a texturizer, stabilizer, humectant and sweetener in bakery goods, beverages, confectionery, fruit jam, breakfast cereals, rice and noodles. Trehalose has not previously been considered by the Committee.

The daily intake of trehalose was predicted on the basis of conservative assumptions, by combining the highest proposed levels of use. For adults in the USA, the mean predicted intake from all proposed uses, except chewing-gum, was 7 g/day, and that of consumers with intakes at the 90th percentile was 16 g/day. The mean intake per eating occasion ranged from 4 g to 10 g, while intake at the 90th percentile ranged from 8 g to 19 g per eating occasion. Consumers with mean intakes of chewing-gum and those with intakes at the 90th percentile would ingest 0.4 g/day and 0.8 g/day of trehalose, respectively. For adults in Australia, the predicted mean intake of trehalose (including from chewing-gum) ranged from 6 g/day to 10 g/day. However, the data from both Australia and the USA were based on short-term dietary recall, which tends to result in overestimates of habitual intake.

Trehalose is hydrolysed to glucose by the enzyme trehalase in the intestinal mucosa, and the small amount of intact trehalose that may

be absorbed is hydrolysed by trehalase in the plasma, liver or kidney. Trehalase deficiency has been identified in some individuals, but its prevalence appears to be very low in most populations, with the possible exception of that of Greenland, where an 8% prevalence has been recorded.

Studies in which trehalose was administered in the diet have been performed in mice and dogs. In a 3-month study in mice, slight, sporadic changes in clinical biochemistry were seen in males at the highest dose tested, 7.3 g/kg of body weight per day, but there was no evidence of pathological alterations. In a 14-day study in dogs, no clinical or morphological evidence of toxicity was seen at 5 g/kg of body weight per day, which was the highest dose tested.

In a two-generation study in rats, no evidence was found of an effect on reproduction. Similarly, in studies of developmental toxicity in rats and rabbits, there was no evidence of teratogenicity. The results of assays for genotoxicity were negative. No long-term studies were available, but these were considered unnecessary since trehalose is rapidly metabolized to glucose at the levels of intake predicted from the proposed uses. The toxicological data available on the enzymes used in the preparation of trehalose, some of which have been evaluated by the Committee previously, did not raise any concern.

Studies in humans indicate that trehalose is well tolerated. Increased frequencies of malabsorption and gastrointestinal symptoms were noted in individuals consuming single doses of 20 g or more. In the limited data on individuals with known or suspected trehalase deficiency, the only effects seen were the gastrointestinal effects expected of an undigested disaccharide.

On the basis of the available information, the Committee established an ADI "not specified"[1] for trehalose.

A toxicological monograph and new specifications were prepared.

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

4. Flavouring agents evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

Four groups of flavouring agents were evaluated using the Procedure for the Safety Evaluation of Flavouring Agents, as outlined in Fig. 1 (Annex 1, references *116*, *122*, *131* and *137*).

The Committee noted that, in applying the Procedure, a flavouring agent is first assigned to a structural class, as identified at the forty-sixth meeting (Annex 1, reference *122*). The structural classes are as follows:

- Class I. Substances that have simple chemical structures and efficient modes of metabolism which would suggest a low order of toxicity when given by the oral route.
- Class II. Substances that have structural features that are less innocuous than those of substances in class I, but are not suggestive of toxicity. Substances in this class may contain reactive functional groups.
- Class III. Substances that have structural features that permit no strong initial presumption of safety or may even suggest significant toxicity.

A key element of the Procedure involves determining whether a flavouring agent and the product(s) of its metabolism are innocuous and/or endogenous substances. For the purpose of the evaluations, the Committee used the following definitions, adapted from the report of its forty-sixth meeting:

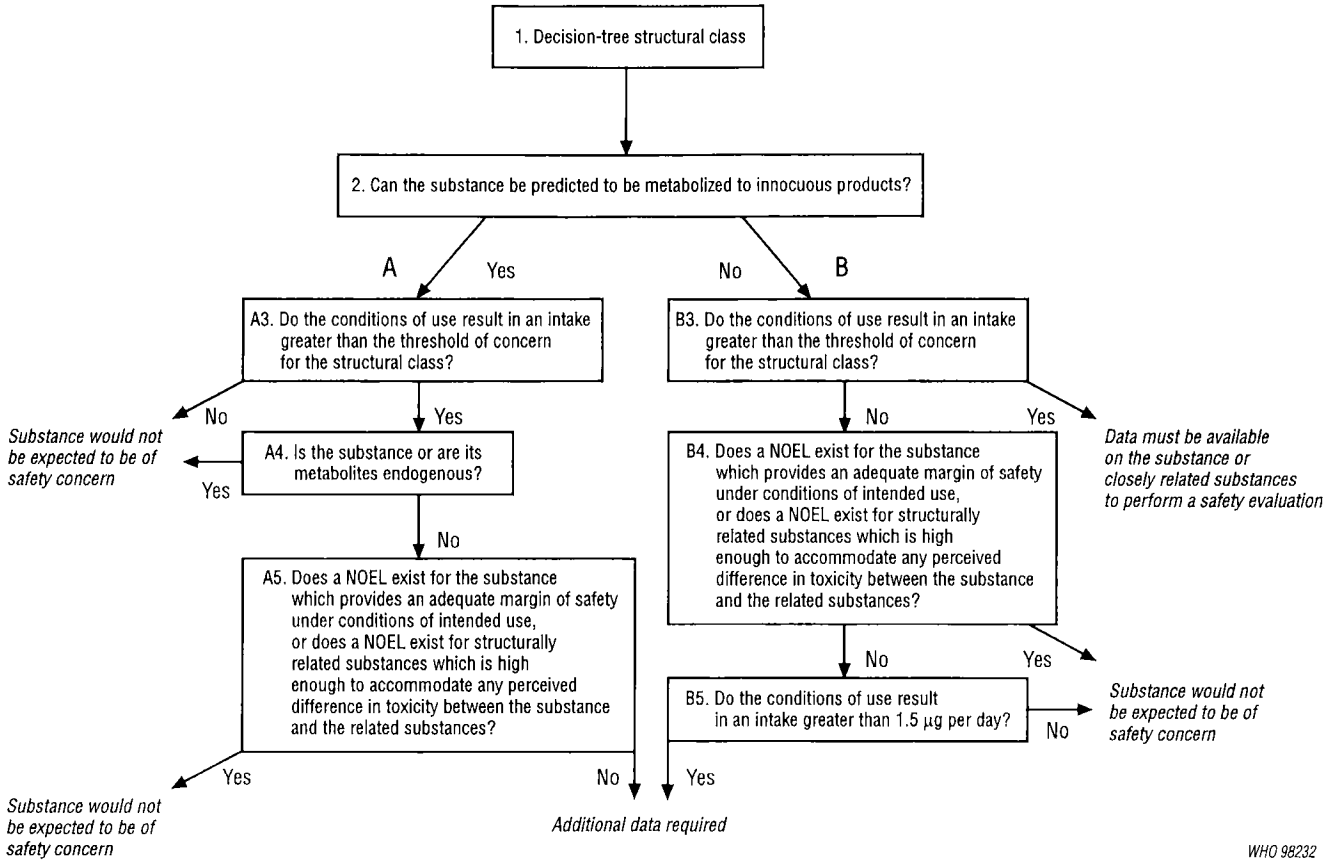
Innocuous metabolic products are defined as products that are known or readily predicted to be harmless to humans at the estimated intake of the flavouring agent.

Endogenous substances are intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included. The estimated intake of a flavouring agent that is, or is metabolized to, an endogenous substance should be judged not to give rise to perturbations outside the physiological range.

Intake data

Estimates of the intake of flavouring agents by populations typically involve the acquisition of data on the amounts used in food. These data were derived from surveys in Europe and the USA. In Europe,

Figure 1
Procedure for the Safety Evaluation of Flavouring Agents



a survey was conducted in 1995 by the International Organization of the Flavour Industry, in which flavour manufacturers reported the total amount of each flavouring agent incorporated into food sold in the European Union during the previous year. Manufacturers were requested to exclude use of flavouring agents in pharmaceutical, tobacco or cosmetic products. In the USA, a series of surveys was conducted between 1970 and 1987 by the National Research Council of the National Academy of Sciences (under contract to the Food and Drug Administration) in which information was obtained from ingredient manufacturers and food processors on the amount of each substance destined for addition to the food supply and on the usual and maximal levels at which each substance was added to a number of broad food categories.

In using the data from these surveys to estimate intakes of flavouring agents, the Committee assumed that only 60% of the total amount used in Europe and only 80% of that used in the USA is reported, and that the total amount used in food is consumed by only 10% of the population.

$$\text{Intake (µg/person per day)} = \frac{\text{Annual volume of production (kg)} \times 10^9 \text{(µg/kg)}}{\text{Population of consumers} \times 0.6 \text{ (or } 0.8) \times 365 \text{ days}}$$

The population of consumers was assumed to be 32×10^6 in Europe and 26×10^6 in the USA.

4.1 Cinnamyl alcohol and related flavouring agents

The Committee evaluated a group of flavouring agents that included cinnamyl alcohol (No. 647), cinnamaldehyde (No. 656), cinnamic acid (No. 657) and 52 structurally related substances (Table 1) using the Procedure for the Safety Assessment of Flavouring Agents (see Fig. 1).

One member of this group, allyl cinnamate (No. 19), had been evaluated previously by the Committee at its forty-sixth meeting in a separate group of allyl ester flavouring agents examined by the Procedure (Annex 1, reference *122*).

Cinnamaldehyde (No. 656) was evaluated by the Committee at its eleventh meeting (Annex 1, reference *14*), when it established a conditional ADI of 0–1.25 mg/kg of body weight. At its twenty-third meeting, the Committee converted the previous conditional ADI to a temporary ADI of 0–0.7 mg/kg of body weight (Annex 1, reference *50*), which was extended at its twenty-fifth and twenty-eighth meetings (Annex 1, references *56* and *66*). At its thirty-fifth meeting,

Table 1

Summary of the results of safety evaluations of cinnamyl alcohol and 54 related flavouring agents[a]

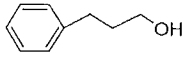
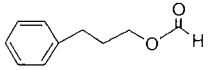
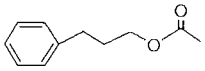
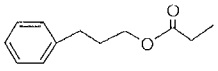
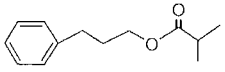
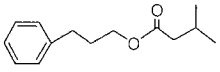
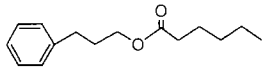
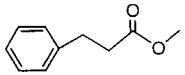
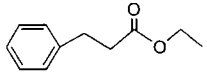
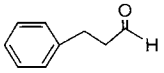
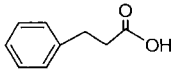
Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
Structural class I							
3-Phenyl-1-propanol (3-phenylpropanol)	636	122-97-4 	No Europe: 60 USA: 31	NR	NR	See note 1	No safety concern
3-Phenylpropyl formate (benzenepropanol formate)	637	104-64-3 	No Europe: ND USA: 0.8	NR	NR	See note 2	
3-Phenylpropyl acetate (benzenepropanol acetate)	638	122-72-5 	No Europe: 41 USA: 9	NR	NR	See note 2	
3-Phenylpropyl propionate (benzenepropanol propionate)	639	122-74-7 	No Europe: 0.2 USA: 0.3	NR	NR	See note 2	
3-Phenylpropyl isobutyrate	640	103-58-2 	No Europe: 4 USA: 16	NR	NR	See note 2	
3-Phenylpropyl isovalerate	641	5452-07-3 	No Europe: 0.01 USA: 0.1	NR	NR	See note 2	

Table 1 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
3-Phenylpropyl hexanoate	642	6281-40-9 	No Europe: ND USA: 0.4	NR	NR	See note 2	No safety concern
Methyl 3-phenylpropionate	643	103-25-3 	No Europe: ND USA: 3	NR	NR	See note 2	
Ethyl 3-phenylpropionate	644	2021-28-5 	No Europe: 1 USA: 0.07	NR	NR	See note 2	
3-Phenylpropionaldehyde (benzenepropanal)	645	104-53-0 	No Europe: 19 USA: 19	NR	NR	See note 1	
3-Phenylpropionic acid (benzenepropanoic acid)	646	501-52-0 	No Europe: 23 USA: 0.5	NR	NR	See note 3	

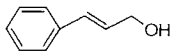
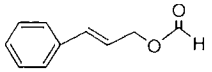
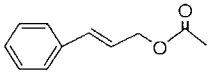
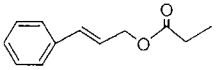
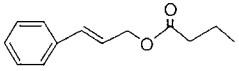
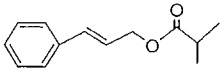
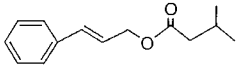
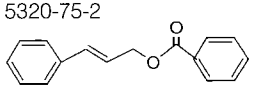
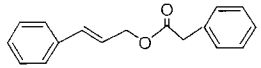
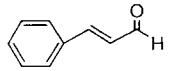
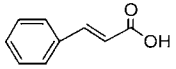
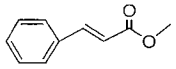
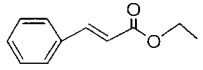
Cinnamyl alcohol	647	104-54-1 	Yes Europe: 1800 USA: 1900	No	Yes[d]	See note 4	No safety concern
Cinnamyl formate	649	104-65-4 	No Europe: 2 USA: 17	NR	NR	See note 5	
Cinnamyl acetate	650	103-54-8 	No Europe: 210 USA: 300	NR	NR	See note 5	
Cinnamyl propionate	651	103-56-0 	No Europe: 4 USA: 25	NR	NR	See note 5	
Cinnamyl butyrate	652	103-61-7 	No Europe: 3 USA: 2	NR	NR	See note 5	
Cinnamyl isobutyrate	653	103-59-3 	No Europe: 13 USA: 22	NR	NR	See note 5	
Cinnamyl isovalerate	654	140-27-2 	No Europe: 5 USA: 8	NR	NR	See note 5	

Table 1 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
Cinnamyl benzoate	760	5320-75-2 	No Europe: ND USA: 1	NR	NR	See note 6	No safety concern
Cinnamyl phenylacetate	655	7492-65-1 	No Europe: 0.003 USA: 1	NR	NR	See note 7	
Cinnamaldehyde (3-phenyl-2-propenal)	656	104-55-2 	Yes Europe: 2500 USA: 59 000	No	Yes[e]	See note 4	
Cinnamic acid (3-phenyl-2-propenoic acid)	657	621-82-9 	No Europe: 32 USA: 44	NR	NR	See note 8	
Methyl cinnamate	658	103-26-4 	Yes Europe: 2800 USA: 830	No	Yes[f]	See note 9	
Ethyl cinnamate	659	103-36-6 	No Europe: 100 USA: 70	NR	NR	See note 9	

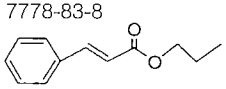
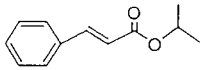
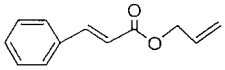
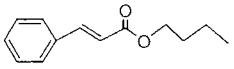
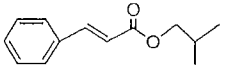
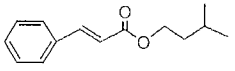
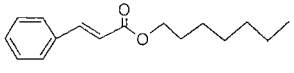
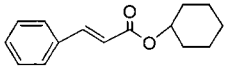
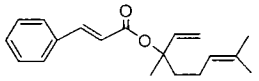
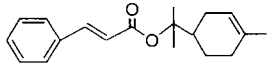
Propyl cinnamate	660	7778-83-8 	No Europe: 0.4 USA: 4	NR	NR	See note 9	No safety concern
Isopropyl cinnamate	661	7780-06-5 	No Europe: 19 USA: 3	NR	NR	See note 9	
Allyl cinnamate (3-propenyl 3-phenyl-2-propenoate)	19	1866-31-5 	No Europe: 5 USA: 0.3	NR	NR	See note 9	
Butyl cinnamate	663	538-65-8 	No Europe: 0.4 USA: 0.2	NR	NR	See note 9	
Isobutyl cinnamate	664	122-67-8 	No Europe: 1 USA: 3	NR	NR	See note 9	
Isoamyl cinnamate (isopentyl cinnamate)	665	7779-65-9 	No Europe: 8 USA: 6	NR	NR	See note 9	
Heptyl cinnamate	666	10032-08-3 	No Europe: 2 USA: 52	NR	NR	See note 9	

Table 1 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
Cyclohexyl cinnamate	667	7779-17-1 	No Europe: 0.4 USA: 0.04	NR	NR	Cyclohexyl cinnamate is hydrolysed to cinnamic acid (see note 8) and cyclohexanol. Cyclohexanol is mainly conjugated with glucuronic acid and excreted	No safety concern
Linalyl cinnamate	668	78-37-5 	No Europe: 7 USA: 3	NR	NR	Linalyl cinnamate is hydrolysed to cinnamic acid (see note 8) and linalool. Linalool undergoes ω- and ω-1-oxidation to yield polar metabolites which are excreted	
Terpinyl cinnamate ((*Z*)-1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl cinnamate)	669	10024-56-3 	No Europe: 0.01 USA: 0.5	NR	NR	Terpinyl cinnamate is hydrolysed to cinnamic acid (see note 8) and terpineol. Terpineol undergoes ω- and ω-1-oxidation to yield polar metabolites which are excreted	

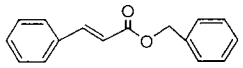
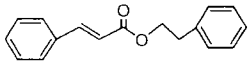
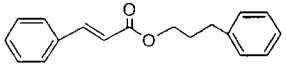
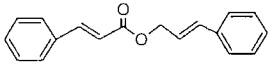
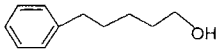
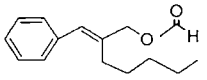
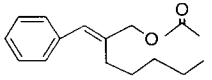
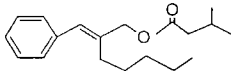
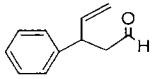
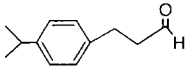
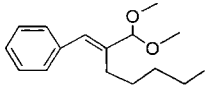
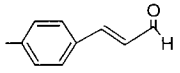
Benzyl cinnamate	670	103-41-3 	No Europe: 44 USA: 69	NR	NR	Benzyl cinnamate is hydrolysed to cinnamic acid (see note 8) and benzyl alcohol. Benzyl alcohol is oxidized to benzoic acid and excreted as hippuric acid	No safety concern
Phenethyl cinnamate	671	103-53-7 	No Europe: 6 USA: 50	NR	NR	Phenethyl cinnamate is hydrolysed to cinnamic acid (see note 8) and phenethyl alcohol. Phenethyl alcohol is oxidized to phenylacetic acid and excreted as the glucuronic acid conjugate	
3-Phenylpropyl cinnamate	672	122-68-9 	No Europe: 0.6 USA: 37	NR	NR	See notes 1 and 8	
Cinnamyl cinnamate	673	122-69-0 	No Europe: 2 USA: 36	NR	NR	See notes 4 and 8	
5-Phenylpentanol (benzenepentan-1-ol)	675	10521-91-2 	No Europe: ND USA: 0.1	NR	NR	See note 1	
α-Amylcinnamyl formate (2-(phenylmethylene)heptyl formate)	676	7493-79-0 	No Europe: 1.4 USA: 0.5	NR	NR	See note 10	

Table 1 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
α-Amylcinnamyl acetate (2-(phenylmethylene)heptyl acetate)	677	7493-78-9 	No Europe: 3 USA: 260	NR	NR	See note 10	No safety concern
α-Amylcinnamyl isovalerate (2-(phenylmethylene)heptyl isovalerate)	678	7493-80-3 	No Europe: 0.01 USA: 0.5	NR	NR	See note 10	
3-Phenyl-4-pentenal (3-phenylpent-4-enal)	679	939-21-9 	No Europe: 1 USA: 2	NR	NR	See note 11	
3-(*p*-Isopropylphenyl) propionaldehyde (3-(*p*-cumenyl)propion-aldehyde)	680	7775-00-0 	No Europe: ND USA: 0.1	NR	NR	See note 1	
α-Amylcinnamaldehyde dimethyl acetal ((2-(dimethoxymethyl)-1-heptenyl)benzene)	681	91-87-2 	No Europe: 0.01 USA: 0.007	NR	NR	See note 10	
p-Methylcinnamaldehyde (3-(4-methylphenyl)-2-propenal)	682	1504-75-2 	No Europe: 0.01 USA: 0.9	NR	NR	See note 4	

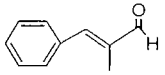
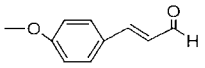
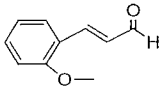
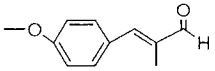
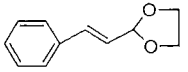
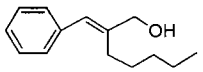
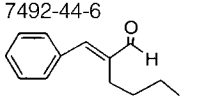
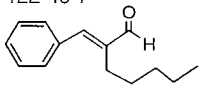
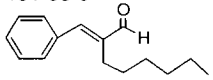
α-Methylcinnamaldehyde	683	101-39-3 	No Europe: 3 USA: 390	NR	NR	See note 4	No safety concern
p-Methoxycinnamaldehyde	687	1963-36-6 	No Europe: 0.04 USA: 0.01	NR	NR	See note 4	
o-Methoxycinnamaldehyde	688	1504-74-1 	No Europe: 0.6 USA: 71	NR	NR	*o*-Methoxycinnamaldehyde is oxidized to the corresponding acid, conjugated with glycine, and excreted. Alternatively, the acid may undergo β-oxidation to yield the β-hydroxycarboxylic acid derivative, which is also excreted	
p-Methoxy-α-methylcinnamaldehyde (4′-methoxy-2-methylcinnamaldehyde)	689	65405-67-6 	No Europe: 0.3 USA: 0.05	NR	NR	See note 4	
Structural class II							
Cinnamaldehyde ethylene glycol acetal (2-styryl-1,3-dioxolane)	648	5660-60-6 	Yes Europe: 690 USA: 0.007	No	Yes[9]	Hydrolysed to the corresponding alcohol and aldehyde	

Table 1 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Comments	Conclusion based on current intake
α-Amylcinnamyl alcohol (2-pentyl-3-phenylprop-2-en-1-ol)	674	101-85-9 	No Europe: 4 USA: 1	NR	NR	α-Amylcinnamyl alcohol is oxidized to the corresponding aldehyde, which is further oxidized to α-amylcinnamic acid and excreted	No safety concern
α-Butylcinnamaldehyde	684	7492-44-6 	No Europe: 0.01 USA: 0.07	NR	NR	See note 11	
α-Amylcinnamaldehyde (α-pentylcinnamaldehyde)	685	122-40-7 	No Europe: 25 USA: 23	NR	NR	See note 11	
α-Hexylcinnamaldehyde	686	101-86-0 	No Europe: 87 USA: 11	NR	NR	See note 11	

CAS: Chemical Abstracts Service; ND: no intake data reported; NR: not required for evaluation because consumption of the substance was determined to be of no safety concern at step A3 of the Procedure.

[a] *Step 2*: All of the substances in this group are expected to be metabolized to innocuous products.

[b] The names of the flavouring agents are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where flavouring agents were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The thresholds for human intake for structural classes I and II are 1800 µg per day and 540 µg per day, respectively. All intake values are expressed in µg per day.

[d] The NOEL of 54 mg/kg of body weight per day in a 4-month toxicity study in rats is >1000 times the estimated intake of cinnamyl alcohol when used as a flavouring agent.

[e] The NOEL of 620 mg/kg of body weight per day in a 13-week toxicity study in rats is >600 times the estimated intake of cinnamaldehyde when used as a flavouring agent.

[f] The NOELs of 54 mg/kg of body weight per day for related substance No. 647 and 80 mg/kg of body weight per day for related substance No. 659 are >1000 times the estimated intake of methyl cinnamate when used as a flavouring agent.

[g] The NOEL of 620 mg/kg of body weight per day for related substance No. 656 is >10 000 times the estimated intake of cinnamaldehyde ethylene glycol acetal when used as a flavouring agent.

Notes to Table 1

1. Oxidized to yield the corresponding acid, which undergoes further β-oxidation of the side-chains and cleavage to yield the benzoic acid derivative. It then conjugates with glycine and/or glucuronic acid, and is excreted in the urine.
2. Hydrolysed to the corresponding acid and alcohol. The acid is completely oxidized and the alcohol, 3-phenyl-1-propanol, is further metabolized and excreted (see note 1).
3. Undergoes β-oxidation of the side-chains and cleavage to yield the corresponding benzoic acid derivative. It then conjugates with glycine and/or glucuronic acid and is excreted in the urine.
4. Oxidized to cinnamic acid (or its corresponding derivative), which is further oxidized to benzoic acid (or its corresponding derivative). The latter substance is excreted as hippuric acid (or its corresponding derivative).
5. Hydrolysed to cinnamyl alcohol and the corresponding carboxylic acid. Cinnamyl alcohol is oxidized and excreted (see note 4); the carboxylic acid is either completely oxidized or conjugated and excreted primarily in the urine.
6. Hydrolysed to cinnamyl alcohol and benzoic acid. Cinnamyl alcohol is oxidized to cinnamic acid, which is further oxidized to benzoic acid (see note 4).
7. Hydrolysed to cinnamyl alcohol and phenylacetic acid. Cinnamyl alcohol is oxidized to cinnamic acid, which is further oxidized to benzoic acid (see note 4). Phenylacetic acid is excreted as the glucuronic acid conjugate.
8. Undergoes β-oxidation and is excreted as hippuric acid.
9. Rapidly hydrolysed to cinnamic acid (see note 8) and the corresponding alcohol. The corresponding alcohol is completely oxidized.
10. Hydrolysed to α-amylcinnamyl alcohol (No. 674) and the corresponding acid, which is excreted. α-Amylcinnamyl alcohol is oxidized to α-amylcinnamaldehyde, which is further oxidized to α-amylcinnamic acid and excreted.
11. Oxidized to the corresponding acid and excreted.

the Committee did not extend the temporary ADI (Annex 1, reference *88*) because the data that were required were not available.

At its twenty-fifth meeting, the Committee concluded that cinnamyl anthranilate should not be used as a food additive (Annex 1, reference *56*). This substance is structurally related to the group of flavouring agents considered here, but differs in that it is hydrolysed to cinnamyl alcohol and anthranilic acid only slowly, resulting in systemic intake of the intact ester. In contrast, cinnamyl alcohol and related flavouring agents undergo rapid hydrolysis.

Twenty-two of the 55 flavouring agents in this group are natural components of foods. Concentrations of cinnamaldehyde of up to 750 g/kg have been detected in oils from natural sources, such as the inner bark and leaves of *Cinnamomum* trees that are used to make cinnamon. However, intake of these 22 agents is primarily via food additives rather than from natural sources.

4.1.1 *Estimated daily per capita intake*

The total annual volume of production of the 55 cinnamyl compounds in this group destined for use as flavouring agents is approximately 60 tonnes in Europe and 480 tonnes in the USA. Approximately 30% of the total annual volume of production in Europe and over 93% of that in the USA is accounted for by cinnamaldehyde (No. 656), while 54% of the total annual volume of production in Europe is accounted for by cinnamyl alcohol (No. 647) and methyl cinnamate (No. 658). The estimated daily per capita intakes in Europe are 2.5 mg of cinnamaldehyde (No. 656), 1.8 mg of cinnamyl alcohol (No. 647) and 2.8 mg of methyl cinnamate (No. 658). The estimated daily per capita intakes in the USA are 59 mg of cinnamaldehyde (No. 656), 1.9 mg of cinnamyl alcohol (No. 647) and 0.83 mg of methyl cinnamate (No. 658). The estimated daily per capita intakes of all the other flavouring agents in the group are in the range 0.003–690 µg, with most of the values being at the low end of this range. The daily per capita intake of each substance in Europe and the USA is reported in Table 1.

4.1.2 *Absorption, metabolism and elimination*

Cinnamyl alcohol (No. 647), cinnamaldehyde (No. 656) and its *p*- and *o*-methoxy derivatives (Nos 687 and 688), cinnamic acid (No. 657) and its corresponding methyl ester (No. 658), and the saturated analogue 3-phenylpropionic acid (No. 646) have all been shown to be rapidly absorbed from the gut, metabolized and excreted primarily in the urine and to a minor extent in the faeces.

Esters of cinnamic acid and structurally related aromatic esters have been shown to be hydrolysed rapidly to the component acid and alcohol. The aromatic primary alcohols and aldehydes in this group and those formed by the hydrolysis of esters and acetals are readily oxidized to cinnamic acid or one of its structurally related carboxylic acids. In animals, most carboxylic acids, including cinnamic acid, are converted to acyl coenzyme A esters. Cinnamoyl coenzyme A undergoes either conjugation with glycine or β-oxidation, eventually leading to the formation of benzoyl coenzyme A. This in turn is either conjugated with glycine, yielding hippuric acid, or hydrolysed to yield free benzoic acid, which is then excreted.

Cinnamyl derivatives containing α-methyl substituents, such as α-methylcinnamaldehyde (No. 683), are extensively metabolized by β-oxidation and cleavage to yield mainly the corresponding hippuric acid derivative. Because *o*-oxygenated ring substituents (e.g. *o*-methoxycinnamaldehyde, No. 688) selectively inhibit oxidation of coenzyme A esters of β-hydroxycarboxylic acid derivatives via the β-oxidation pathway, these derivatives are excreted as glycine conjugates. In contrast, *p*-oxygenated ring substituents (e.g. *p*-methoxycinnamaldehyde, No. 687) are oxidized via the β-oxidation pathway, eventually yielding hippuric acid derivatives.

4.1.3 *Application of the Procedure for the Safety Evaluation of Flavouring Agents*

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) to the above-mentioned substances, the Committee assigned 50 of the 55 substances to structural class I. These are the simple aromatic compounds with a saturated propyl or unsaturated propenyl side-chain containing a primary oxygenated functional group, which have little toxic potential. The remaining five substances, which are those containing a heterocyclic ring (No. 648) or aromatic rings bearing substituents other than 1–5 carbon aliphatic groups (Nos 674, 684–686), were assigned to structural class II.

Step 2

All the substances in this group are predicted to be metabolized to innocuous products (see page 20). The evaluation of these substances therefore proceeded via the left-hand side of the decision-tree.

Step A3

The estimated daily per capita intakes of 47 of the 50 substances in structural class I and of four of the five substances in structural class II were below the thresholds for substances in these classes (1800μg

and 540μg, respectively). According to the Procedure, the safety of these 51 flavouring agents raises no concern when they are used at their currently estimated levels of intake.

The estimated daily per capita intake of cinnamyl alcohol (No. 647) is 1800μg in Europe and 1900μg in the USA. The estimated daily per capita intake of cinnamaldehyde (No. 656) is 2500μg in Europe and 59000μg in the USA. The estimated daily per capita intake of methyl cinnamate (No. 658) is 2800μg in Europe and 830μg in the USA. The estimated daily per capita intake of cinnamaldehyde ethylene glycol acetal (No. 648) is 690μg in Europe and 0.007μg in the USA. The estimated daily per capita intakes of these four flavouring agents therefore exceed the thresholds for their respective structural classes (i.e. 1800μg for Nos 647, 656 and 658, and 540μg for No. 648). Accordingly, the evaluation of these substances proceeded to step A4.

Step A4

None of these four flavouring agents is endogenous. Accordingly, the evaluation of these agents proceeded to step A5.

Step A5

The NOEL of 54mg/kg of body weight per day for cinnamyl alcohol (No. 647) in a 4-month toxicity study in rats is >1000 times the estimated intake of this substance from its use as a flavouring agent in Europe (30μg/kg of body weight) and the USA (32μg/kg of body weight). The NOEL of 620mg/kg of body weight per day for cinnamaldehyde (No. 656) in a 13-week toxicity study in rats is >10000 times the estimated intake of this substance from its use as a flavouring agent in Europe (42μg/kg of body weight) and >600 times that in the USA (990μg/kg of body weight).

The Committee considered the NOEL of 54mg/kg of body weight per day for cinnamyl alcohol (No. 647) appropriate for evaluating the safety of methyl cinnamate (No. 658), because cinnamyl alcohol is oxidized to cinnamic acid, which is a product of hydrolysis of methyl cinnamate. In addition, the Committee noted that a NOEL of 80mg/kg of body weight per day had been identified for a closely related ester, ethyl cinnamate (No. 659), in a 4-month toxicity study in rats. Both of these NOELs are >1000 times the estimated intake of methyl cinnamate (No. 658) from its use as a flavouring agent in Europe and the USA. Cinnamaldehyde ethylene glycol acetal (No. 648) is rapidly hydrolysed to cinnamaldehyde (No. 656); the NOEL of 620mg/kg of body weight per day for cinnamaldehyde is >10000 times the estimated intake of cinnamaldehyde ethylene glycol acetal from its use as a flavouring agent in Europe and the USA.

The Committee therefore concluded that cinnamyl alcohol (No. 647), cinnamaldehyde (No. 656), methyl cinnamate (No. 658) and cinnamaldehyde ethylene glycol acetal (No. 648) would not be expected to be of safety concern.

Table 1 summarizes the evaluation of cinnamyl alcohol and 54 related substances used as flavouring agents.

4.1.4 *Consideration of combined intakes*

In the unlikely event that all foods containing all 50 substances in structural class I were to be consumed concurrently on a daily basis, the estimated combined intake would exceed the threshold for human intake for class I. In the unlikely event that all foods containing all five substances in structural class II were consumed concurrently on a daily basis, the estimated combined intake would exceed the threshold for human intake for class II. However, all 55 substances in this group are expected to be efficiently metabolized and would not saturate the metabolic pathways. Overall evaluation of the data indicates that combined intake would not present a safety concern.

4.1.5 *Conclusions*

The Committee concluded that the substances in this group would not present safety concerns at the current estimated levels of intake. In using the Procedure, the Committee noted that where toxicity data were available, they were consistent with the results of the safety evaluation.

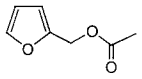
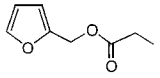
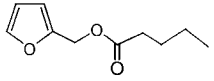
A monograph summarizing the safety data available on this group of flavouring agents was prepared.

4.2 Furfuryl alcohol and related flavouring agents

The Committee evaluated a group of flavouring agents that included furfuryl alcohol (No. 451), furfural (No. 450), five esters formed from furfuryl alcohol and simple aliphatic carboxylic acids (Nos 739–743), five esters formed from simple aliphatic alcohols and furoic acid (Nos 746–750), and three structurally related furfuryl derivatives, namely 5-methylfurfural (No. 745), 2-benzofurancarboxaldehyde (No. 751) and 2-phenyl-3-carbethoxyfuran (No. 752) (Table 2) using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1). These flavouring agents were grouped on the basis of the criterion that all are hydrolysed and/or metabolized to furoic acid or a substituted furoic acid.

The Committee has evaluated only one member of this group previously, namely furfural (No. 450). Furfural was considered by the

Table 2
Summary of the results of the safety evaluation of furfuryl alcohol and 14 related flavouring agents[a]

Flavouring agent[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* NOEL for substance or structurally related substance?	Conclusion based on current intake
Structural class II					
Furfuryl alcohol[d] (2-hydroxymethylfuran)	451	98-00-0 	No Europe: 210 USA: 24	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10 000 times the estimated intake of furfuryl alcohol when used as a flavouring agent	No safety concern
Furfuryl acetate[d] (2-furanmethanol acetate)	739	623-17-6 	No Europe: 18 USA: 21	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >100 000 times the estimated intake of furfuryl acetate when used as a flavouring agent	
Furfuryl propionate[d] (2-furanmethanol propionate)	740	623-19-8 	No Europe: 2 USA: 5	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >100 000 times the estimated intake of furfuryl propionate when used as a flavouring agent	
Furfuryl pentanoate[d] (2-furanylmethyl pentanoate)	741	36701-01-6 	No Europe: 0.3 USA: 14	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >100 000 times the estimated intake of furfuryl pentanoate when used as a flavouring agent	

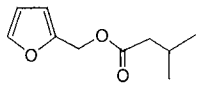
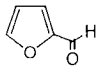
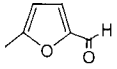
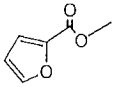
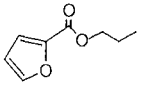
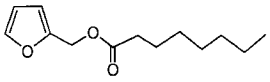
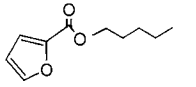
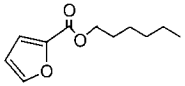
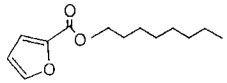
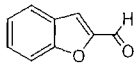
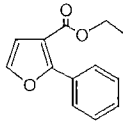
Furfuryl 3-methylbutanoate[d] (2-furanylmethyl-3-methylbutanoate)	743	13678-60-9 	No Europe: 0.03 USA: 1	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >1 million times the estimated intake of furfuryl 3-methylbutanoate when used as a flavouring agent	No safety concern
Furfural[d] (2-furfuraldehyde)	450	98-01-1 	No Europe: 520 USA: 460	Yes The NOEL of 53 mg/kg of body weight per day in a 13-week toxicity study in rats is >1000 times the estimated intake of furfural when used as a flavouring agent	
5-Methylfurfural (5-methyl-2-furfuraldehyde)	745	620-02-0 	No Europe: 160 USA: 25	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10000 times the estimated intake of 5-methylfurfural when used as a flavouring agent	
Methyl 2-furoate[d]	746	611-13-2 	No Europe: 35 USA: 37	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10000 times the estimated intake of methyl 2-furoate when used as a flavouring agent	
Propyl 2-furoate[d]	747	615-10-1 	No Europe: ND USA: 0.1	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10 million times the estimated intake of propyl 2-furoate when used as a flavouring agent	

Table 2 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* NOEL for substance or structurally related substance?	Conclusion based on current intake
Structural class III					
Furfuryl octanoate[d] (2-furanylmethyl octanoate)	742	39252-03-4 	No Europe: 0.01 USA: 6	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >100 000 times the estimated intake of furfuryl octanoate when used as a flavouring agent	No safety concern
Amyl 2-furoate[d] (pentyl 2-furoate)	748	1334-82-3 	No Europe: ND USA: 0.1	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10 million times the estimated intake of amyl 2-furoate when used as a flavouring agent	
Hexyl 2-furoate[d]	749	39251-86-0 	No Europe: ND USA: 0.1	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >10 million times the estimated intake of hexyl 2-furoate when used as a flavouring agent	

Octyl 2-furoate[d]	750	39251-88-2 	No Europe: 3 USA: 0.1	Yes The NOEL of 53 mg/kg of body weight per day for related substance No. 450 is >1 million times the estimated intake of octyl 2-furoate when used as a flavouring agent	No safety concern
2-Benzofuran-carboxaldehyde	751	4265-16-1 	No Europe: ND USA: 0.01	Yes The NOEL of 25 mg/kg of body weight per day in a 90-day toxicity study in rats is >100 million times the estimated intake of 2-benzofuran-carboxaldehyde when used as a flavouring agent	
2-Phenyl-3-carbethoxyfuran (ethyl 2-phenyl-3-furoate)	752	50626-02-3 	No Europe: 0.01 USA: 2	Yes The NOEL of 13 mg/kg of body weight per day in a 90-day toxicity study in rats is >400 times the estimated intake of 2-phenyl-3-carbethoxyfuran when used as a flavouring agent	

CAS: Chemical Abstracts Service; ND: no intake data reported.

[a] *Step 2*: None of the substances in this group is expected to be metabolized to innocuous products.

[b] The names of the flavouring agents are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where flavouring agents were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The thresholds for human intake for structural classes II and III are 540 µg per day and 90 µg per day, respectively. All intake values are expressed in µg per day.

[d] An ADI for furfural of 0–0.5 mg/kg of body weight was established at the present meeting. Furfuryl alcohol and a number of derivatives of furfuryl alcohol and furoic acid are metabolized to the same metabolite (furoic acid) as furfural. The ADI for furfural should be considered a group ADI for furfural, furfuryl alcohol and these derivatives, which include furfuryl acetate, furfuryl propionate, furfuryl pentanoate, furfuryl octanoate, furfuryl 3-methylbutanoate, methyl 2-furoate, propyl 2-furoate, amyl 2-furoate, hexyl 2-furoate and octyl 2-furoate.

Committee at its thirty-ninth and fifty-first meetings, but no ADI was established (Annex 1, references *101* and *137*). At its present meeting, the Committee established a group ADI of 0–0.5 mg/kg of body weight for furfural (No. 450), furfuryl alcohol (No. 451), and 10 derivatives of furfuryl alcohol and furoic acid on the basis of a NOEL of 53 mg/kg of body weight per day in a 13-week study on furfural in rats and a safety factor of 100 (see section 3.1.1).

Seven of the 15 substances in this group have been detected as natural components of foods, including roasted coffee, beer, milk, roasted almonds, white bread and whisky.

4.2.1 *Estimated daily per capita intake*

The total annual volume of production of the 15 substances in this group is 6600 kg in Europe and 4500 kg in the USA. These values are equivalent to total daily per capita intakes of 940 µg in Europe and 590 µg in the USA. Furfural (No. 450) accounted for approximately 55% of the total daily per capita intake in Europe (520 µg) and 77% of that in the USA (460 µg).

4.2.2 *Absorption, metabolism and elimination*

Furfuryl esters are hydrolysed to furfuryl alcohol (No. 451) and the corresponding carboxylic acid. Furfuryl alcohol (No. 451) is subsequently oxidized to furfural (No. 450), which is then oxidized to 2-furoic acid. Furoate esters (Nos 746–750) are or are predicted to be hydrolysed directly to 2-furoic acid and the corresponding alcohol. Furoic acid forms a coenzyme A thioester, which may be either metabolized to a glycine conjugate that is excreted in urine or condensed with acetyl coenzyme A to form 2-furanacryloyl coenzyme A, which is converted to a glycine conjugate and excreted in urine. The three remaining furfuryl derivatives (5-methylfurfural (No. 745), 2-benzofurancarboxaldehyde (No. 751) and 2-phenyl-3-carbethoxyfuran (No. 752)) are expected to follow similar metabolic pathways, i.e. hydrolysis of the ester, oxidation and conjugation with glycine, followed by side-chain oxidation (No. 745) or aromatic oxidation (Nos 751 and 752). In rodents, a minor pathway has been identified which involves oxidation of the furan ring to produce carbon dioxide and as yet unidentified metabolites.

4.2.3 *Application of the Procedure for the Safety Evaluation of Flavouring Agents*

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) to the above-mentioned substances, the Com-

mittee assigned nine of the 15 substances (Nos 450, 451, 739–741, 743 and 745–747) to structural class II. The remaining six substances (Nos 742 and 748–752) were assigned to structural class III.

Step 2

The available data on the metabolism of individual members of the group were sufficient to draw conclusions about the probable metabolic fate of all members of the group. Most (Nos 450, 451, 739–743 and 746–750) are predicted to be metabolized to 2-furoic acid or a 2-furoic acid derivative, which is either conjugated with glycine and excreted in the urine, or condensed with acetyl coenzyme A and conjugated with glycine before excretion in the urine. Because of concern about the results of the toxicological studies on furfural in rodents, these substances cannot be predicted to be metabolized to innocuous products. The evaluation of all substances in this group therefore proceeded via the right-hand side of the decision-tree.

Step B3

The estimated daily per capita intakes of all nine substances in structural class II and all six substances in structural class III are below the thresholds of concern for these classes (540 μg and 90 μg, respectively). Accordingly, the evaluation of all 15 substances proceeded to step B4.

Step B4

For furfural (No. 450), the NOEL of 53 mg/kg of body weight per day in a 13-week feeding study in rats provides an adequate margin of safety (>1000 times) in relation to the estimated intake of this substance in Europe and the USA. This NOEL is also appropriate for evaluating the safety of furfuryl alcohol (No. 451) and the structurally related substances furfuryl acetate (No. 739), furfuryl propionate (No. 740), furfuryl pentanoate (No. 741), furfuryl octanoate (No. 742) and furfuryl 3-methylbutanoate (No. 743), because all of these esters would be hydrolysed to furfuryl alcohol and then oxidized to furfural. The NOEL for furfural is also appropriate for evaluating the safety of the esters of furoic acid, namely methyl 2-furoate (No. 746), propyl 2-furoate (No. 747), amyl 2-furoate (No. 748), hexyl 2-furoate (No. 749) and octyl 2-furoate (No. 750), which would be hydrolysed to furoic acid (the major metabolite of furfural). This NOEL is also appropriate for assessing the safety of 5-methylfurfural (No. 745), which would participate in the same metabolic pathways as the furoic acid esters and also undergoes alkyl oxidation. For 2-benzofurancarboxaldehyde (No. 751), the NOEL of 25 mg/kg of body weight per day in a 90-day

feeding study in rats provides an adequate margin of safety (>100 million) in relation to the estimated intake of this substance in the USA. For 2-phenyl-3-carbethoxyfuran (No. 752), the NOEL of 13 mg/kg of body weight per day in a 90-day feeding study in rats provides an adequate margin of safety (>400) in relation to the estimated intake of this substance in Europe and the USA.

Table 2 summarizes the evaluation of furfuryl alcohol and 14 related substances used as flavouring agents.

4.2.4 *Consideration of combined intakes*

In the unlikely event that all foods containing all nine substances in structural class II (together with allyl 2-furoate evaluated previously by the Committee) were consumed concurrently on a daily basis, the estimated combined intake would exceed the threshold for human intake for class II. In the unlikely event that all foods containing all six substances in structural class III were consumed concurrently on a daily basis, the estimated combined intake would exceed the threshold for human intake for class III. However, on the basis of the wide margin of safety between the levels of estimated intake and the NOEL for furfural and the fact that the available detoxification pathways (glycine conjugation or condensation followed by glycine conjugation) would not be saturated at the current estimated levels of intake, the Committee concluded that the combined intake would not be of safety concern.

4.2.5 *Conclusions*

On the basis of the predicted metabolism of these substances and data on their toxicity, the Committee concluded that consumption of furfuryl alcohol and the 14 related substances in this group would not give rise to safety concerns at the current estimated levels of intake. In applying the Procedure, the Committee noted that all of the available data on toxicity were consistent with the results of the safety evaluation.

A monograph summarizing the safety data available on this group of flavouring agents was prepared.

4.3 Phenol and phenol derivatives

The Committee evaluated a group of 48 flavouring agents (Table 3) using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1). The group included phenol (No. 690), two esters of phenol (Nos 734 and 736) and resorcinol (No. 712); alkyl-, alkenyl- or

Table 3
Summary of the results of safety evaluations of phenol and 47 phenol derivatives used as flavouring agents[a]

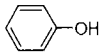
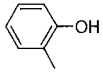
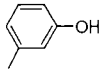
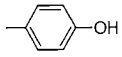
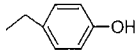
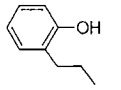
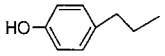
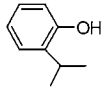
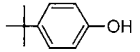
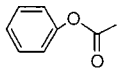
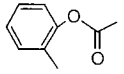
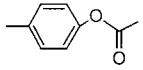
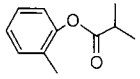
Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate margin of safety for the substance or related substance?	Comments	Conclusion based on current intake
Structural class I							
Phenol	690	108-95-2 	No Europe: 6 USA: 1	NR	NR	See note 1	No safety concern
o-Cresol	691	95-48-7 	No Europe: 290 USA: 0.1	NR	NR	See note 1	
m-Cresol	692	108-39-4 	No Europe: 0.1 USA: 0.1	NR	NR	See note 1	
p-Cresol	693	106-44-5 	No Europe: 1 USA: 1	NR	NR	See note 1	
p-Ethylphenol (4-ethylphenol)	694	123-07-9 	No Europe: 4 USA: 0.1	NR	NR	See note 1	
o-Propylphenol (2-propylphenol)	695	644-35-9 	No Europe: 0.1 USA: 1	NR	NR	See note 1	

Table 3 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate margin of safety for the substance or related substance?	Comments	Conclusion based on current intake
p-Propylphenol (4-propylphenol)	696	645-56-7 	No Europe: 0.1 USA: 0.1	NR	NR	See note 1	No safety concern
2-Isopropylphenol	697	88-69-7 	No Europe: 16 USA: 0.3	NR	NR	See note 1	
4-(1,1-Dimethylethyl)-phenol (*p-tert*-butylphenol)	733	98-54-4 	No Europe: 0.01 USA: 0.01	NR	NR	See note 1	
Phenyl acetate	734	122-79-2 	No Europe: 0.01 USA: 0.01	NR	NR	See note 2	
o-Tolyl acetate	698	533-18-6 	No Europe: 0.1 USA: 40	NR	NR	See note 2	
p-Tolyl acetate	699	140-39-6 	No Europe: ND USA: 70	NR	NR	See note 2	
o-Tolyl isobutyrate	700	36438-54-7 	No Europe: 0.03 USA: 0.1	NR	NR	See note 2	

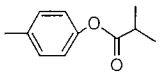
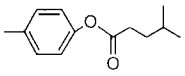
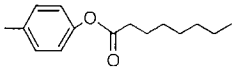
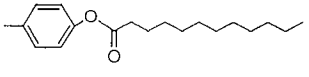
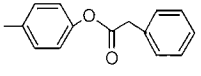
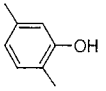
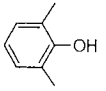
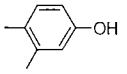
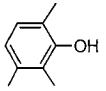
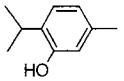
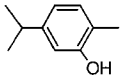
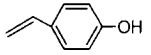
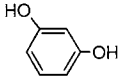
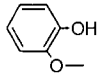
p-Tolyl isobutyrate	701	103-93-5 	No Europe: 0.04 USA: 0.01	NR	NR	See note 2	No safety concern
p-Tolyl 3-methyl-butyrate (*p*-tolyl isovalerate)	702	55066-56-3 	No Europe: 0.4 USA: 0.1	NR	NR	See note 2	
p-Tolyl octanoate	703	59558-23-5 	No Europe: 0.03 USA: 1	NR	NR	See note 2	
p-Tolyl laurate	704	10024-57-4 	No Europe: ND USA: 0.3	NR	NR	See note 2	
p-Tolyl phenyl-acetate	705	101-94-0 	No Europe: 0.7 USA: 0.1	NR	NR	See note 2	
2,5-Xylenol	706	95-87-4 	No Europe: 1 USA: 0.03	NR	NR	See note 1	
2,6-Xylenol	707	576-26-1 	No Europe: 2 USA: 1	NR	NR	See note 1	
3,4-Xylenol	708	95-65-8 	No Europe: 7 USA: 1	NR	NR	See note 1	

Table 3 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate margin of safety for the substance or related substance?	Comments	Conclusion based on current intake
2,3,6-Trimethylphenol	737	2416-94-6 	No Europe: 0.3 USA: 0.3	NR	NR	See note 1	No safety concern
Thymol (5-methyl-2-(1-methylethyl)phenol)	709	89-83-8 	No Europe: 59 USA: 160	NR	NR	See note 1	
Carvacrol (2-methyl-5-(1-methylethyl)-phenol)	710	499-75-2 	No Europe: 16 USA: 0.3	NR	NR	See note 1	
p-Vinylphenol (4-ethenylphenol)	711	2628-17-3 	No Europe: 0.1 USA: 6	NR	NR	See note 1	
Resorcinol	712	108-46-3 	No Europe: 1 USA: 0.3	NR	NR	See note 1	
Guaiacol (*o*-methoxyphenol)	713	90-05-1 	No Europe: 51 USA: 16	NR	NR	See note 1	

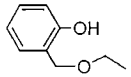
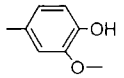
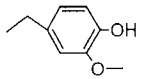
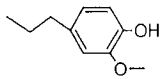
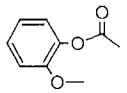
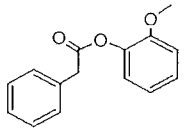
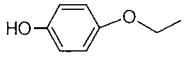
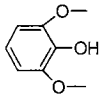
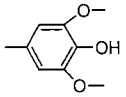
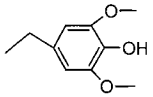
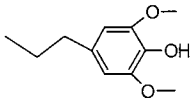
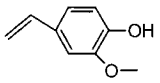
o-(Ethoxymethyl)-phenol	714	20920-83-6 	No Europe: 2 USA: 0.01	NR	NR	See note 1	No safety concern
2-Methoxy-4-methylphenol (2-methoxy-*p*-cresol)	715	93-51-6 	No Europe: 37 USA: 3	NR	NR	See note 1	
4-Ethylguaiacol	716	2785-89-9 	No Europe: 8 USA: 0.4	NR	NR	See note 1	
2-Methoxy-4-propylphenol	717	2785-87-7 	No Europe: 210 USA: 0.1	NR	NR	See note 1	
Guaiacyl acetate (2-methoxyphenyl acetate)	718	613-70-7 	No Europe: 0.01 USA: 0.1	NR	NR	See note 2	
Guaiacyl phenylacetate (2-methoxyphenyl phenylacetate)	719	4112-89-4 	No Europe: 0.4 USA: 2	NR	NR	See note 2	
Hydroquinone monoethyl ether (*p*-ethoxyphenol)	720	622-62-8 	No Europe: ND USA: 0.4	NR	NR	See note 1	

Table 3 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate margin of safety for the substance or related substance?	Comments	Conclusion based on current intake
2,6-Dimethoxyphenol	721	91-10-1 	No Europe: 6 USA: 12	NR	NR	See note 1	No safety concern
4-Methyl-2,6-dimethoxyphenol (2,6-dimethoxy-*p*-cresol)	722	6638-05-7 	No Europe: ND USA: 0.04	NR	NR	See note 1	
4-Ethyl-2,6-dimethoxyphenol	723	14059-92-8 	No Europe: ND USA: 1	NR	NR	See note 1	
4-Propyl-2,6-dimethoxyphenol	724	6766-82-1 	No Europe: ND USA: 0.1	NR	NR	See note 1	
2-Methoxy-4-vinylphenol	725	7786-61-0 	No Europe: 3 USA: 1	NR	NR	See note 1	

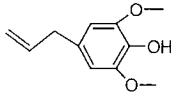
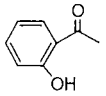
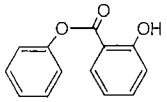
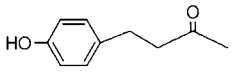
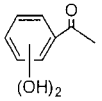
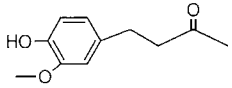
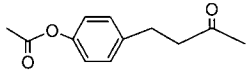
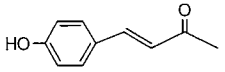
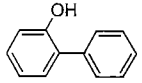
4-Allyl-2,6-dimethoxyphenol	726	6627-88-9 	No Europe: 0.01 USA: 6	NR	NR	See note 1	No safety concern
2-Hydroxyacetophenone (2′-hydroxyaceto-phenone)	727	118-93-4 	No Europe: 0.1 USA: 0.01	NR	NR	See note 1	
Phenyl salicylate (phenyl 2-hydroxy-benzoate)	736	118-55-8 	No Europe: 9 USA: 8	NR	NR	See note 1	
4-(*p*-Hydroxyphenyl)-2-butanone (4-(4-hydroxyphenyl)-butan-2-one)	728	5471-51-2 	Yes Europe: 2800 USA: 3800	No	Yes[a]	See note 1	
Dihydroxy-acetophenone (dihydroxy-1-phenylethanone)	729	28631-86-9 	No Europe: 0.01 USA: 0.1	NR	NR	See note 1	
Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone)	730	122-48-5 	No Europe: 40 USA: 83	NR	NR	See note 1	

Table 3 (*continued*)

Flavouring agent[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate margin of safety for the substance or related substance?	Comments	Conclusion based on current intake
4-(*p*-Acetoxyphenyl)-2-butanone (4-(*p*-hydroxyphenyl)-2-butanone acetate)	731	3572-06-3 	No Europe: ND USA: 0.1	NR	NR	See note 1	No safety concern
Vanillylidene acetone (methyl 3-methoxy-4-hydroxystyryl ketone)	732	1080-12-2 	No Europe: ND USA: 0.1	NR	NR	See note 1	
Structural class III							
2-Phenylphenol[e] (biphenyl-2-ol)	735	90-43-7 	No Europe: 0.01 USA: 0.01	NR	NR	See note 1	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported; NR: not required for evaluation because consumption of the substance was determined to be of no safety concern at Step A3 of the Procedure.

[a] *Step 2*: All of the substances in this group are expected to be metabolized to innocuous products.

[b] The names of the flavouring agents are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where flavouring agents were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The thresholds for human intake for structural classes I and III are 1800 μg per day and 90 μg per day, respectively. All intake values are expressed in μg per day.

[d] The NOEL of 280 mg/kg of body weight per day in a 13-week study in rats is >1000 times the estimated intake of 4-(*p*-hydroxyphenyl)-2-butanone when used as a flavouring agent.

[e] An ADI of 0–0.4 mg/kg of body weight was established for this substance at the 1999 Joint FAO/WHO Meeting on Pesticide Residues (*6*).

Notes to Table 3

1. Detoxification of phenol primarily involves conjugation of the hydroxyl group with sulfate and glucuronic acid.
2. Phenyl esters undergo rapid hydrolysis, followed by conjugation with sulfate and glucuronic acid.

aryl-substituted phenols and their corresponding esters (Nos 691–711, 733, 735 and 737); alkoxy phenols and their corresponding esters (Nos 713–726); and phenol derivatives with alkyl side-chains containing a ketone function (Nos 727–732).

2-Phenylphenol (No. 735) was evaluated by the Committee at its eighth meeting, when an ADI of 0–0.2 mg/kg of body weight was established (Annex 1, reference *8*). The 1999 Joint FAO/WHO Meeting on Pesticide Residues evaluated 2-phenylphenol and established an ADI of 0–0.4 mg/kg of body weight (*6*).

Thirty-two of the 48 flavouring agents in this group are natural components of foods. They have been detected in berries, coffee and meat.

4.3.1 *Estimated daily per capita intake*

The total annual volume of production of the 48 flavouring agents considered here is approximately 25 tonnes in Europe and 32 tonnes in the USA. About 78% of the total annual volume in Europe and 90% of that in the USA is accounted for by 4-(*p*-hydroxyphenyl)-2-butanone ("raspberry ketone"; No. 728). The estimated daily per capita intake of this flavouring agent is 2.8 mg in Europe and 3.8 mg in the USA.

Other flavouring agents for which the estimated daily per capita intakes are in the range 37–300 µg include *o*-cresol (No. 691) (290 µg in Europe), *o*- and *p*-tolyl acetate (Nos 698 and 699) (40 µg and 70 µg, respectively, in the USA), 2-methoxy-4-methylphenol (No. 715) (37 µg in Europe), thymol (No. 709) (59 µg in Europe and 160 µg in the USA), guaiacol (No. 713) (51 µg in Europe), 2-methoxy-4-propylphenol (No. 717) (210 µg in Europe) and zingerone (No. 730) (40 µg in Europe and 83 µg in the USA). The estimated daily per capita intakes of all other flavouring agents in the group are in the range 0.01–16 µg. Annual production volumes were not reported in Europe for seven flavouring agents used in the USA.

4.3.2 *Absorption, metabolism and elimination*

Phenol (No. 690) and its derivatives are rapidly absorbed from the gastrointestinal tract and share common pathways of metabolism. Phenol (No. 690), phenyl acetate (No. 734), phenyl salicylate (No. 736), resorcinol (No. 712), and alkyl-, alkenyl- and aryl-substituted phenols and their corresponding esters (Nos 691–711, 733, 735 and 737) are conjugated with sulfate and glucuronic acid after hydrolysis of the esters and excreted primarily in the urine. Other

metabolic pathways, observed mainly at high doses, include hydroxylation of the phenol ring and oxidation of side-chains. Phenols containing alkoxy groups (Nos 713–717 and 720–726) and those that contain a ketone function on an alkyl side-chain (Nos 727–732) are also metabolized mainly by conjugation with sulfate and glucuronic acid.

Alternative metabolic pathways include dealkylation of alkoxyphenols, reduction of ketones on alkyl side-chains, oxidation of side-chains and ring hydroxylation. At very high doses (>500 mg/kg of body weight), small amounts of *p*-cresol (No. 693), *p*-ethylphenol (No. 694), 2-methoxy-4-methylphenol (No. 715), 2-methoxy-4-propylphenol (No. 717), 2-methoxy-4-vinylphenol (No. 725) and 4-allyl-2,6-dimethoxyphenol (No. 726) are oxidized to reactive quinone methide intermediates. However, given the presence of a detoxification pathway (glutathione conjugation) for such quinone methides, the toxicity of the intermediates potentially formed after high doses of these derivatives would not raise concern under the conditions of their use as flavouring agents.

4.3.3 *Application of the Procedure for the Safety Evaluation of Flavouring Agents*

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) to the above-mentioned substances, the Committee assigned 47 of the 48 flavouring agents with low toxic potential to structural class I. The remaining flavouring agent, 2-phenylphenol (No. 735), was assigned to structural class III.

Step 2

At current levels of intake, the flavouring agents can be predicted to be metabolized to innocuous products, and the pathways involved would not be expected to be saturated. The evaluation of these substances therefore proceeded via the left-hand side of the decision-tree.

Step A3

The estimated daily per capita intakes of 46 of the 47 flavouring agents in structural class I and of the single agent in structural class III are below the thresholds of concern for these classes (1800 µg and 90 µg, respectively). The Committee concluded that these substances would not be expected to be of safety concern when used at their currently estimated levels of intake.

The estimated daily per capita intake of 4-(*p*-hydroxyphenyl)-2-butanone (No. 728) in Europe and the USA is above the threshold of

concern for structural class I (1800μg). Accordingly, the evaluation of this substance proceeded to step A4.

Step A4

4-(*p*-Hydroxyphenyl)-2-butanone (No. 728) does not occur endogenously in humans. The evaluation of this substance therefore proceeded to step A5.

Step A5

The NOEL of 280mg/kg of body weight per day for 4-(*p*-hydroxyphenyl)-2-butanone (No. 728) in a 13-week study in rats provides a margin of safety of >1000 in relation to the estimated intake in Europe (46μg/kg of body weight per day) and in the USA (63μg/kg of body weight per day).

Table 3 summarizes the evaluation of phenol and 47 phenol derivatives used as flavouring agents.

4.3.4 *Consideration of combined intakes*

In the unlikely event that all foods containing *p*-cresol (No. 693) and all six esters of *p*-cresol (Nos 699, 701–705) in structural class I were consumed concurrently on a daily basis, the combined intake of *p*-cresol equivalents (see Table 3) would not exceed the threshold for human intake for this class (1800μg per day). In the unlikely event that all foods containing all 47 substances in structural class I were consumed daily, the estimated combined intake would exceed the threshold for human intake for this class, but would not saturate the available high-capacity conjugation pathways involved in the metabolism of these substances. Moreover, approximately 78% of the annual volume consumed in Europe and approximately 90% of that consumed in the USA are accounted for by 4-(*p*-hydroxyphenyl)-2-butanone (No. 728), for which a NOEL providing an adequate margin of safety was available.

4.3.5 *Conclusions*

The Committee concluded that the safety of phenol and the 47 derivatives of phenol in this group would not raise concern at the currently estimated levels of intake. In using the Procedure, the Committee noted that all of the available data on the toxicity of phenol and its derivatives were consistent with the results of the safety evaluation.

The Committee took note of the ADI of 0–0.4mg/kg of body weight for 2-phenylphenol (No. 735) established by the 1999 Joint FAO/WHO Meeting on Pesticide Residues (*6*).

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.4 Pulegone and related flavouring agents

The Committee evaluated a group of flavouring agents that included pulegone (No. 753), isopulegone (No. 754), isopulegol (No. 755), isopulegyl acetate (No. 756), an unsaturated analogue of pulegone, *p*-menth-1,4(8)-dien-3-one (No. 757), and a principal metabolite of pulegone, menthofuran (No. 758) (Table 4) using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1). With the exception of the metabolite, menthofuran (No. 758), all of these substances contain a 3-menthyl (2-isopropyl-5-methyl-3-cyclohexyl) carbon skeleton. Isopulegone (No. 754), isopulegol (No. 755) and isopulegyl acetate (No. 756) contain an isopropenyl side-chain, while pulegone (No. 753) and *p*-menth-1,4(8)-dien-3-one (No. 757) contain an isopropylidene side-chain. None of these flavouring agents has been evaluated previously by the Committee.

Of the six flavouring agents reviewed, only isopulegyl acetate (No. 756) has not been found to occur naturally in food. All the other agents occur naturally in several plant and fruit juices and in oils such as peppermint and pennyroyal oil. Isopulegol (No. 755) has been found in citrus peel oils, cognac, rum and lemon balm. Isopulegone (No. 754) has a minty, herbaceous aroma and has been detected in ginger and buchu oil. *p*-Menth-1,4(8)-dien-3-one (No. 757) has been detected in orange and grapefruit juices.

4.4.1 *Estimated daily per capita intake*

The total annual volume of production of the six flavouring agents considered here is 250kg in Europe and 180kg in the USA. The flavouring agents produced in the highest volumes are menthofuran (No. 758) (170kg in Europe and 95kg in the USA) and isopulegol (No. 755) (50kg in Europe and 45kg in the USA). These two flavouring agents account for >90% of the total annual volume of production of this group of substances in Europe and the USA. On the basis of the reported total annual volume of production, the total estimated daily per capita intake of menthofuran from use of this substance as a flavouring agent is approximately 13μg in Europe and 25μg in the USA. Similarly, the total estimated daily per capita intake of isopulegol from use of this substance as a flavouring agent is 6μg in Europe and 7μg in the USA. The total estimated daily per capita intakes of the other substances in this group are 2μg or less in both Europe and the USA.

4.4.2 *Absorption, metabolism and elimination*

Isopulegone (No. 754) is predicted to be rapidly absorbed and metabolized in vivo (mainly by reduction) to yield isopulegol (No. 755) and undergoes reversible isomerization to pulegone (No. 753). Isopulegol, which may also be formed by hydrolysis of acetate isopulegyl (No. 756), is predicted to be conjugated with glucuronic acid and excreted in the urine. Pulegone (No. 753) and *p*-menth-1,4(8)-dien-3-one (No. 757) are either reduced to the corresponding alcohols and excreted or undergo allylic oxidation to yield the corresponding 9-hydroxy derivatives. In the case of pulegone (No. 753), the 9-hydroxy derivative cyclizes to yield menthofuran (No. 758) as the principal metabolite.

The metabolic pathway involving conversion of pulegone (No. 753) to menthofuran (No. 758) is considered to be a significant source of toxic products. Menthofuran is a proximate hepatotoxic agent that is transformed via an epoxide intermediate to the toxic agent, 8-pulegone aldehyde. This γ-ketoenal has been shown to bind covalently to mouse, rat and human liver microsomes, and this binding parallels the hepatotoxicity of menthofuran in these species. *p*-Menth-1,4(8)-dien-3-one (No. 757) is presumed to participate in the same pathway, since its effects are similar to those of pulegone, but there was no direct evidence of the mechanism of toxicity of this compound. Other major routes of metabolism can be considered to be detoxification pathways.

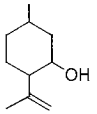
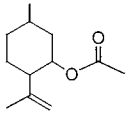
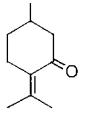
At low levels of intake, pulegone (No. 753), menthofuran (No. 758) and their metabolites, menthofuran epoxide and the γ-ketoenal, are conjugated with glutathione and glucuronic acid. Metabolism of these substances may lead to formation of a reactive metabolite, glutathione depletion and, eventually, hepatotoxicity at intakes of 100 mg/kg of body weight or more. Because these compounds may undergo metabolic bioactivation, the evaluation of their safety was based on a comparison with available data on toxicity, although the estimated daily per capita intakes would not be sufficient to result in appreciable depletion of hepatic glutathione.

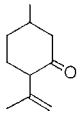
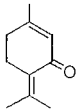
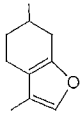
4.4.3 *Application of the Procedure for the Safety Evaluation of Flavouring Agents*

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) to the above-mentioned substances, the Committee assigned isopulegol (No. 755) and isopulegyl acetate

Table 4
Summary of the results of safety evaluations of pulegone and five related flavouring agents[a]

Flavouring agent[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or related substance?	Conclusion based on current intake
Structural class I					
Isopulegol (*p*-menth-8-en-3-ol)	755	89-79-2 	No Europe: 6 USA: 7	Yes The NOEL of 0.44 mg/kg of body weight per day for related substance No. 753 is >1000 times the estimated intake of isopulegol when used as a flavouring agent	No safety concern
Isopulegyl acetate	756	57576-09-7 	No Europe: 0.4 USA: 1	Yes The NOEL of 0.44 mg/kg of body weight per day for related substance No. 753 is >10000 times the estimated intake of isopulegyl acetate when used as a flavouring agent	
Structural class II					
Pulegone (*p*-menth-4(8)-en-3-one)	753	89-82-7 	No Europe: 2 USA: 2	Yes The NOEL of 0.44 mg/kg of body weight per day in a 90-day study in rats is >10000 times the estimated intake of pulegone when used as a flavouring agent	No safety concern

Isopulegone (*trans-p*-menth-8-en-3-one)	754	29606-79-9 	No Europe: 1 USA: 0.01	Yes The NOEL of 0.44 mg/kg of body weight per day for related substance No. 753 is >10000 times the estimated intake of isopulegone when used as a flavouring agent	No safety concern
p-Menth-1,4(8)-dien-3-one (3-methyl-6-(1-methylethylidene)-cyclohex-2-en-1-one)	757	491-09-8 	No Europe: 2 USA: 0.01	Yes The NOEL of 0.44 mg/kg of body weight per day for related substance No. 753 is >10000 times the estimated intake of *p*-menth-1,4(8)-dien-3-one when used as a flavouring agent	
Menthofuran (4,5,6,7-tetrahydro-3,6-dimethylbenzofuran)	758	494-90-6 	No Europe: 13 USA: 25	Yes The NOEL of 0.44 mg/kg of body weight per day for related substance No. 753 is >1000 times the estimated intake of menthofuran when used as a flavouring agent	

CAS: Chemical Abstracts Service.

[a] *Step 2*: None of the substances in this group is expected to be metabolized to innocuous products.

[b] The names of the flavouring agents are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where flavouring agents were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The thresholds for human intake for structural classes I and II are 1800 µg per day and 540 µg per day, respectively. All intake values are expressed in µg per day.

(No. 756) to structural class I. The remaining substances, which included three monocycloalkenones (Nos 753, 754 and 757) and a heterocyclic compound that is a common component of food (No. 758), were assigned to structural class II.

Step 2

At current levels of intake, the six flavouring agents in this group would not be expected to saturate the available metabolic pathways, but they are not completely metabolized to innocuous products. The evaluation of these substances therefore proceeded via the right-hand side of the decision-tree.

Step B3

The estimated daily per capita intakes of both substances in structural class I and all four substances in structural class II are below the thresholds for human intake for these classes (1800 μg and 540 μg, respectively). Accordingly, the evaluation of these substances proceeded to step B4.

Step B4

The lack of toxicity of pulegone (No. 753) at low levels of intake was demonstrated in a 90-day study in rats fed peppermint oil that contained 1.1% pulegone. The NOEL of 0.44 mg/kg of body weight per day for pulegone derived from this study is >10 000 times the estimated intake of 0.033 μg/kg of body weight from use of pulegone as a flavouring agent. Since pulegone is metabolized to menthofuran (No. 758) and *p*-menth-1,4(8)-dien-3-one (No. 757), data on pulegone can be used to evaluate the safety of these flavouring agents, although menthofuran was about three times more hepatotoxic than pulegone after single doses. Isopulegone (No. 754) was less hepatotoxic than pulegone after single doses. The NOEL of 0.44 mg/kg of body weight per day for pulegone in the 90-day study in rats is >1000 times the estimated intake of 0.4 μg/kg of body weight per day from use of menthofuran as a flavouring agent. Isopulegone (No. 754), isopulegol (No. 755) and isopulegyl acetate (No. 756) are expected to be partly metabolized to menthofuran. Even if these compounds are assumed to be metabolized to menthofuran to the same extent as pulegone, however, the NOEL for pulegone is >10 000 times the estimated intake from use of isopulegone and isopulegyl acetate and is >1000 times the estimated intake from use of isopulegol as a flavouring agent.

Table 4 summarizes the evaluation of pulegone and five related substances.

4.4.4 *Consideration of combined intakes*

In the unlikely event that all foods containing isopulegol (No. 755) and isopulegyl acetate (No. 756) were consumed concurrently on a daily basis, the estimated combined intake would not exceed the threshold for human intake for class I (1800 μg per day). In the unlikely event that all foods containing isopulegone (No. 754), pulegone (No. 753), *p*-menth-1,4(8)-dien-3-one (No. 757) and menthofuran (No. 758) were consumed concurrently on a daily basis, the estimated combined intake would not exceed the threshold for human intake for class II (540 μg per day). Furthermore, there is an adequate safety margin between the estimated combined intake of all six substances (approximately 40 μg/person per day) and the NOEL for pulegone.

4.4.5 *Conclusions*

The Committee concluded that the substances in this group would not be of safety concern at the current estimated levels of intake. In using the Procedure, the Committee noted that all of the available data on toxicity, including the results of short-term toxicity studies and genotoxicity studies on pulegone (No. 753) and related compounds, were consistent with the results of the safety evaluation.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

5. Contaminants

5.1 Cadmium

Cadmium was evaluated by the Committee at its sixteenth, thirty-third and forty-first meetings (Annex 1, references *30*, *83* and *107*). At its sixteenth meeting, the Committee allocated a provisional tolerable weekly intake (PTWI) of 400–500 μg of cadmium per person. At its thirty-third meeting, the Committee retained this PTWI but expressed it in terms of intake per kg of body weight (7 μg/kg of body weight). In 1992, the International Programme on Chemical Safety (IPCS) produced a monograph on cadmium, which provided a detailed review of the available information on the health effects of cadmium and a description of the models on which the PTWI was based (*7*). At its forty-first meeting, the Committee maintained the PTWI of 7 μg/kg of body weight, pending future research.

In acknowledging the need for research in areas recommended in the monograph, the Committee at its forty-first meeting highlighted the following topics:

- Further studies on the dose–response relationship between the daily or accumulative intake of cadmium and renal dysfunction (β_2-microglobulinuria) in the general population.
- Re-examination of the existing epidemiological information correlating cadmium intake and β_2-microglobulinuria among inhabitants of a cadmium-polluted region.
- Examination of data on cadmium intake and its health effects among the general population in various countries, including data on cadmium concentrations in foods.
- Evaluation of the critical concentration of cadmium in the renal cortex in two groups exposed to high and low concentrations of cadmium.
- Studies on the chemical identity and bioavailability of cadmium compounds in food.
- Re-examination of mathematical models for estimating the biological half-life of cadmium.
- Studies on the involvement of renal glomeruli in chronic cadmium intoxication.

At that meeting, the Committee also reaffirmed that "there is only a relatively small safety margin between exposure in the normal diet and exposure that produces deleterious effects".

At its present meeting, the Committee based its evaluation on the IPCS monograph (*7*) and on updated information on the intake, bioavailability and health effects of cadmium.

5.1.1 *Bioavailability*

The bioavailability of cadmium can be affected markedly by nutritional factors. Low iron status, as determined from serum ferritin levels, which is prevalent among women, increases the uptake of cadmium from the gastrointestinal tract. Furthermore, the bioavailability of cadmium from some grains or seeds and foods in which cadmium is bound to phytates, metallothionein and other proteins may be reduced. The Committee examined the information on bioavailability that had become available since its forty-first meeting and concluded that it did not significantly differ from that considered previously. While information suggesting altered bioavailability due to dietary and nutritional factors exists, the bulk of the evidence indicates that the overall point estimate of 5% for bioavailability that was used in previous models of the relationship between cadmium intake and critical effects is appropriate. For specific populations, such as people with iron deficiency, the bioavailability of cadmium may range from 5% to 10%. The Committee also considered that studies in which experimental animals were given parenteral

injections of cadmium are not appropriate for determining the bioavailability of ingested cadmium.

5.1.2 *Health effects*

The presence of cadmium in food can result in long-term intake of low concentrations. Cadmium has an extremely long biological half-life in mammals (estimated to be at least 17 years in humans) and has a strong affinity for the liver and kidney. The toxic effects of this metal on the kidneys (e.g. tubule dysfunction) are the most sensitive for evaluation of its health effects. While cadmium can affect organs other than the kidneys, it generally does so at doses higher than those associated with renal effects. Acute effects can occur after ingestion of very high concentrations, and these may be fatal, owing to widespread systemic distribution. Such outcomes do not arise from typical dietary concentrations.

Non-renal effects

Neurodevelopmental and neurobehavioural effects have been demonstrated in experimental animals given repeated doses of cadmium by gavage. However, studies in which cadmium was administered by injection showed that it cannot easily enter the brain, its entry being blocked by the blood–brain barrier. Cadmium can replace zinc in a number of metallo-enzymes, proteins and ion channels, generally increases the brain concentrations of noradrenaline and dopamine, and impairs enzymes required for the production of neurotransmitters. The peripheral nervous system may also be susceptible to chronic exposure to cadmium, but the investigations of these effects are limited. Studies of occupationally exposed adults have shown increased prevalences of peripheral neuropathies and neurobehavioural deficits in specific domains (e.g. attention, psychomotor speed, memory). No population-based studies of neurotoxicity after environmental exposure of adults or children to cadmium were available in which validated biomarkers of exposure were used.

Experimental studies have shown that cadmium can induce metallothionein synthesis in the placenta and that cadmium is retained in the placenta at low concentrations. Large doses of cadmium compounds administered parenterally to several rodent species at a late stage of gestation induced severe placental damage and fetal deaths, whereas similar doses given parenterally in the early stages of gestation had teratogenic effects. Teratogenic effects have not been reported after oral intake of cadmium by animals or humans.

Cadmium is carcinogenic in experimental animals when given by injection or inhalation, and occupational exposure of humans by

inhalation has been shown to result in pulmonary cancer. There was no evidence that cadmium is carcinogenic to humans exposed by the oral route.

Large, population-based studies have provided little evidence that changes in blood pressure or in the prevalence of ischaemic heart disease are related to blood or urinary cadmium concentrations.

Excretion of cadmium in the urine is weakly but significantly associated with elevated urinary calcium concentrations and increased serum alkaline phosphatase activity. Studies of occupationally exposed persons suggest that high urinary and blood cadmium concentrations are associated with low bone mineral density. In environmentally exposed postmenopausal women, higher urinary cadmium excretion was associated with hypercalciuria, osteoporosis and reduced bone density, and an increased risk of fracture. The relationship between the effect of cadmium on calcium metabolism and osteoporosis should be investigated further in so far as the effects on bone might be a more sensitive indicator of the toxicity of cadmium than the renal effects.

Renal effects

The kidney is the critical target organ in mammals, including humans, exposed for long periods to small amounts of cadmium. Cadmium produces renal tubule dysfunction characterized by hypercalciuria and increased excretion of several proteins of low relative molecular mass. In particular, β_2-microglobulin has served as a biomarker of toxicity and may complement urinary cadmium as a biomarker of exposure.

The renal tubule dysfunction seen in non-human mammalian species exposed to low dietary concentrations of cadmium is analogous to that produced in humans; in animals, this may progress to interstitial nephropathy and glomerulopathy with longer exposure. The critical renal concentration of cadmium that is associated with cadmium-induced nephropathy in animals is 50–200 μg/g of renal cortex, which is consistent with the results of studies in humans. Recent studies in various species indicate that when the concentration of cadmium in the renal cortex exceeds 250 μg/g, continued exposure results in further increases in the concentration in the liver but not in the renal cortex. It has been suggested that this effect reflects increased loss of cadmium in the urine due to tubule dysfunction. Experimental studies have shown that impaired glomerular filtration (i.e. increased serum creatinine and blood urea nitrogen concentrations) is a less sensitive indicator of cadmium-induced nephropathy than are indicators of tubule dysfunction or injury.

Many reports from Japan and a large population-based study of environmental exposure to cadmium in Belgium confirm that the major risk factors for cadmium-induced renal effects in non-occupationally exposed humans include increasing age, high alcohol consumption, cigarette smoking and residence in a cadmium-contaminated region. In these studies, renal effects were investigated by using urinary biomarkers of renal dysfunction. Several markers of proximal tubule function, including *N*-acetyl-β-glucosaminidase activity and the concentrations of retinol-binding protein, β_2-microglobulin, amino acids and calcium, are related to the urinary cadmium concentrations of environmentally exposed individuals. No threshold was found for the relationship between *N*-acetyl-β-glucosaminidase activity and urinary cadmium concentration. The prevalence of abnormal values for these markers was 10% when urinary cadmium concentrations exceeded 2–4 μg/24 h or the estimated concentration in the renal cortex was >50 μg/g. Estimates of the relationship between urinary cadmium concentration and abnormal values for these markers were considerably lower in studies of environmental exposure than in studies of occupational exposure; however, past exposure would be underestimated in areas where cadmium concentrations in the environment had been reduced prior to the time the study was conducted. Certain individuals, such as patients with diabetes or pre-existing renal disorders, appear to be at increased risk for cadmium-related renal dysfunction.

Follow-up studies of workers with cadmium-related renal dysfunction suggest that many of the changes are irreversible, with continued declines in glomerular function for decades after cessation of heavy exposure. The low-relative-molecular-mass proteinuria associated with long-term exposure to cadmium is assumed to be irreversible. This assumption is based on the observation in studies of occupational and environmental exposure that for people who excrete >1000 μg of β_2-microglobulin in the urine per 24 h, renal tubule function does not improve or worsens within 5 years of a reduction in cadmium exposure. The prognosis appears to be more favourable for individuals with lower body burdens. In the study in Belgium, some of the subtle effects on renal tubule function seen at the time the participants entered the study were no longer apparent at follow-up or, at least, were not associated with a decline in glomerular function in the interim.

A comprehensive meta-analysis of the relevant epidemiological studies and a risk assessment suggested that the risk for renal dysfunction and progression to clinical disease could be lowered if exposure to cadmium were reduced such that the concentrations of

cadmium in the kidney and urine were maintained below 50 μg/g of renal cortex and 2.5 μg/g of creatinine, respectively.

5.1.3 *Dietary intake*

The diet is the major route of human exposure to cadmium. Contamination of foods with cadmium results from its presence in soil and water. Estimation of the intake of cadmium, like that of most contaminants, is complicated by the skewed distributions of residues, since cadmium does not reach foods through controlled or predictable agricultural or manufacturing processes. In addition, crops differ widely with respect to their absorption of cadmium from soil, depending on the type and salinity of the soil and the bioavailability of cadmium (see section 5.1.1). The cadmium concentrations in food samples vary widely, but the highest mean concentrations are found in molluscs, kidney, liver, cereals, cocoa and leafy vegetables. Estimates of mean cadmium intake from national food surveys and total diet studies generally range from 0.1 to 0.5 μg/kg of body weight per day. The estimates derived from the WHO GEMS/Food regional diets, based on food balance sheets, ranged from 0.35 to 0.63 μg/kg of body weight per day.

5.1.4 *Estimates of the relationship between dietary intake and renal tubule dysfunction*

Analysis of new data from population-based studies indicates that the early renal effects of cadmium are prevalent at lower intakes than those indicated by the model used by the Committee to confirm the PTWI at its forty-first meeting. That model was based on the assumption that about 10% of a population with a concentration of cadmium in the renal cortex of about 200 μg/g would experience renal tubule dysfunction.

In the recent meta-analysis of data from several studies of workers and general populations exposed to cadmium, the prevalence of cadmium-induced tubule proteinuria that would be expected to occur in individuals with specific levels of urinary cadmium was estimated. This analysis suggests that the risk of tubule dysfunction begins to increase when the urinary excretion of cadmium exceeds 2.5 μg/g of creatinine. The Committee considered this value to represent no excess prevalence of renal tubule dysfunction.

The Committee used data in the literature to investigate the empirical relationship between the concentration of cadmium in the diet and urinary concentrations. This relationship is a function of increasing cadmium concentration in the renal cortex and increasing urinary excretion with age. Furthermore, diets are made up of a mixture of

foods with different cadmium contents, and its bioavailability from some of the foods that contain high concentrations, such as shellfish and some grains, is low. The estimates were derived from data from Japan, Sweden and the USA. The mean dietary intake of cadmium by female non-smokers in many areas of Japan was 26 μg/day (range, 19–51 μg/day), and the mean urinary excretion of cadmium was 4.4 μg/g of creatinine (range, 3.6–7.0 μg/g of creatinine). These data indicate a ratio of dietary cadmium to urinary cadmium excretion of 6 (range, 3–14). The data from Sweden indicate that female non-smokers have a urinary cadmium excretion of 0.15 μg/g of creatinine and a median dietary intake of 10 μg/day (range, 5.7–26 μg/day). The estimated ratio of dietary cadmium to urinary cadmium excretion ranged from 40 to 170. The mean dietary intake of cadmium in the Total Diet Study in the USA was 5.5 μg/day, and the mean value for urinary excretion of cadmium obtained independently in the National Health and Nutrition Examination Survey in the USA was 0.5 μg/g of creatinine, resulting in a ratio of dietary cadmium to urinary cadmium excretion of 11.

The relationship between urinary cadmium excretion and dietary intake of cadmium can be predicted from a theoretical model. Possible dietary intakes can be predicted from the amount of cadmium excreted in the urine if it is assumed that there are no significant changes in the dietary intake of cadmium over time. Once a set of assumptions has been chosen, a table can be constructed, relating dietary intake to urinary cadmium excretion (see Table 5). The three sets of assumptions described in Table 5 are based on data on the toxicokinetics of cadmium. This table can be used to predict a range of dietary intakes for different urinary cadmium concentrations, which depend on the assumed values for bioavailability and for the percentage of absorbed cadmium that is excreted in urine. Table 5 can also be used to predict the prevalence rates of renal tubule dysfunction associated with different dietary intakes. For population groups in which it is reasonable to assume that 10% of dietary cadmium is bioavailable and that 100% of the absorbed cadmium is excreted in urine, the model predicts that dietary intakes of cadmium of more than 0.5 μg/kg of body weight per day would result in an increased prevalence of renal tubule dysfunction.

5.1.5 *Conclusion*

The estimates of excess prevalence shown in Table 5 were derived from studies of large, heterogeneous populations. As the confidence intervals for the point estimates are unknown and may be wide, the estimates may represent overestimates of the risks associated with

Table 5
Predicted intake of cadmium from the diet and excess prevalence of renal tubule dysfunction, based on three different sets of assumptions[a]

Assumptions	Urinary excretion of cadmium (µg/g of creatinine)[b]	Predicted intake of cadmium[c]		Predicted excess prevalence of renal tubule dysfunction (%)
		µg/day[d]	µg/kg of body weight per day[d,e]	
Bioavailability of cadmium in the diet = 10%; excretion of absorbed cadmium in urine = 100%[f]	2.5	30	0.5	0
	4.2	50	0.8	4
	8.2	100	1.7	20
Bioavailability of cadmium in the diet = 10%; excretion of absorbed cadmium in urine = 50%[g]	2.5	60	1.0	0
	4.2	100	1.7	4
	8.2	200	3.3	20
Bioavailability of cadmium in the diet = 5%; excretion of absorbed cadmium in urine = 50%[h]	2.5	120	2.0	0
	4.2	200	3.3	4
	8.2	400	6.7	20

[a] In each scenario, it is assumed that there are no significant changes in cadmium dietary intake over time and that 1.2 g of creatinine are excreted per day.
[b] Values derived primarily from studies of occupational exposure to cadmium.
[c] Predicted dietary intake = $\frac{\text{Urinary excretion of cadmium (µg of cadmium/g of creatinine)} \times 1.2}{\text{Fraction bioavailable} \times \text{Absorbed fraction excreted in urine}}$
[d] Cadmium intake corresponding to the excretion in urine in each scenario.
[e] The body weight is assumed to be 60 kg. The PTWI corresponds to a daily intake of 1 µg/kg of body weight.
[f] Ratio of dietary intake to urinary excretion = 12.
[g] Ratio of dietary intake to urinary excretion = 24.
[h] Ratio of dietary intake to urinary excretion = 48.

dietary intake of cadmium, especially at lower levels. The Committee concluded that the incidences of renal tubule dysfunction in populations with various dietary intakes of cadmium can serve as a reasonable basis for risk assessment if the assumptions made when applying the predictive model are scientifically based and clearly described.

Even though new information indicates that a proportion of the general population may be at increased risk of cadmium-induced tubule dysfunction when exposed at the current PTWI of 7 µg/kg of body weight, the Committee maintained this value because the risk estimates that can be made at present are imprecise. The range of predicted dietary intakes that may be associated with an excess prevalence of renal tubule dysfunction (see Table 5) can be used to

indicate the risk at various levels of intake for potentially sensitive groups within a population.

The Committee recommended that seven areas be investigated in order to increase confidence in the estimates of predicted excess prevalence of renal tubule dysfunction:

1. The toxicokinetics of cadmium should be investigated in controlled experimental studies in humans of the relationship between dietary intake and urinary excretion of cadmium in the general population and in groups at high risk, such as people with iron deficiency, renal disease or diabetes mellitus.
2. Dietary surveys should be conducted in which individual records of the food consumption of specific population subgroups are kept.
3. Studies should be conducted on the bioavailability of cadmium from specific foods and on the factors that affect its bioavailability, such as age, health status and dietary nutrients.
4. The relationship between biomarkers of renal tubule dysfunction and biomarkers of cadmium exposure should be elucidated.
5. The relationship between renal tubule dysfunction (as determined by specific biomarkers), clinical disease and mortality should be studied.
6. The influence of cadmium on calcium metabolism and osteoporosis should be examined.
7. Studies should be conducted to determine the effect of exposure to cadmium (integrated over a lifetime) on the subsequent development of osteoporosis.

5.2 Tin

Tin was previously evaluated by the Committee at its fourteenth, fifteenth, twenty-second, twenty-sixth and thirty-third meetings (Annex 1, references *22*, *26*, *47*, *59* and *83*). At its thirty-third meeting, the Committee converted the previously established provisional maximum tolerable daily intake (PMTDI) of 2 mg/kg of body weight to a PTWI of 14 mg/kg of body weight. At its present meeting, the Committee retained the PTWI at its current value.

At its Thirty-first Session, the Codex Committee on Food Additives and Contaminants requested the Expert Committee to review information on the toxicity of tin in order to establish an acute reference dose (*4*). At its present meeting, the Expert Committee considered studies of the acute toxic effects seen after consumption of foodstuffs containing high concentrations of inorganic compounds of tin. It did not consider studies of organic tin compounds, since it had concluded at its twenty-second meeting (Annex 1, reference *47*) that

these compounds, which differ considerably with respect to toxicity, should be considered individually.

The major dietary source of tin is the tinplate of unlacquered or partially lacquered cans used for the preservation of foods. The migration of tin from tinplate into foods is greater:

— for highly acidic foods such as pineapples and tomatoes;
— with increased time and temperature of food storage;
— for foods, such as fruit juice, stored in opened cans.

The tin content of canned foods is variable, and some foods may have concentrations high enough to cause an acute toxic reaction. The mean dietary intakes of tin by individuals reported from seven countries ranged from <1 mg/day to about 14 mg/day and were considerably lower than the PTWI established previously by the Committee. Population groups with higher intakes of canned foods may have higher intakes of tin.

Inorganic tin may be present as Sn (II) or Sn (IV); it may occur in cationic form (stannous and stannic compounds) or as inorganic anions (stannites or stannates). Studies in rats provided evidence that the chemical form of inorganic tin is important in determining its toxicity. Inorganic tin compounds generally have little systemic toxicity in animals because of limited absorption from the gastrointestinal tract, low accumulation in tissues and rapid excretion, primarily in the faeces. Insoluble tin compounds, such as stannous sulfide, had minimal toxic effects in rats when administered for 28 days in the diet at concentrations similar to those at which soluble tin salts are clearly toxic. In short-term studies in rats in which several tin salts were used, histological examination revealed changes to the gastrointestinal tract, kidneys, liver and adrenal cortex. Alterations in haematological parameters indicative of anaemia have also been recorded. The acute toxicity of tin results from irritation of the mucosa of the gastrointestinal tract. Vomiting and diarrhoea were reported in cats given soluble salts of tin, but there was no clear dose–response relationship, and the vehicle in which the tin was administered may have affected its toxicity.

Episodes of human poisoning resulting from consumption of tin-contaminated foods and drinks have resulted in abdominal distension and pain, vomiting, diarrhoea and headache. These symptoms commonly appear within 0.5–3 h, and recovery occurs within 48 h. The doses of tin ingested in such episodes of poisoning were not estimated. In one study with five volunteers, all experienced symptoms when they ingested juice containing tin at a concentration of 1400 mg/kg (corresponding to a dose of 4.4–6.7 mg/kg of body weight).

Administration of the same dose 1 month later to these individuals resulted in symptoms in only one person.

The Committee concluded that insufficient data were available to establish an acute reference dose for tin. It noted that the gastric irritation that may occur after ingestion of a foodstuff containing tin may depend on the concentration and chemical form of the tin. It reiterated its opinion, expressed at its thirty-third meeting (Annex 1, reference *83*), that the limited human data available indicate that concentrations of 150mg/kg in canned beverages and 250mg/kg in other canned foods may produce acute manifestations of gastric irritation in certain individuals. In addition, the Committee reiterated its advice, given at its twenty-sixth and thirty-third meetings (Annex 1, references *59* and *83*), that consumers should not store food in open tin-coated cans. It welcomed the information that estimates of the intake of tin by the populations of several countries do not exceed the PTWI of 14mg/kg of body weight.

6. Intake assessments of specific food additives

6.1 Calcium from calcium salts of food additives

The Committee was asked by the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*4*) to estimate the contribution to the diet of calcium from food additives in relation to that from other sources (e.g. naturally occurring calcium, food fortificants, discretionary use of supplements, and pharmaceutical (antacid) preparations). No data on this source of calcium intake were available to the Committee for consideration at its present meeting.

The Committee concluded that it was not feasible to estimate the contribution of calcium salts of food additives to total calcium intake. Although these salts are widely used in the food supply, intake from this source alone could not be estimated because the actual food categories and levels of use are generally unknown. As an alternative, total calcium intake from food was evaluated, as reported in national surveys of the total diet and of nutrition, assuming that the calcium content of foods analysed in total diet surveys and reported in national tables of food composition includes calcium derived from food additives. This assumption has the limitation that the increased availability of calcium-fortified foods may not be reflected in national tables of food composition.

The best data for estimating the contribution of calcium salts of food additives to total calcium intake were considered to be those collected in surveys of the total diet, in which the actual content of the nutrient

of interest is measured at the time of the survey. However, no data from surveys conducted since 1994 were found. In addition, nutrients are rarely considered in such surveys.

Bearing in mind the limitations of the methods used to estimate calcium intake, the Committee noted that the total calcium intake from food of consumers with intakes at the 95th percentile reported from various sources did not exceed 2.7 g/person per day for any age group. The Committee also noted that although the available data on the adverse effects of calcium relate to intake from nutrient supplements and antacids and not from foods, many surveys cover only calcium intake from the diet. The potential contribution of calcium from food additives to total calcium intake will remain difficult to assess until data on food consumption are linked in national surveys to data on the intake of calcium from other sources at an individual level.

In order to determine the contribution of calcium salts of food additives to the total intake of calcium, the Committee would require data on the levels of use and the food groups in which those food additives are permitted.

7. Revision of certain specifications

7.1 Food additives

A total of 45 food additives (other than flavouring agents) were examined for specifications only at the present meeting (Annex 2). In general, all of the specifications were revised in line with the Committee's current policy on metal contaminants (see section 2.3.2).

7.1.1 *Food additives for which previous specifications were designated as "tentative"*

At its fifty-third meeting (Annex 1, reference *143*), the Committee noted that many of the specifications for food additives published in the *Compendium of food additive specifications* and its addenda (Annex 1, references *96*, *103*, *109*, *118*, *124*, *133*, *139* and *145*) were designated as "tentative", indicating that some data were missing or incomplete at the time the specifications were prepared.

As no responses to the call for data for several of these substances were received for consideration at the current meeting, their specifications were withdrawn. These substances are: acetone peroxides, aluminium sodium sulfate, ammonium persulfate, benzoin gum, calcium iodate, calcium peroxide, carbohydrase from *Aspergillus awamori*, var., carbohydrase from *Aspergillus oryzae*, var., chlorine dioxide, diethyl pyrocarbonate, isoamyl gallate, lipase from

Aspergillus oryzae, var., potassium persulfate and rennet from *Endothia parasitica.*

Information was received on aluminium potassium sulfate, aluminium sulfate (anhydrous), ammonium salts of phosphatidic acid, diatomaceous earth and rennet from *Mucor* species. The specifications of these substances were revised, and the "tentative" designations deleted. The title of the specifications for rennet from *Mucor* species was changed to "rennet from *Rhizomucor* species" to reflect the new classification of the source organisms.

7.1.2 *Food additives considered for revision of specifications*

The existing specifications for curcumin, microcrystalline wax, shellac (bleached) and sorbitan monolaurate were revised, with minor changes.

The existing "tentative" specifications for *d*-α-tocopherol (concentrate), diethyl ether, pentasodium triphosphate and sodium sulfate were revised, and the "tentative" qualification was deleted.

The Committee received a request from the Thirty-first Session of the Codex Committee on Food Additives and Contaminants (*4*) for an alternative method of assay for microcrystalline cellulose, but no supporting information was received. Although the Expert Committee was unable to make the requested change, it revised the existing specifications, to include other minor changes.

The Committee also received a request from the Thirty-first Session of the Codex Committee on Food Additives and Contaminants (*4*) to delete the following sentence from the definition in the specifications for talc: "Talc derived from deposits that are known to contain associated asbestos is not food grade". The Committee decided to retain the sentence, but made other minor changes.

At its seventeenth meeting, the Committee requested information on the assay and method of assay of guaiac resin and designated the specifications as "tentative" (Annex 1, reference *32*). At its present meeting, the Committee concluded that no specific assay value was appropriate for guaiac resin, as with other gums, because of its complexity. The specifications were revised without inclusion of an assay value or a method of assay, and the "tentative" designation was removed.

The existing "tentative" specifications for smoke flavourings were extensively revised to include a modified definition, and a lower limit and an updated analytical procedure for benzo[*a*]pyrene. The specification for residual diethyl ether was deleted, and that for heavy metals (as lead) was replaced by a specific limit for lead. The "tentative" designation was maintained, pending the receipt of

information on an alternative solvent to benzene for use in the analysis of the carbonyl content. Proposals should be supported by a comparative test of the analytical method with benzene and the proposed alternative solvent.

The existing "tentative" specifications for oxystearin were revised. The "tentative" qualification was maintained, with the stipulation that the specifications would be withdrawn if information on the levels of, and a suitable analytical method for, epoxides was not provided by 1 May 2001. The Committee noted that this substance is no longer in commercial use.

The existing "tentative" specifications for blackcurrant extract were revised. The "tentative" qualification was maintained, pending the receipt of information on a chromatographic identification test and on the adequacy of the sample size for the test for sulfur dioxide.

The existing "tentative" specifications for tagetes extract were revised. The "tentative" qualification was maintained, pending the receipt of information on the composition of the commercial products, a test for the identification of xanthophylls, and a method of assay.

The existing "tentative" specifications for Quillaia extract were extensively revised, and the "tentative" status deleted. The name was changed to "Quillaia extracts", in order to include unrefined and semi-refined extracts obtained by aqueous extraction of the milled inner bark of *Quillaja saponaria* Molina or of the wood, including stems and branches.

2-Nitropropane was previously considered by the Committee at its twenty-third, twenty-fifth, twenty-eighth and thirty-fifth meetings (Annex 1, references *50*, *56*, *66* and *88*). The temporary acceptance of 2-nitropropane for use as a fractionating solvent in the production of fats and oils was not extended at the thirty-fifth meeting because of toxicological concerns. In the absence of further information on the use of this substance at its present meeting, the Committee withdrew the specifications.

At its twenty-seventh meeting, the Committee recommended that use of 1,1,2-trichloroethylene as an extraction solvent be limited because of toxicological concerns, and requested information on the nature, level(s) and methods of analysis for the added stabilizers and breakdown products. As the requested information was not submitted for consideration at the present meeting, the Committee withdrew the specifications.

The existing "tentative" specifications for eight enzyme preparations were revised on the basis of Annex 1 (General specifications for

enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*).

The existing "tentative" specifications for three enzyme preparations (α-amylase, α-amylase and glucoamylase, and protease) from *Aspergillus oryzae*, var., were revised to include the requirement that the microbial strain used as the source organism must be non-toxicogenic and non-pathogenic. The Committee deleted the maximum limits and associated methods of analysis for the known mycotoxins α-cyclopiazonic acid, β-nitropropionic acid and kojic acid, and removed the "tentative" designation from the specifications.

The existing "tentative" specifications for β-glucanase from *Trichoderma harzianum*, cellulase from *Penicillium funiculosum*, hemicellulase from *Aspergillus niger*, var., and pectinase from *Aspergillus niger*, var., were revised and the "tentative" qualifications removed.

The existing "tentative" specifications for amyloglucosidase from *Aspergillus niger*, var., were revised. The "tentative" qualification was maintained, pending the receipt of information on the assay for amyloglucosidase in formulated products with glucose.

7.1.3 *Food additives that are also flavouring agents*

In reviewing the specifications for flavouring agents, the Committee noted that monographs existed for acetic acid (glacial), triethyl citrate, *o*-phenylphenol, formic acid and butan-1-ol. The specifications had been prepared several years previously, however, and might be in need of revision to include uses other than those reviewed at the present meeting. The Committee concluded that these specifications should be reviewed at its next meeting on food additives in order to consider more up-to-date information.

7.2 Flavouring agents

7.2.1 *Procedure for evaluating proposed specifications for flavouring agents*

At its fifty-third meeting, the Committee developed a set of criteria for determining whether specifications for the purity of flavouring agents should be designated as "tentative" or full specifications (Annex 1, reference *143*). It agreed that specifications submitted for consideration should be designated as "tentative" if information had not been provided on:

- chemical formula and relative molecular mass, identity test, and the minimum amount that can be determined (minimum assay value);
- the additional criteria related to purity, including boiling-point (for liquids), melting-point (for solids), refractive index (for liquids) and specific gravity (for liquids).

The Committee also agreed, however, that it would consider assigning full specifications when the absence of one or more of the additional criteria relating to purity could be justified.

7.2.2 *Specifications established up to and including the fifty-third meeting*

At its fifty-third meeting, the Committee used the system described above to review the specifications for flavouring agents developed at its forty-sixth, forty-ninth and fifty-first meetings (Annex 1, references *122*, *131* and *137*) and to assess the specifications submitted for consideration at the fifty-third meeting. It agreed that further data were required on 284 of the 636 flavouring agents that had been evaluated at the forty-sixth, forty-ninth, fifty-first and fifty-third meetings, and these agents were included in the call for data for the present meeting. In addition, data were requested on 59 flavouring agents for which the minimum assay values were less than 95%.

At its present meeting, the Committee noted that data were still needed on 57 flavouring agents for which the minimum assay values were less than 95%. It reaffirmed that these data were needed in order to establish full specifications and agreed that the 57 specifications for which data were still lacking should be reclassified as "tentative", pending receipt of the information.

Information provided in response to the call for data for the present meeting enabled the Committee to assign "full" specifications to 475 of the 636 flavouring agents that had been considered up to and including the fifty-third meeting. Thus, 161 flavouring agents still have "tentative" specifications.

At its fifty-third meeting, the Committee indicated that unless the relevant data were supplied on the specifications designated as "tentative", they would be withdrawn. As a good response had been received from the manufacturers, the Committee relaxed this requirement, although it stressed that the data missing from the 161 flavouring agents that still have "tentative" specifications must be provided in time for consideration at its fifty-seventh meeting, to be held in 2001.

7.2.3 *Proposed specifications considered for the first time at the present meeting*

Draft specifications for 125 flavouring agents were submitted for consideration by the Committee at its present meeting. The Committee noted that specifications for three of the substances — furfural,

Table 6
Summary of specifications for flavouring agents considered up to and including the present meeting

Meeting at which the specifications were considered	Total no.	No. classified as "full"	No. classified as "tentative"
Forty-sixth, forty-ninth, fifty-first and fifty-third[a]	636	475 (75%)	161 (25%)
Present	122	83 (68%)	39 (32%)
Total	758	558 (74%)	200 (26%)

[a] For details, see Annex 1, references *122, 131, 137* and *143.*

furfuryl alcohol and allyl cinnamate — had been considered at earlier meetings. The information provided on these three substances was used to revise the existing specifications, and this enabled the previous "tentative" designation of the specifications for allyl cinnamate and furfuryl alcohol to be deleted.

The Committee considered the draft specifications for the remaining 122 flavouring agents and classified 83 as "full" and 39 as "tentative". The Committee requested that the data necessary to enable the tentative specifications to be designated as full specifications be provided by 2001.

Table 6 summarizes the status of the specifications for all the flavouring agents considered at the forty-sixth, forty-ninth, fifty-first, fifty-third and present meetings (Annex 1, references *122*, *131*, *137* and *143*).

The Committee noted that the information provided about the nature of the flavouring agents often did not specify which isomers were present. Unless more specific information is provided on the isomers present in individual flavouring agents, the Committee will proceed on the assumption that all the possible isomers may be present.

7.2.4 *Comments made at the Thirty-second Session of the Codex Committee on Food Additives and Contaminants*

At its Thirty-second Session, the Codex Committee on Food Additives and Contaminants asked the Expert Committee to consider three questions relating to specifications for flavouring agents (*2*):

- whether information on identification tests should include a relevant spectrum of a reference compound;
- whether it was necessary to use several different spectroscopic methods of identification, as one is usually sufficient; and

- whether boiling-points should be given in specifications for information only and not as a requirement.

The Codex Committee on Food Additives and Contaminants also asked the Expert Committee to consider using a mathematical formula for converting values for specific gravity obtained at 20 °C to values corresponding to 25 °C.

In response, the Expert Committee agreed that identification tests must be accompanied by a relevant spectrum of a reference compound. It noted that the spectra that were now being provided were of much better quality than those available at earlier meetings but that it was still important that unsatisfactory spectra be updated and that those still missing be provided.

The Committee also agreed that it was unnecessary to require more than one spectroscopic method of identification for a flavouring agent. When more than one method is given, the sponsor will be asked to indicate which it considers to be the most appropriate.

The Committee considered that, in principle, boiling-points for liquids should be submitted for inclusion in specifications as an additional check on the nature and/or purity of the material. However, the Committee agreed that these boiling-points may not always be relevant, for example, for flavouring agents that are mixtures of different substances.

The Committee reaffirmed that the values for specific gravity included in future proposed specifications for flavouring agents should be given at 25 °C. It considered it unlikely that a single mathematical formula could be developed for converting values for specific gravity measured at 20 °C to equivalent values at 25 °C. In the absence of supporting information, it did not consider the issue further.

7.3 Limits for metals in food additives

7.3.1 *Emulsifiers*

At its fifty-third meeting, the Committee reaffirmed its policy of replacing the outdated limit test for heavy metals (as lead) with limits for the individual metals of concern in all existing specifications (Annex 1, reference *143*). On the basis of data received at the present meeting on the organic emulsifiers listed in Table 7, the Committee deleted the limits for arsenic and heavy metals (as lead) and replaced them with a limit for lead of 2 mg/kg, in accordance with the principles stated in Section C of FAO Food and Nutrition Paper No. 52, Add. 7 (Annex 1, reference *145*).

Table 7
Limits for arsenic and lead in 43 organic and inorganic phosphate emulsifiers

Emulsifier	INS No.	Limit for arsenic (mg/kg)	Limit for lead (mg/kg)
Acetic and fatty acid esters of glycerol	472a	—	2
Ammonium polyphosphate	452(v)	3	4
Ammonium salts of phosphatidic acid	442	—	2
Calcium polyphosphate	452(iv)	3	4
Calcium stearoyl-2-lactylate	482(i)	—	2
Cholic acid	1000	—	2
Citric and fatty acid esters of glycerol	472c	—	2
Desoxycholic acid	—	—	2
Diacetyltartaric and fatty acid esters of glycerol	472e	—	2
Dicalcium pyrophosphate (diphosphate)	450(vi)	3	4
Dioctyl sodium sulfosuccinate	480	—	2
Disodium pyrophosphate (diphosphate)	450(i)	3	4
Glycerol ester of wood rosin	445	—	2
Lactic and fatty acid esters of glycerol	472b	—	2
Lecithin, partially hydrolysed	322	—	2
Mono- and diglycerides	471	—	2
Polyglycerol esters of fatty acids	475	—	2
Polyglycerol esters of interesterified ricinoleic acid	476	—	2
Polyoxyethylene (20) sorbitan monolaurate	432	—	2
Polyoxyethylene (20) sorbitan monooleate	433	—	2
Polyoxyethylene (20) sorbitan monopalmitate	434	—	2
Polyoxyethylene (20) sorbitan monostearate	435	—	2
Polyoxyethylene (20) sorbitan tristearate	436	—	2
Polyoxyethylene (8) stearate	430	—	2
Polyoxyethylene (40) stearate	431	—	2
Propylene glycol esters of fatty acids	477	—	2
Salts of fatty acids	470	—	2
Sodium aluminium phosphate, basic	541(ii)	3	4
Sodium metaphosphate, insoluble	—	3	4
Sodium polyphosphates, glassy	452(i)	3	4
Sodium stearoyl-2-lactylate	481(i)	—	2
Sorbitan monooleate	494	—	2
Sorbitan monopalmitate	495	—	2
Sorbitan monostearate	491	—	2
Sorbitan tristearate	492	—	2
Stearyl citrate	484	—	2
Stearyl monoglyceridyl citrate	—	—	2
Succinylated monoglycerides	472g	—	2
Sucroglycerides	474	—	2

Table 7 (*continued*)

Emulsifier	INS No.	Limit for arsenic (mg/kg)	Limit for lead (mg/kg)
Tetrapotassium pyrophosphate	450(v)	3	4
Tetrasodium pyrophosphate	450(iii)	3	4
Thermally oxidized soya bean oil	—	—	2
Thermally oxidized soya bean oil interacted with mono- and diglycerides of fatty acids	479	—	2

INS: International Numbering System.

Information on limits for lead in inorganic phosphates used as emulsifiers was also received, but no supporting analytical data were provided. The data were sufficient to replace the previous limits for arsenic and lead by limits of 3 mg/kg and 4 mg/kg, respectively, and to delete the limits for heavy metals (as lead) for the phosphate emulsifiers listed in Table 7.

When the limit test for heavy metals (as lead) is replaced by limits for individual metals, the absence of a particular metal from specifications indicates that the Committee has concluded that the level of contamination is so low as to be of no toxicological concern. Comments on the proposed limits are invited.

7.3.2 *Food additives other than emulsifiers*

The Committee agreed on priorities for reviewing the limits for metals in specifications for groups of food additives other than emulsifiers (Table 8).

8. Future work

1. The Committee noted that Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*) was originally drawn up in 1984. It also recalled that Annex 1 and Appendix B of that annex (General considerations and specifications for enzyme preparations from genetically modified microorganisms) were reviewed and revised at its fifty-first and fifty-third meetings and included with the specifications (Annex 1, references *139* and *145*). The Committee reiterated its view, expressed at its fifty-third meeting, that Annex 1 required updating in the light of technological developments and to ensure consistency and coherence with the appendices, including Appendix B.

Table 8
Priorities for the review of specifications for metals in food additives other than emulsifiers

Group[a]	Category	No. of specifications
1	Flavour enhancers	19
	Sweeteners	14
	Thickeners	30
	Anti-caking agents	15
	Subtotal	78
2	Acidity regulators	52
	Antioxidants	35
	Subtotal	87
3	Preservatives	43
	Other additives	45
	Subtotal	88
4	Glazing agents	11
	Flour treatment agents	16
	Colours	54
	Subtotal	81
	Total	334

[a] The Group numbers refer to the order of priority for reviewing the specifications.

2. The Committee reiterated its recommendation, made at its forty-sixth meeting, concerning the need for periodic updating of the *Compendium of food additive specifications* (Annex 1, reference *96*) and the *Guide to specifications* (Annex 1, reference *100*) to take into account developments in analytical procedures and new methods for the production of food additives. The Committee recommended that such revision should be undertaken without delay.

9. Recommendation

In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, the important role of the recommendations of the Committee in the development of international food standards and of regulations in many countries, and the need for maintaining consistency and continuity within the Committee, it is strongly recommended that meetings of the Joint FAO/WHO Expert Committee on Food Additives continue to be held at least once yearly to evaluate these substances.

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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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146. *Evaluation of certain veterinary drug residues in food* (Fifty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 900, 2001.
147. *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 45, 2000.
148. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, No. 41/13, 2000.

Annex 2

Acceptable Daily Intakes, other toxicological information and information on specifications

Specific food additives

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg/kg of body weight and other toxicological recommendations
Flavouring agents		
Furfural (No. 450)	R	0–0.5 (group ADI)[b]
Paprika oleoresin	S	Use of paprika oleoresin as a spice is acceptable[c]
Food colours		
Caramel colour II	R[d]	0–160
Cochineal extract	R	May be allergenic[e]
Carmines	R	May be allergenic[e]
Sweetening agents		
Aspartame–acesulfame salt	N	Aspartame and acesulfame moieties are covered by the ADIs established previously for aspartame (0–40) and acesulfame potassium (0–15)
D-Tagatose	N	No ADI allocated[f]
Miscellaneous substances		
Benzoyl peroxide	R	Additional uses could not be evaluated[g]
Nitrous oxide	R	Use as a packaging gas could not be evaluated[h]
Stearyl tartrate	R	Additional uses could not be evaluated[g]
Trehalose	N	ADI "not specified"[i]

[a] N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required.

[b] Group ADI for furfural, furfuryl alcohol, furfuryl acetate, furfuryl propionate, furfuryl pentanoate, furfuryl octanoate, furfuryl 3-methylbutanoate, methyl 2-furoate, propyl 2-furoate, amyl 2-furoate, hexyl 2-furoate and octyl 2-furoate.

[c] Paprika oleoresin was not evaluated at the present meeting. The Committee's recommendation was based on the report of its fourteenth meeting (WHO Technical Report Series, No. 462, 1971).

[d] Included in the existing specifications for caramel colours.

[e] The Committee concluded that cochineal extract, carmines, and, possibly, carminic acid in foods and beverages may initiate or provoke allergic reactions in some individuals.

[f] An ADI could not be allocated to D-tagatose because of concern about its potential to induce liver glycogen deposition and hypertrophy and to increase serum uric acid concentrations; see Annex 3.

[g] No conclusions could be drawn about the acceptability of the uses proposed in the draft General Standard for Food Additives of the Codex Committee on Food Additives and Contaminants because information on toxicity and intake was not available.

[h] No information on intake of nitrous oxide resulting from the proposed use was available.

[i] ADI "not specified" is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary

intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in the individual evaluation, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

Flavouring agents

The substances listed here were evaluated by the Procedure for the Safety Evaluation of Flavouring Agents. For further details, see sections 2.2.1 and 4 of the main report.

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Cinnamyl alcohol and related flavouring agents			
Structural class I			
3-Phenyl-1-propanol (3-phenylpropanol)	636	N	
3-Phenylpropyl formate (benzenepropanol formate)	637	N	
3-Phenylpropyl acetate (benzenepropanol acetate)	638	N	
3-Phenylpropyl propionate (benzenepropanol propionate)	639	N	
3-Phenylpropyl isobutyrate	640	N	
3-Phenylpropyl isovalerate	641	N	
3-Phenylpropyl hexanoate	642	N, T	
Methyl 3-phenylpropionate	643	N	
Ethyl 3-phenylpropionate	644	N	
3-Phenylpropionaldehyde (benzenepropanal)	645	N, T	
3-Phenylpropionic acid (benzenepropionic acid)	646	N	No safety concern
Cinnamyl alcohol	647	N	
Cinnamyl formate	649	N	
Cinnamyl acetate	650	N	
Cinnamyl propionate	651	N	
Cinnamyl butyrate	652	N, T	
Cinnamyl isobutyrate	653	N	
Cinnamyl isovalerate	654	N	
Cinnamyl benzoate	760	N, T	
Cinnamyl phenylacetate	655	N	
Cinnamaldehyde (3-phenyl-2-propenal)	656	N, T	
Cinnamic acid (3-phenyl-2-propenoic acid)	657	N	
Methyl cinnamate	658	N	
Ethyl cinnamate	659	N	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Propyl cinnamate	660	N, T	
Isopropyl cinnamate	661	N	
Allyl cinnamate (2-propenyl 3-phenyl-2-propenoate)	19	R	
Butyl cinnamate	663	N, T	
Isobutyl cinnamate	664	N	
Isoamyl cinnamate (isopentyl cinnamate)	665	N	
Heptyl cinnamate	666	N, T	
Cyclohexyl cinnamate	667	N	
Linalyl cinnamate	668	N, T	
Terpinyl cinnamate ((*Z*)-1-methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl cinnamate)	669	N, T	
Benzyl cinnamate	670	N	
Phenethyl cinnamate	671	N, T	
3-Phenylpropyl cinnamate	672	N, T	
Cinnamyl cinnamate	673	N, T	
5-Phenylpentanol (benzenepentan-1-ol)	675	N	
α-Amylcinnamyl formate (2-(phenylmethylene)heptyl formate)	676	N, T	No safety concern
α-Amylcinnamyl acetate (2-(phenylmethylene)heptyl acetate)	677	N, T	
α-Amylcinnamyl isovalerate (2-(phenylmethylene)heptyl isovalerate)	678	N, T	
3-Phenyl-4-pentenal (3-phenylpent-4-enal)	679	N	
3-(*p*-Isopropylphenyl)propionaldehyde (3-(*p*-cumenyl)propionaldehyde)	680	N	
α-Amylcinnamaldehyde dimethyl acetal ((2-(dimethoxymethyl)-1-heptenyl) benzene)	681	N, T	
p-Methylcinnamaldehyde (3-(4-methylphenyl)-2-propenal)	682	N	
α-Methylcinnamaldehyde	683	N	
p-Methoxycinnamaldehyde	687	N	
o-Methoxycinnamaldehyde	688	N	
p-Methoxy-α-methylcinnamaldehyde (4′-methoxy-2-methylcinnamaldehyde)	689	N	
Structural class II			
Cinnamaldehyde ethylene glycol acetal (2-styryl-1,3-dioxolane)	648	N, T	
α-Amylcinnamyl alcohol (2-pentyl-3-phenylprop-2-en-1-ol)	674	N	No safety concern
α-Butylcinnamaldehyde	684	N	
α-Amylcinnamaldehyde (α-pentyl cinnamaldehyde)	685	N	
α-Hexylcinnamaldehyde	686	N	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Furfuryl alcohol and related flavouring agents[c]			
Structural class II			
Furfuryl alcohol[d] (2-hydroxymethylfuran)	451	R	No safety concern
Furfuryl acetate[d] (2-furanmethanol acetate)	739	N	
Furfuryl propionate[d] (2-furanmethanol propionate)	740	N, T	
Furfuryl pentanoate[d] (2-furanylmethyl pentanoate)	741	N, T	
Furfuryl 3-methylbutanoate[d] (2-furanylmethyl-3-methylbutanoate)	743	N, T	
Furfural[d] (2-furfuraldehyde)	450	R	
5-Methylfurfural (5-methyl-2-furfuraldehyde)	745	N	
Methyl 2-furoate[d]	746	N	
Propyl 2-furoate[d]	747	N	
Structural class III			
Furfuryl octanoate[d] (2-furanylmethyl octanoate)	742	N, T	No safety concern
Amyl 2-furoate[d] (pentyl 2-furoate)	748	N, T	
Hexyl 2-furoate[d]	749	N, T	
Octyl 2-furoate[d]	750	N, T	
2-Benzofurancarboxaldehyde	751	N	
2-Phenyl-3-carbethoxyfuran (ethyl 2-phenyl-3-furoate)	752	N, T	
Phenol and phenol derivatives			
Structural class I			
Phenol	690	N	No safety concern
o-Cresol	691	N	
m-Cresol	692	N	
p-Cresol	693	N	
p-Ethylphenol (4-ethylphenol)	694	N	
o-Propylphenol (2-propylphenol)	695	N	
p-Propylphenol (4-propylphenol)	696	N	
2-Isopropylphenol	697	N	
4-(1,1-Dimethylethyl)phenol (*p-tert*-butylphenol)	733	N	
Phenyl acetate	734	N	
o-Tolyl acetate	698	N, T	
p-Tolyl acetate	699	N	
o-Tolyl isobutyrate	700	N	
p-Tolyl isobutyrate	701	N	
p-Tolyl 3-methylbutyrate (*p*-tolyl isovalerate)	702	N	
p-Tolyl octanoate	703	N	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
p-Tolyl laurate	704	N, T	
p-Tolyl phenylacetate	705	N	
2,5-Xylenol	706	N	
2,6-Xylenol	707	N	
3,4-Xylenol	708	N	
2,3,6-Trimethylphenol	737	N, T	
Thymol (5-methyl-2-(1-methylethyl)-phenol)	709	N	
Carvacrol (2-methyl-5-(1-methylethyl)-phenol)	710	N	
p-Vinylphenol (4-ethenylphenol)	711	N, T	
Resorcinol	712	N	
Guaiacol (*o*-methoxyphenol)	713	N	
o-(Ethoxymethyl)phenol	714	N	
2-Methoxy-4-methylphenol (2-methoxy-*p*-cresol)	715	N	
4-Ethylguaiacol	716	N	
2-Methoxy-4-propylphenol	717	N	
Guaiacyl acetate (2-methoxyphenyl acetate)	718	N	
Guaiacyl phenylacetate (2-methoxyphenyl phenylacetate)	719	N, T	
Hydroquinone monoethyl ether (*p*-ethoxy-phenol)	720	N, T	No safety concern
2,6-Dimethoxyphenol	721	N	
4-Methyl-2,6-dimethoxyphenol (2,6-dimethoxy-*p*-cresol)	722	N	
4-Ethyl-2,6-dimethoxyphenol	723	N, T	
4-Propyl-2,6-dimethoxyphenol	724	N, T	
2-Methoxy-4-vinylphenol	725	N	
4-Allyl-2,6-dimethoxyphenol	726	N, T	
2-Hydroxyacetophenone (2′-hydroxy-acetophenone)	727	N	
Phenyl salicylate (phenyl 2-hydroxy-benzoate)	736	N	
4-(*p*-Hydroxyphenyl)-2-butanone (4-(4-hydroxyphenyl)butan-2-one)	728	N	
Dihydroxyacetophenone (dihydroxy-1-phenylethanone)	729	N, T	
Zingerone (4-(4-hydroxy-3-methoxy-phenyl)-2-butanone)	730	N	
4-(*p*-Acetoxyphenyl)-2-butanone (4-(*p*-hydroxyphenyl)-2-butanone acetate)	731	N	
Vanillylidene acetone (methyl 3-methoxy-4-hydroxystyryl ketone)	732	N, T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Structural class III			
2-Phenylphenol[e] (biphenyl-2-ol)	735	N, T	No safety concern
Pulegone and related flavouring agents			
Structural class I			
Isopulegol (*p*-menth-8-en-3-ol)	755	N	No safety concern
Isopulegyl acetate	756	N	
Structural class II			
Pulegone (*p*-menth-4(8)-en-3-one)	753	N	No safety concern
Isopulegone (*trans-p*-menth-8-en-3-one)	754	N	
p-Menth-1,4(8)-dien-3-one (3-methyl-6-(1-methylethylidene)cyclohex-2-en-1-one)	757	N	
Menthofuran (4,5,6,7-tetrahydro-3,6-dimethylbenzofuran)	758	N	

[a] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.

[b] N, new specifications prepared; R, existing specifications revised; T, the existing new or revised specifications are tentative and further information is required.

[c] Specifications were prepared for furfuryl butyrate, but its safety was not assessed because the Committee had no information on its intake.

[d] A group ADI of 0–0.5 mg/kg of body weight was established by the Committee at its present meeting for furfural, furfuryl alcohol, furfuryl acetate, furfuryl propionate, furfuryl pentanoate, furfuryl octanoate, furfuryl 3-methylbutanoate, methyl 2-furoate, propyl 2-furoate, amyl 2-furoate, hexyl 2-furoate and octyl 2-furoate.

[e] An ADI of 0–0.4 mg/kg of body weight was established for this substance by the 1999 Joint FAO/WHO Meeting on Pesticide Residues (FAO Plant Production and Protection Paper, No. 153, 1999).

Contaminants

Cadmium

The provisional tolerable weekly intake (PTWI) of 7 μg/kg of body weight was maintained. Ranges of predicted dietary intakes that may be associated with an excess prevalence of renal tubule dysfunction were estimated, as summarized in the following table. These values provide an indication of the risk at various levels of intake for potentially sensitive groups within the population. See Annex 3 for recommended studies.

Predicted intake of cadmium from the diet and excess prevalence of renal tubule dysfunction, based on three different sets of assumptions[a]

Assumptions	Urinary excretion of cadmium (μg/g of creatinine)[b]	Predicted intake of cadmium[c]		Predicted excess prevalence of renal tubule dysfunction (%)
		μg/day[d]	μg/kg of body weight per day[d,e]	
Bioavailability of cadmium in the diet = 10%; excretion of absorbed cadmium in urine = 100%[f]	2.5	30	0.5	0
	4.2	50	0.8	4
	8.2	100	1.7	20
Bioavailability of cadmium in the diet = 10%; excretion of absorbed cadmium in urine = 50%[g]	2.5	60	1.0	0
	4.2	100	1.7	4
	8.2	200	3.3	20
Bioavailability of cadmium in the diet = 5%; excretion of absorbed cadmium in urine = 50%[h]	2.5	120	2.0	0
	4.2	200	3.3	4
	8.2	400	6.7	20

[a] In each scenario, it is assumed that there are no significant changes in cadmium dietary intake over time and that 1.2 g of creatinine are excreted per day.

[b] Values derived primarily from studies of occupational exposure to cadmium.

[c] Predicted dietary intake = $\frac{\text{Urinary excretion of cadmium (μg of cadmium/g of creatinine)} \times 1.2}{\text{Fraction bioavailable} \times \text{Absorbed fraction excreted in urine}}$

[d] Cadmium intake corresponding to the excretion in urine in each scenario.

[e] The body weight is assumed to be 60 kg. The PTWI corresponds to a daily intake of 1 μg/kg of body weight.

[f] Ratio of dietary intake to urinary excretion = 12.

[g] Ratio of dietary intake to urinary excretion = 24.

[h] Ratio of dietary intake to urinary excretion = 48.

Tin

The PTWI of 14 mg/kg of body weight was not reconsidered and was maintained. The Committee assessed the acute toxicity of tin, but the data were insufficient for establishing an acute reference dose. The Committee reiterated its opinion, expressed at its thirty-third meeting (WHO Technical Report Series, No. 776, 1989), that the limited human data available indicate that concentrations of 150 mg/kg in canned beverages and 250 mg/kg in other canned foods may produce acute manifestations of gastric irritation in certain individuals. In addition, the Committee reiterated its advice, given at its twenty-sixth and thirty-third meetings (WHO Technical Report Series, No. 683, 1982 and No. 776, 1989), that consumers should not store food in open tin-coated cans.

Intake assessments of specific food additives

Calcium from calcium salts of food additives

Data on the levels of use and the food groups in which calcium salts of food additives are permitted would be required in order to determine their contribution to the total intake of calcium.

Substances considered for specifications only

Substance	No.	Specifications[a]
Food additives for which previous specifications were designated as "tentative"		
Acetone peroxides[b]	—	W
Aluminium potassium sulfate	—	R
Aluminium sodium sulfate[b]	—	W
Aluminium sulfate (anhydrous)	—	R
Ammonium persulfate[b]	—	W
Ammonium salts of phosphatidic acid	—	R
Benzoin gum[b]	—	W
Calcium iodate[b]	—	W
Calcium peroxide[b]	—	W
Carbohydrase from *Aspergillus awamori*, var.[b]	—	W
Carbohydrase from *Aspergillus oryzae*, var.[b]	—	W
Chlorine dioxide[b]	—	W
Diatomaceous earth	—	R
Diethyl pyrocarbonate[b]	—	W
Isoamyl gallate[b]	—	W
Lipase from *Aspergillus oryzae*, var.[b]	—	W
Potassium persulfate[b]	—	W
Rennet from *Endothia parasitica*[b]	—	W
Rennet from *Rhizomucor* species (*Mucor* species)	—	R
Food additives considered for revision of specifications		
α-Amylase from *Aspergillus oryzae*, var.	—	R
α-Amylase and glucoamylase from *Aspergillus oryzae*, var.	—	R
Amyloglucosidase from *Aspergillus niger*, var.[c]	—	R, T
Blackcurrant extract[c]	—	R, T
Cellulase from *Penicillium funiculosum*	—	R
Curcumin	—	R
Diethyl ether	—	R
β-Glucanase from *Trichoderma harzianum*	—	R
Guaiac resin	—	R
Hemicellulase from *Aspergillus niger*, var.	—	R
Microcrystalline cellulose	—	R
Microcrystalline wax	—	R
2-Nitropropane[d]	—	W
Oxystearin[c]	—	R, T
Pectinase from *Aspergillus niger*, var.	—	R
Pentasodium triphosphate	—	R

Substance	No.	Specifications[a]
Protease from *Aspergillus oryzae*, var.	—	R
Quillaia extracts	—	R
Shellac, bleached	—	R
Smoke flavourings[c]	—	R, T
Sodium sulfate	—	R
Sorbitan monolaurate	—	R
Tagetes extract[c]	—	R, T
Talc	—	R
d-α-Tocopherol, concentrate	—	R
1,1,2-Trichloroethylene[e]	—	W
Flavouring agents[f]		
Allyl propionate (2-propenyl propanoate)	1	R
Allyl tiglate (2-propenyl *trans*-2-methyl 2-butenoate)	10	R, T
Allyl phenylacetate (2-propenyl phenylacetate)	17	R
Allyl anthranilate (2-propenyl 2-aminobenzoate)	20	R
Allyl 2-furoate (2-propenyl furan-2-carboxylate)	21	R
Ethyl undecanoate	36	R
Ethyl hexadecanoate	39	R
Ethyl octadecanoate	40	R
Ethanol	41	R
Isoamyl octanoate (3-methylbutyl octanoate)	47	R
Isoamyl nonanoate (3-methylbutyl nonanoate)	48	R
Isoamyl 2-methylbutyrate (3-methylbutyl 2-methylbutanoate)	51	R, T
Geranyl acetate (3,7-dimethyl-2,6-octadien-1-yl acetate)	58	R, T
Rhodinyl propionate (3,7-dimethyl-7-octen-1-yl propionate)	64	R, T
Citronellyl valerate (3,7-dimethyl-6-octen-1-yl pentanoate)	69	R
Geranyl hexanoate (*trans*-3,7-dimethyl-2,6-octadien-1-yl hexanoate)	70	R, T
Geranyl isobutyrate (3,7-dimethyl-2,6-octadienyl-2-methylpropanoate)	72	R, T
Rhodinyl isobutyrate (3,7-dimethyl-7-octen-1-yl-2-methylpropanoate)	74	R, T
Geranyl isovalerate (3,7-dimethyl-2,6-octadienyl-3-methylbutanoate)	75	R
Rhodinyl isovalerate (3,7-dimethyl-7-octen-1-yl-3-methylbutanoate)	77	R, T
Formic acid	79	R
Acetaldehyde	80	R
Acetic acid[g]	81	R
Propionaldehyde (propanal)	83	R
Propionic acid (propanoic acid)	84	R
Butyl alcohol (1-butanol)	85	R
Butyraldehyde (butanal)	86	R
Hexyl alcohol (1-hexanol)	91	R
Octanoic acid	99	R
Decanoic acid	105	R
Undecanoic acid	108	R
Lauric acid (dodecanoic acid)	111	R, T
Myristic acid (tetradecanoic acid)	113	R, T

Substance	No.	Specifications[a]
Palmitic acid (hexadecanoic acid)	115	R, T
Stearic acid (octadecanoic acid)	116	R, T
Heptyl formate	121	R
Lauryl acetate (dodecyl acetate)	133	R
2-Ethylbutyl acetate	140	R
cis-3- and *trans*-2-Hexenyl propionate (*cis*-3- and *trans*-2-hexenyl propanoate)	147	R
Heptyl butyrate (heptyl butanoate)	154	R
Octyl butyrate (octyl *n*-butyrate)	155	R
Decyl butyrate	156	R
cis-3-Hexenyl hexanoate (*cis*-3-hexen-1-ol hexanoate)	165	R
Isobutyl hexanoate (2-methylpropyl hexanoate)	166	R
Propyl heptanoate	168	R
Butyl heptanoate	169	R
Octyl heptanoate	171	R
Isobutyl heptanoate (2-methylpropyl heptanoate)	172	R, T
Heptyl octanoate	176	R
Octyl octanoate	177	R
Nonyl octanoate	178	R, T
Isoamyl laurate (3-methylbutyl dodecanoate)	182	R, T
Butyl stearate (butyl octadecanoate)	184	R, T
Dodecyl isobutyrate (dodecyl-2-methylpropanoate)	193	R
2-Methylbutyl 3-methylbutanoate	204	R
Ethyl 2-methylbutyrate (ethyl-2-methylbutanoate)	206	R
n-Butyl 2-methylbutyrate (butyl-2-methylbutanoate)	207	R
Hexyl 2-methylbutanoate	208	R
Octyl 2-methylbutyrate (octyl 2-methylbutanoate)	209	R
Isopropyl 2-methylbutyrate (1-methylethyl-2-methylbutanoate)	210	R
3-Hexenyl 2-methylbutanoate (3-hexenylethyl-2-methylbutanoate)	211	R
Methyl 2-methylpentanoate	213	R
Ethyl 2-methylpentanoate	214	R
Ethyl 3-methylpentanoate	215	R
Methyl 4-methylvalerate	216	R
Citric acid (2-hydroxy-1,2,3-propanetricarboxylic acid)	218	R
5-Ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone	222	R
γ-Heptalactone (5-propyldihydro-2(3*H*)-furanone)	225	R
γ-Octalactone (5-butyldihydro-2(3*H*)-furanone)	226	R
4,4-Dibutyl-γ-butyrolactone (5,5-dibutyldihydro-2(3*H*)-furanone)	227	R
δ-Octalactone (6-propyltetrahydro-2-pyrone)	228	R
γ-Nonalactone (5-pentyldihydro-2(3*H*)-furanone)	229	R
δ-Decalactone (6-pentyltetrahydro-2-pyrone)	232	R
δ-Dodecalactone (6-heptyltetrahydro-2-pyrone)	236	R
ω-Pentadecalactone (oxacyclohexadecan-2-one)	239	R
ω-6-Hexadecenlactone (oxacycloheptadec-7-en-2-one)	240	S, T
ε-Decalactone (7-butyl-2-oxooxacycloheptane)	241	R
ε-Dodecalactone (7-hexyl-2-oxooxacycloheptane)	242	R
4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one (3-hydroxy-4,5-dimethyl-2(5)-furanone)	243	R
3-Heptyldihydro-5-methyl-2(3*H*)-furanone	244	R, T

Substance	No.	Specifications[a]
5-Hydroxy-2,4-decadienoic acid δ-lactone (6-pentyl-2-pyrone)	245	R
5-Hydroxy-7-decenoic acid δ-lactone (6-pentyltetrahydro-2-pyrone)	247	R
5-Hydroxy-8-undecenoic acid δ-lactone (6-hexyltetrahydro-2-pyrone)	248	R
Isobutyl alcohol (2-methylpropanol)	251	R
Isobutyraldehyde (2-methylpropanal)	252	R
2-Ethylbutyraldehyde (2-ethylbutanal)	256	R
2-Methylpentanal	260	R, T
4-Methyloctanoic acid	271	R
2-Tridecanone (tridecan-2-one)	298	R
2-Pentadecanone (pentadecan-2-one)	299	R
3-Methyl-2-butanol (3-methylbutan-2-ol)	300	R
Isopropyl propionate	306	R, T
Isopropyl hexanoate	308	R, T
Isopropyl isovalerate (isopropyl 3-methylbutanoate)	310	R
Isopropyl myristate (isopropyl tetradecanoate)	311	R
cis-3-Hexenal ((*Z*)-hex-3-enal)	316	R
3-Hexenoic acid (hex-3-enoic acid)	317	R
cis-4-Hexenal ((*Z*)-hex-4-enal)	319	R
cis-4-Heptenal ((*Z*)-hept-4-en-1-al)	320	R
cis-6-Nonen-1-ol ((*Z*)-non-6-en-1-ol)	324	R
5- and 6-Decenoic acid (mixture)	327	R
9-Undecenal (undec-9-en-1-al)	329	R, T
Oleic acid ((*Z*)-octadeca-9-enoic acid)	333	R
Methyl 3-hexenoate (methyl hex-3-enoate)	334	R, T
Methyl *cis*-4-octenoate ((*Z*)-methyl oct-4-enoate)	337	R, T
Ethyl *cis*-4-octenoate ((*Z*)-ethyl oct-4-enoate)	338	R, T
Ethyl *cis*-4,7-octadienoate (ethyl (*Z*)-octa-4,7-dienoate)	339	R
Methyl 3-nonenoate (methyl non-3-enoate)	340	R
Ethyl *trans*-4-decenoate (ethyl (*E*)-4-decenoate)	341	R
Methyl 9-undecenoate (methyl undec-9-enoate)	342	R
Butyl 10-undecenoate (butyl undec-10-enoate)	344	R, T
2-Methyl-3-pentenoic acid (2-methyl pent-3-enoate)	347	R, T
Ethyl 2-methyl-3,4-pentadienoate (ethyl 2-methylpenta-3,4-dienoate)	353	R
Methyl 3,7-dimethyl-6-octenoate (methyl 3,7-dimethyloct-6-enoate)	354	R
Linalyl isovalerate (1,5-dimethyl-1-ethenylhex-4-enyl 3-methylbutyrate)	363	R
Linalyl octanoate (1,5-dimethyl-1-ethenylhex-4-enyl octanoate)	365	R
Terpinyl formate (*p*-menth-1-en-8-yl formate)	367	R, T
Terpinyl butyrate (*p*-menth-1-en-8-yl butyrate)	370	R, T
Terpinyl isobutyrate (*p*-menth-1-en-8-yl isobutyrate)	371	R
Terpinyl isovalerate (*p*-menth-1-en-8-yl isovalerate)	372	R, T
p-Menth-3-en-1-ol	373	R
p-Menthan-2-ol	376	R
Dihydrocarvone (*p*-menth-8-en-2-one)	377	R
l-Carvone (*p*-mentha-6,8-dien-2-one)	380.2	R
Carvyl propionate (1-*p*-mentha-6,8-dien-2-yl propionate)	383	R

Substance	No.	Specifications[a]
β-Ionol (4-(2,6,6-trimethyl-1-cyclohexenyl)-3-butene-2-ol)	392	R
Dihydro-β-ionone (4-(2,6,6-trimethyl-1-cyclohexenyl)-3-butan-2-one)	394	R
Methyl-α-ionone (5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-4-penten-3-one)	398	R
Methyl-δ-ionone (4-(2,6,6-trimethyl-3-cyclohexen-1-yl)-3-methyl-3-buten-2-one)	400	R
1,4-Dimethyl-4-acetyl-1-cyclohexene	402	R
2-Acetoxy-3-butanone (1-methyl-2-oxopropyl acetate)	406	R
Butan-3-one-2-yl butanoate (1-methyl-2-oxopropyl butyrate)	407	R
3-Hydroxy-2-pentanone (3-hydroxypentan-2-one)	409	R, T
4-Methyl-2,3-pentanedione (4-methylpentane-2,3-dione)	411	R
2,3-Hexanedione (hexane-2,3-dione)	412	R
5-Methyl-2,3-hexanedione (5-methylhexane-2,3-dione)	414	R
5-Hydroxy-4-octanone (5-hydroxyoctan-4-one)	416	R, T
2,3-Undecadione (undeca-2,3-dione)	417	R, T
Methylcyclopentenolone (3-methylcyclopentane-1,2-dione)	418	R
3,4-Dimethyl-1,2-cyclopentanedione (3,4-dimethylcyclopentane-1,2-dione)	420	R
3,5-Dimethyl-1,2-cyclopentanedione (3,5-dimethylcyclopentane-1,2-dione)	421	R
2-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (2-hydroxy-3,5,5-trimethylcyclohex-2-en-1-one)	426	R
l-Menthyl lactate	433	R
5-Hydroxy-2-dodecenoic acid δ-lactone (6-heptyl-2*H*-dihydro-2-pyrone)	438	R
4-Carvomenthenol (*p*-menth-1-en-4-ol)	439	R
4-Thujanol (2-methyl-5-(1-methylethyl)bicyclo[3.1.0]-hexan-2-ol)	441	R
dl-Menthone 1,2-glycerol ketal (1,4-dioxaspiro[4,5]decane-2-menthanol)	446	R
1,4-Dithiane	456	R
Allyl sulfide (diallyl sulfide)	458	R
4-(Methylthio)butanol (4-(methylthio)-1-butanol)	462	R
2-Methyl-4-propyl-1,3-oxathiane	464	R
3-(Methylthio)propionaldehyde	466	R
3-(Methylthio)butanal	467	R
Ethyl 2-(methylthio)acetate	475	R
3-(Methylthio)propyl acetate	478	R, T
3-(Methylthio)hexyl acetate	481	R
S-Methyl thioacetate (*S*-methyl acetothioate)	482	R
Methyl thiobutyrate (*S*-methyl butanethioate)	484	R
S-Methyl 2-methylbutanethioate	486	R
S-Methyl 3-methylbutanethioate	487	R
4-(Methylthio)-2-butanone	497	R
4,5-Dihydro-3(2*H*)-thiophenone	498	R
2-Methyltetrahydrothiophen-3-one (4,5-dihydro-2-methyl-3(2*H*)-thiophenone)	499	R
4-(Methylthio)-4-methyl-2-pentanone (4-methyl-4-(methylthio)-2-pentanone)	500	R

Substance	No.	Specifications[a]
Di(butan-3-one-1-yl) sulfide (di-(3-oxobutyl) sulfide)	502	R, T
o-(Methylthio)phenol (2-(methylthio)phenol)	503	R
Methylsulfinylmethane	507	R
Methyl mercaptan (methanethiol)	508	R
Propanethiol (1-propanethiol)	509	R
2-Propanethiol	510	S, T
2-Methyl-1-propanethiol	512	R
3-Methylbutanethiol (3-methyl-1-butanethiol)	513	R
2-Pentanethiol	514	R
Cyclopentanethiol	516	R
1-Hexanethiol	518	R
2-, 3- or 10-Mercaptopinane (mixture of 2,6,6-trimethylbicyclo-[3.1.1]heptane-(2-, 3- and 10-)thiols)	520	R
Allyl mercaptan (allylthiol)	521	R
1-*p*-Menthene-8-thiol	523	R
Thiogeraniol (3,7-dimethyl-2(*trans*),6-octadiene-1-thiol)	524	R
o-Toluenethiol (2-methylbenzenethiol)	528	R
2-Ethylthiophenol (2-ethylbenzenethiol)	529	R
bis(Methylthio)methane	533	R
1,2-Propanedithiol	536	R
3-Mercapto-3-methyl-1-butanol	544	R
2-Mercapto-3-butanol (3-mercapto-2-butanol)	546	R
Ethyl 2-mercaptopropionate	552	R
3-Mercapto-2-butanone	558	R
3-Mercapto-2-pentanone	560	R
p-Mentha-8-thiol-3-one (8-mercapto-3-*p*-menthanone)	561	R
Methyl propyl disulfide	565	R
Allyl disulfide (diallyl sulfide)	572	R
3,5-Dimethyl-1,2,4-trithiolane	573	R
3-Methyl-1,2,4-trithiane	574	R
Dicyclohexyl disulfide	575	R
Benzyl disulfide (dibenzyl disulfide)	579	R
Dimethyl trisulfide	582	R
Methyl propyl trisulfide	584	R
Dipropyl trisulfide	585	R
Diallyl trisulfide	587	R
Diallyl polysulfide (mixture of diallyl di-, tri-, tetra- and pentasulfides)	588	R
2-Oxobutyric acid	589	R
Citronelloxyacetaldehyde (6,10-dimethyl-3-oxa-9-undecenal)	592	R, T
Ethyl 3-hydroxybutyrate	594	R
Butyl acetoacetate (butyl 3-oxobutyrate)	596	R
Isobutyl acetoacetate (2-methylpropyl 3-oxobutyrate)	597	R
Isoamyl acetoacetate (3-methylbutyl 3-oxobutyrate)	598	R
Methyl 3-hydroxyhexanoate	600	R
3-(Hydroxymethyl)-2-heptanone	604	R, T
1,3-Nonanediol acetate (mixed esters) (mixture of 3-acetoxynonyl acetate, 3-hydroxynonyl acetate and 1-(2-hydroxyethyl)heptyl acetate)	605	R, T
Hydroxycitronellol (2,6-dimethyl-2,8-octanediol)	610	R

Substance	No.	Specifications[a]
Hydroxycitronellal diethyl acetal (8,8-diethoxy-2,6-dimethyl-2-octanol)	613	R
Fumaric acid (2(*trans*)-butenedioic acid)	618	R
l-Malic acid (2-hydroxybutanedioic acid)	619	R
Diethyl malate (diethyl 2-hydroxybutanedioate)	620	R
Triethyl citrate (triethyl 2-hydroxy-1,2,3-propanetricarboxylate)	629	R
3-Methyl-2-oxobutanoic acid, sodium salt (sodium 3-methyl-2-oxobutyrate)	631.1	R, T
Tributyl acetylcitrate (tributyl 2-acetoxy-1,2,3-propane-tricarboxylate)	630	R
3-Methyl-2-oxopentanoic acid, sodium salt (sodium 3-methyl-2-oxovalerate)	632.1	R, T
4-Methyl-2-oxopentanoic acid, sodium salt (sodium 4-methyl-2-oxovalerate)	633.1	R, T
Furfuryl butyrate (2-furanylmethyl butanoate)	759	N, T

[a] R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new or revised specifications are tentative and comments are invited; W, existing specifications withdrawn.

[b] Relevant information was not provided so the tentative specifications were withdrawn.

[c] See Annex 3.

[d] The temporary acceptance of 2-nitropropane for use as a fractionating solvent in the production of fats and oils was not extended by the Committee at its thirty-fifth meeting (WHO Technical Report Series, No. 789, 1990). In the absence of further information on use, the Committee withdrew the specifications.

[e] At its twenty-seventh meeting (WHO Technical Report Series, No. 696, 1983), the Committee recommended that use of 1,1,2-trichloroethylene as an extraction solvent be limited because of toxicological concerns and requested information on the nature, level(s) and methods of analysis for stabilizers and breakdown products. As the requested information was not submitted for consideration at the present meeting, the Committee withdrew the specifications.

[f] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 8, 2000). In cases where substances were considered under their trivial name, the systematic name is given in parentheses.

[g] The Committee concluded that the specifications of this substance should be reviewed at its next meeting on food additives in order to consider more up-to-date information.

Annex 3
Further information required or desired

Toxicological information

D-Tagatose

Before reviewing the compound again, the Committee would wish to evaluate the final reports of the two studies in Sprague-Dawley and Wistar rats that were available in draft form, which might help to resolve the relevance of the induction of liver glycogen deposition and hypertrophy. It also wished to evaluate data to clarify the extent, mechanism and toxicological consequences of the increased serum uric acid concentrations observed in humans exposed to D-tagatose.

Cadmium

The Committee recommended that seven areas be investigated in order to increase confidence in the estimates of predicted excess prevalence of renal tubule dysfunction:

1. The toxicokinetics of cadmium should be investigated in controlled experimental studies in humans of the relationship between dietary intake and urinary excretion of cadmium in the general population and in groups at high risk, such as people with iron deficiency, renal disease or diabetes mellitus.
2. Dietary surveys should be conducted in which individual records of the food consumption of specific population subgroups are kept.
3. Studies should be conducted on the bioavailability of cadmium from specific foods and on the factors that affect its bioavailability, such as age, health status and dietary nutrients.
4. The relationship between biomarkers of renal tubule dysfunction and biomarkers of cadmium exposure should be elucidated.
5. The relationship between renal tubule dysfunction (as determined by specific biomarkers), clinical disease and mortality should be studied.
6. The influence of cadmium on calcium metabolism and osteoporosis should be examined.
7. Studies should be conducted to determine the effect of exposure to cadmium (integrated over a lifetime) on the subsequent development of osteoporosis.

Information on specifications

Amyloglucosidase from Aspergillus oryzae, var.

Information is required on the assay for amyloglucosidase in formulated products with glucose. Comments on other aspects of the monograph are invited.

Blackcurrant extract

Information is required on a chromatographic identification test and on the adequacy of the sample size for the test for sulfur dioxide. Comments on other aspects of the monograph are invited.

Oxystearin

Information on the levels of, and a suitable analytical method for, epoxides is required for consideration by the Committee at its meeting in June 2001. Comments on other aspects of the monograph are invited. If no information is received by 1 May 2001, the monograph will be withdrawn.

Smoke flavourings

Information is required on an alternative solvent to benzene for use in the analysis of the carbonyl content (proposals should be supported by a comparative test of the analytical method with benzene and the proposed alternative solvent). Comments on other sections of the monograph are invited.

Tagetes extract

Information is required on the composition of the commercial products, a test for the identification of xanthophylls, and a method of assay. Comments on other sections of the monograph are invited.

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