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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

World Health Organization

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Geneva, 9–18 February 1993

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

Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 32, 1993.

Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 52, Add. 2, 1993.

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 Organisation, 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 9 to 18 February 1993. The meeting was opened by Dr N.P. Napalkov, Assistant Director-General, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Napalkov noted that the Committee's recommendations had probably contributed more to the elaboration of sound principles for the scientific assessment of food additives than had those of any other international body concerned with problems of food safety and technology and the control of food additives and contaminants. In view of the growing need to harmonize scientific assessments carried out by governments and international organizations, Dr Napalkov stressed that the Committee should enunciate its assessment principles clearly and be consistent in their application so that everyone would be able to understand the basis for its decisions.

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 forty previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the thirty-ninth meeting (Annex 1, reference *101*).

The tasks before the Committee were:

(a) to further elaborate principles for evaluating the safety of food additives and contaminants (section 2);
(b) to undertake toxicological evaluations of certain food additives and contaminants (section 3 and Annexes 2 and 3);
(c) to review and prepare specifications for selected food additives (sections 3 and 4 and Annexes 2 and 3); and
(d) to discuss and advise on matters arising from the Twenty-fourth Session of the Codex Committee on Food Additives and Contaminants (*2*) (Annex 4).

2.1 Modification of the agenda

(+)-Limonene, maltitol and maltitol syrup were added to the agenda for evaluation, together with quinine (specified as the hydrochloride and sulfate salts).

Sodium iron ethylenediamine tetraacetate (EDTA) was added for assessment of its safety for use in supervised food fortification programmes in populations in which iron-deficiency anaemia is endemic.

Alginic acid, ammonium alginate, calcium alginate, carmines, erythrosine, potassium alginate and sodium alginate were added for preparation of specifications only.

Cyclodextrin B and carbamide were evaluated under the designations β-cyclodextrin and urea respectively, the substances for which specifications were established at the present meeting.

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 WHO Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as principles elaborated subsequently at meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94* and *101*), including the present one. WHO 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 document 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 *Vegetable extracts*

In considering extracts of carrots or alfalfa as sources of natural colours (specifically β-carotene), the Committee had, at its thirty-first meeting, expressed the view that the need for toxicity tests might be obviated if detailed analytical data confirmed that the levels of exposure would not exceed those resulting from normal use of the vegetables (Annex 1, reference *77*). At its present meeting, the Committee confirmed this general principle, stressing that the extraction process should not lead to the concentration of naturally occurring toxicants or extraneous chemicals, such as pesticides, or to the generation of reaction products or residues of a nature or in such amounts as to be toxicologically significant. The Committee concluded that suitable specifications were required for these substances.

2.2.2 *Corn oil gavage*

At its present meeting, the Committee reviewed studies in which substances were administered by gavage in corn oil, and noted that in one of these studies the incidence of pancreatic tumours was higher than expected in all groups. Assessment of the carcinogenic potential of substances administered by gavage in corn oil is complicated by the possibility that the mode of administration may independently influence tumour rates. In a recent report based on results from 37 long-term studies from the National Toxicology Program in the USA, an association was

demonstrated between use of corn oil gavage and an increased incidence of pancreatic acinar cell hyperplasia and adenomas in male F-344 rats (*3*). The overall incidence of these lesions was approximately five times as high in the corn oil gavage controls as in untreated controls. Similarly, a more recent analysis of 88 long-term studies from the National Toxicology Program found an association between use of corn oil gavage and an increased incidence of pancreatic acinar cell tumours in male rats. The corn oil gavage controls also showed a lower incidence of leukaemia, higher body weights and higher survival rates than untreated controls (*4*).

On the basis of these findings, the Committee concluded that studies involving substances administered by corn oil gavage must be carefully evaluated to assess the possible influence of this mode of administration on the incidence of tumours. Careful attention should be paid to the design of future studies to assess the carcinogenicity of food additives and contaminants with respect to the vehicle and mode of administration.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *Enzyme preparations from microbial sources*

The Committee has, on several previous occasions, addressed problems associated with the formulation of specifications for enzyme preparations used in food processing and manufacture. At its thirty-fifth meeting (Annex 1, reference *88*), the Committee prepared revised general specifications, which were subsequently published as an annex in FAO Food and Nutrition Paper, No. 49 (Annex 1, reference *90*). At its thirty-seventh meeting, the Committee discussed new issues relating to enzyme preparations from genetically modified organisms and prepared an addendum to its "General specifications for enzyme preparations used in food processing", which was published in the *Compendium of food additive specifications* (Annex 1, reference *96*). At that time, the Committee recommended that, whenever such products were to be evaluated, a fully documented taxonomic history of the organisms concerned, together with detailed information for their identification, should be provided. In addition, the Committee encouraged the use of national and international culture collections as sources of reference material by manufacturers to assist in the identification of microorganisms used commercially. In line with this, the Committee had begun to include international culture collection numbers and strain types in new specifications for enzyme preparations. At its present meeting, the Committee reconsidered the need for specifying strain type and culture collection numbers in all specifications.

The Committee noted that submission of a well characterized microorganism to a culture collection does not guarantee that the particular strain will remain unmutated during use. The Committee also agreed that the citation of a specific strain type and culture collection

number might give an unfair advantage to particular companies that submit organisms to the culture collection.

The Committee reaffirmed that information submitted in relation to specifications for enzyme preparations of microbial origin should continue to be prepared in accordance with its previously published "General specifications for enzyme preparations used in food processing" (Annex 1, reference *90*), and that strain types and culture collection numbers should continue to be specified in all submissions.

The Committee also reaffirmed that in certain instances it was essential for the strain type of an organism to be indicated in the specifications to provide the necessary safety assurances, as, for example, for enzymes derived from strains of *Escherichia coli*, some of which are known to produce endotoxins. However, the Committee considered that it was not necessary to include this information in all specifications and decided that it would consider the need for including strain types and collection numbers in specifications on a case-by-case basis.

2.3.2 *Limits for heavy metals*

In response to a request by the Working Group on Specifications of the Codex Committee on Food Additives and Contaminants (*2*), the Committee considered limits for metals as they relate to the intake and manufacture of food additives. Although food additives generally account for only a small proportion of the total human exposure to heavy metals, the Committee drew attention to the desirability of continuing to lower dietary exposure to lead and certain other heavy metals, particularly from additives consumed at high levels. In setting limits for lead and other heavy metals in food additives, the Committee agreed to the importance of considering the relationships between the intake of a food additive, the feasibility of manufacturing a product within the prescribed limits, and the availability of analytical methods to ensure compliance. The Committee recognized that the constraints of good manufacturing practice and the availability of reliable analytical methods are often limiting factors in setting lower limits for lead and other heavy metals.

So that limits for heavy metals and specifically lead can be set at the lowest levels practical, the Committee recommended that future submissions on specifications include, especially in the case of lead, actual concentrations found for the substance under consideration, together with details of the analytical methods employed. The Committee also noted that, because not all additives are consumed at the same levels or can be produced at the same level of purity, it is not reasonable to fix uniform limits for lead or other heavy metals in all food additives.

2.3.3 *Specifications for substances derived from natural sources*

The Committee has, on previous occasions, encountered difficulties with the formulation of specifications for additives obtained from plant, animal

and other natural sources. In revising the specifications for processed *Eucheuma* seaweed, carotenes (algal and vegetable), and ammonium phosphate, disodium pyrophosphate and tetrasodium pyrophosphate at its present meeting, the Committee recognized that additives that can be derived from more than one natural source are likely to vary in their composition, particularly with respect to the quantity and nature of impurities, because of differences in, for example, climatic and geological conditions and species of origin. The Committee therefore drew particular attention to the need for appropriate and sufficient chemical analytical data to be provided on both the additive and the source material. The substances for which data are provided should be representative of those to be specified as sources of food-grade material and of the additives that will undergo toxicological evaluation.

The Committee also recognized that, in certain instances, specifications for a natural product may be formulated to include more than one species as a source, without the need for review of toxicological studies on the product from each proposed source. Such instances may arise if the product can be demonstrated to be consistently produced in a highly purified form or to be well characterized with respect to its principal components and impurities among the various proposed sources.

2.3.4 *Provision of information for revision of specifications*

At its present meeting, the Committee again had on its agenda a group of substances that had been referred back via the Codex Committee on Food Additives and Contaminants with a request for certain criteria in the specifications to be changed. Such requests have, however, often been presented to the Committee without any supporting documentation. In these circumstances the Committee is unable to carry out an evaluation. The Committee therefore underlined the need for appropriate documentation to be provided in support of proposed revisions and emphasized that in the absence of such information it is unable to amend purity specifications.

3. Comments on specific food additives and contaminants[1]

The Committee evaluated several food additives and contaminants for the first time and re-evaluated several food additives and contaminants considered at previous meetings. 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.

[1] When the Committee's evaluations have included dietary studies, the levels of the substance administered to animals are often given in the form of percentages; these are calculated on a weight-for-weight basis, so that 0.1% = 1 g/kg of feed, 1.0% = 10 g/kg of feed, etc.

3.1 Specific food additives

3.1.1 *Antioxidants*

Gallates (dodecyl, octyl and propyl)

These substances were previously evaluated by the Committee at its third, sixth, eighth, tenth, fifteenth, sixteenth, seventeenth, twentieth, twenty-fourth and thirtieth meetings (Annex 1, references *3*, *6*, *8*, *13*, *26*, *30*, *32*, *41*, *53* and *73*). At the twenty-fourth meeting, a group ADI of 0–0.2 mg per kg of body weight was established, based on the supposed similarity in the biotransformation of these compounds. In setting this ADI, the Committee had used a higher than normal safety factor (250), because of concern about adverse effects shown in reproduction studies. The gallates were again reviewed by the Committee at its thirtieth meeting, when an ADI of 0–2.5 mg per kg of body weight was established for propyl gallate. However, the Committee was unable to establish an ADI for octyl and dodecyl gallate owing to lack of adequate data, and requested that studies be carried out on the metabolism of these substances, including identification of their metabolites in the milk of lactating animals, and the toxicity of their known hydrolysis products.

Since the previous evaluation, 4-week and 90-day toxicity studies have been performed in rats with propyl gallate and *in vitro* studies conducted on the hydrolysis of the gallates in different tissues.

Although there are similarities in the metabolism of the different gallates as evidenced by earlier limited data and the recent *in vitro* metabolism study, the Committee concluded that there was not enough evidence to allocate a group ADI for the gallates when *in vivo* pharmacokinetic and metabolic studies were not available. In addition, a 150-day gavage study with dodecyl gallate revealed a no-observed-effect level (NOEL) that was 10-fold lower than the dietary NOEL for propyl gallate.

In the 90-day toxicity study in rats, propyl gallate administered in the diet at 7450 mg/kg caused changes in haematological parameters (decreased haemoglobin, erythrocyte volume fraction and red blood cell count), morphological changes (increased extramedullary haematopoiesis) in the spleen, and increased activity of hepatic ethoxyresorufin *O*-deethylase (EROD). The Committee allocated an ADI of 0–1.4 mg per kg of body weight for propyl gallate, which was based on the NOEL in this study of 1910 mg/kg propyl gallate in the diet (equal to 135 mg per kg of body weight per day) and a safety factor of 100.

The Committee concluded that it was unlikely that either octyl or dodecyl gallate was carcinogenic or genotoxic. Therefore, the Committee allocated temporary ADIs to both these substances, based on the NOELs observed in limited toxicological studies.

With octyl gallate, a slight hypochromic anaemia was observed at 100 mg per kg of body weight per day in a study in rats in which the substance was administered for two generations. A temporary ADI of 0–0.1 mg per kg of

body weight was allocated for octyl gallate, based on a NOEL of 17.5 mg per kg of body weight per day in this study and a safety factor of 200.

With dodecyl gallate, a reduction in spleen weight and pathological changes in the liver, kidney and spleen were observed in a 150-day study in rats in which the substance was administered by gavage. A temporary ADI of 0–0.05 mg per kg of body weight was allocated for dodecyl gallate, based on a NOEL of 10 mg per kg of body weight per day in this study and a safety factor of 200.

The Committee concluded that additional studies on the pharmacokinetics and metabolism of dodecyl, octyl and propyl gallate might help to explain the differences in toxicological potency of these compounds and requested data from such studies to be made available by 1996. If these studies do not satisfactorily resolve the issue with respect to the similarity of octyl and dodecyl gallate to propyl gallate, further toxicological studies (including long-term toxicity/carcinogenicity studies and genotoxicity studies) on octyl and dodecyl gallate might be required.

A toxicological monograph was prepared. The existing specifications for each of the three substances were revised.

3.1.2 *Flavouring agents*

Benzyl acetate

This compound was previously evaluated at the eleventh, twenty-seventh, twenty-ninth, thirty-first and thirty-fifth meetings of the Committee (Annex 1, references *14*, *62*, *70*, *77* and *88*). During some of these meetings, the Committee also considered related substances, including benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts.

Benzyl acetate was first evaluated by the Committee at its eleventh meeting (Annex 1, reference *14*), when an ADI of 0–5 mg per kg of body weight was allocated in terms of benzoic acid, representing total benzoate from all food additive sources. At the twenty-seventh meeting (Annex 1, reference *62*), the ADI for benzyl acetate was retained but made temporary because of concern raised by preliminary findings from screening tests for carcinogenicity. At its twenty-ninth meeting (Annex 1, reference *70*), the Committee considered new data on the metabolism of benzyl acetate and on the occurrence of tumours in rats and mice given benzyl acetate by gavage. The Committee extended the temporary ADI of 0–5 mg per kg of body weight, pending results from carcinogenicity studies with benzyl alcohol. The temporary ADI was again extended at the thirty-first meeting of the Committee (Annex 1, reference *77*), as the expected data were not available. At its thirty-fifth meeting (Annex 1, reference *89*), the Committee reviewed lifetime gavage studies with benzyl alcohol and found no evidence of a tumorigenic effect. The Committee extended the temporary ADI of 0–5 mg per kg of body weight for benzyl acetate until 1993, pending the evaluation of results from ongoing long-term studies

with benzyl acetate incorporated into the diet of mice and rats, and requested data from an *in vivo* test for chromosome damage in bone marrow.

At its present meeting, the Committee reviewed data from short-term and long-term studies in rats and mice in which benzyl acetate had been incorporated into the diet. These studies did not show any increase in the incidence of either hepatocellular or forestomach tumours in mice or of pancreatic tumours in rats, which had been observed previously in studies with benzyl acetate administered by gavage in corn oil.

The Committee noted a documented association between the use of corn oil as a vehicle control and an increased incidence of pancreatic acinar cell hyperplasia and adenomas in male rats (see section 2.2.2). In addition, an altered incidence of other site-specific neoplasms has been observed after administration of corn oil by gavage (*4*).

Considering the use of both modes of administration in long-term studies, the Committee concluded that the administration of benzyl acetate in the diet was more relevant to its safety assessment as a food additive than administration by gavage in corn oil.

The Committee also reviewed data from new genotoxicity studies. These studies showed no evidence of *in vivo* genotoxicity of benzyl acetate when tested for induction of sister chromatid exchange, chromosomal aberrations or micronuclei in mouse bone marrow cells.

The Committee noted the induction of necrosis of the brain involving the cerebellum and/or hippocampus in rats and mice given benzyl acetate at a dose level of 5% in the diet for 13 weeks. No such effect was observed in the long-term toxicity/carcinogenicity studies in mice or rats at lower doses. In the long-term study in rats, no adverse effects were observed at levels of up to 550 mg per kg of body weight per day in the diet.

In the long-term toxicity/carcinogenicity study in mice given 330, 1000 or 3000 mg/kg benzyl acetate in the diet (equal to 37, 112 and 345 mg per kg of body weight per day in males and 42, 132 and 382 mg per kg of body weight per day in females), dose-related degeneration and atrophy of the olfactory epithelium, cystic hyperplasia of the nasal submucosal glands, and pigmentation of the nasal mucosal epithelium were observed. The Committee considered the changes of the nasal cavity to be a result of local irritant effects of the test compound and not toxicologically relevant to the assessment of food safety.

At the end of the study, treated male and female mice showed lower mean body weights than controls. In the absence of associated pathological lesions in the long-term toxicity/carcinogenicity study in mice and on the basis of the NOEL of 550 mg per kg of body weight per day in the long-term study in rats, the Committee included benzyl acetate in the existing group ADI of 0–5 mg per kg of body weight for benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts.

The Committee noted the absence of reproduction/teratogenicity studies for substances in this group, and recommended that a full review of benzyl acetate, benzoic acid, the benzoate salts, benzaldehyde and benzyl alcohol be performed in 1995 to determine whether these or other studies are required.

An addendum to the toxicological monograph was prepared. The existing specifications were retained.

2-Ethyl-1-hexanol

2-Ethyl-1-hexanol has not been previously evaluated by the Committee.

In rats, orally administered 2-ethyl-1-hexanol is absorbed and rapidly eliminated within 28 hours, mainly in urine and faeces. The major urinary metabolite is 2-ethylhexanoic acid.

In mice, rats and monkeys, the compound is oxidized by β-, ω-, and ω-1-oxidation to various metabolites, including 2-ethylhexanoic acid, ethylhexanedioic acid, and 5-hydroxyethylhexanoic acid. Glucuronic acid conjugates are formed in all three species.

The Committee concluded that the available data do not indicate that 2-ethyl-1-hexanol is genotoxic. With a single exception, in which a positive result occurred in the presence of significantly decreased cell survival (cytotoxicity), the results of both *in vivo* and *in vitro* genotoxicity tests were negative.

Although teratogenic effects were reported in the offspring of mice administered 2-ethyl-1-hexanol by gavage at 1500 mg per kg of body weight per day on days 6–13 of gestation, these effects occurred in the presence of severe maternal toxicity (the body weight gain of treated females was approximately 40% less than that of untreated controls). In rats, administration of 2-ethyl-1-hexanol by gavage at a dose of 1600 mg per kg of body weight on day 12 of gestation was associated with a statistically significant increase in the number of malformed live fetuses (malformations included hydronephrosis, tail defects and limb defects). No adverse effects were observed in rats at a dose of 800 mg per kg of body weight. Maternal toxicity was not reported in this study.

The results of several short-term toxicity studies suggested that 2-ethyl-1-hexanol administered orally to rats and mice at doses greater than approximately 350 mg per kg of body weight per day induces liver peroxisome proliferation and/or marker enzymes for peroxisome proliferation. However, the results of carcinogenicity studies did not indicate that long-term oral administration of 2-ethyl-1-hexanol leads to induction of liver tumours in mice or rats.

The results of long-term carcinogenicity studies in which 2-ethyl-1-hexanol was administered orally to rats for 24 months and to mice for 18 months indicated that it is not carcinogenic. The incidence of hepatocellular carcinomas at 750 mg per kg of body weight per day in female mice was slightly higher than in historical controls; however, this

effect was considered to be incidental and unrelated to the administration of 2-ethyl-1-hexanol. The increase was statistically significant when compared with the incidence in female mice serving as vehicle controls, but not when compared with the incidence in control females given distilled water by gavage. In these studies, a dose of 750 mg per kg of body weight per day produced a number of significant, non-carcinogenic adverse effects; however, these effects were not observed at 50 or 200 mg per kg of body weight per day in mice or at 50 mg per kg of body weight per day in rats.

On the basis of a NOEL of 50 mg per kg of body weight per day from the long-term study in rats and a safety factor of 100, the Committee established an ADI of 0-0.5 mg per kg of body weight for 2-ethyl-1-hexanol.

A toxicological monograph and new specifications were prepared.

(+)-Limonene

(+)-Limonene (*d*-limonene) was previously evaluated at the thirty-ninth meeting of the Committee (Annex 1, reference *101*), when an ADI of 0-1.5 mg per kg of body weight was established. The Committee noted that (+)-limonene occurred naturally in foods and that only a small proportion of total intake was likely to be derived from direct additive use. At that time, the Committee recommended that food additive intake be restricted to 75 µg per kg of body weight per day, which represents 5% of the maximum ADI for (+)-limonene.

The principal toxicological finding was that (+)-limonene exacerbates the spontaneously occurring nephropathy in mature male rats, with the subsequent occurrence of renal tumours. At the thirty-ninth meeting, there was an extensive discussion of the mechanism of this toxic effect, its relationship to the accumulation of α_{2u}-globulin in the phagolysosomes of epithelial cells of the proximal convoluted tubules of the kidney, and the relevance of this toxic response to humans, which do not generate appreciable amounts of this androgen-dependent protein. The Committee concluded that the postulated mechanism for (+)-limonene-induced nephropathy and renal tumours in the male rat was probably not relevant to humans, and that toxic end-points associated with this effect were not appropriate bases for the derivation of an ADI for (+)-limonene.

The ADI established at the thirty-ninth meeting was based upon the significant decreases in body weight gain associated with the administration of (+)-limonene to male and female rats and mice and female rabbits. It was based on the lowest NOEL for this effect, which was 150 mg per kg of body weight per day (administered by gavage) in a 2-year study in male rats. The use of such an end-point is discussed in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), which indicates that reduced weight gain, as distinct from a generalized weight loss, may be used as an end-point in toxicological

studies for determining the ADI in the absence of other manifestations, provided that reduced food intake is not the obvious cause.

At its present meeting, the Committee reviewed the ADI for (+)-limonene because of concern that the reduction in weight gain, which served as the basis for the ADI, may have been influenced by the nephrotoxic response in male rats, which had been considered to be inappropriate for establishing an ADI.

The critical NOEL was the higher of the two dose levels (75 and 150 mg per kg of body weight per day) administered by gavage to male rats in the long-term studies, while female rats (300 and 600 mg per kg of body weight per day), male mice (250 and 500 mg per kg of body weight per day) and female mice (500 and 1000 mg per kg of body weight per day) received higher doses. Lower doses were chosen for the male rats because of the nephrotoxic response seen in short-term range-finding studies. The reduction in weight gain was no greater than 4–7% at any dose used in the two long-term toxicity studies (except at 1000 mg per kg of body weight per day in female mice after week 28, when the reduction was 5–15%), so that any of the doses used, apart from 1000 mg per kg of body weight per day, could have qualified as the NOEL for reduced weight gain. In 13-week studies using higher doses, the reductions in body weight gain were only moderate even in male rats, which developed renal lesions at all dose levels (6% at 600 mg per kg of body weight per day, 12% at 1200 mg per kg of body weight per day and 23% at the significantly lethal dose level of 2400 mg per kg of body weight per day). In female rats, a reduction in weight gain (11%) was only observed at the significantly lethal dose level of 2400 mg per kg of body weight per day. In teratogenicity studies in mice and rabbits, reduced weight gains due to (+)-limonene were observed at significantly maternally toxic and embryotoxic doses (2400 and 1000 mg per kg of body weight per day, respectively).

At its present meeting, the Committee concluded that the ADI should not be set on the basis of the highest dose level in the long-term rat study, where nephrotoxicity in male rats precluded testing at higher doses. The Committee noted that no toxicity, other than decreased weight gain, had been observed at sub-lethal doses in female rats or in other species, and that current patterns of use indicate that most (+)- limonene consumption would be associated with natural sources. The Committee therefore withdrew the previous ADI for (+)-limonene and allocated an ADI "not specified".

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

α-Methylbenzyl alcohol

α-Methylbenzyl alcohol (1-phenylethanol) has not previously been evaluated by the Committee. This substance is used as a flavouring agent in foods and beverages; it also occurs naturally in a variety of foods at levels of up to 1.3 mg/kg.

Following oral administration, this compound is rapidly excreted in the urine. The principal metabolites have been identified as hippuric acid and the glucuronide conjugate.

The Committee reviewed a series of acute, short-term and long-term toxicity studies in which α-methylbenzyl alcohol was administered by gavage in corn oil to rats and mice. In addition, the Committee evaluated a dermal teratogenicity study in rats and a battery of *in vitro* genotoxicity tests, which included bacterial and mammalian point mutation and mammalian chromosomal aberration studies.

In the short-term toxicity studies, high rates of mortality were associated with dose levels of 1000 and 2000 mg per kg of body weight per day in the mouse and 2000 mg per kg of body weight per day in the rat.

An increase in haemosiderin deposits in macrophages of the spleen was noted at 750 mg per kg of body weight per day in male rats during a 13-week study. This effect was not, however, noted during a 2-year study. A dose-related increase in liver weight that was noted in both male and female rats in the 13-week study could not be assessed in the 2-year study since liver weights were not recorded. However, an increase in the incidence of centrilobular necrosis was observed in male rats at both dose levels (375 and 750 mg per kg of body weight per day) in the latter study.

In the long-term studies, the body weight gains were at least 10% higher in untreated controls than in male and female mice and female rats at 750 mg per kg of body weight per day and in male rats at 375 and 750 mg per kg of body weight per day. The long-term survival of the rats, but not the mice, was significantly reduced by oral administration of α-methylbenzyl alcohol at 375 or 750 mg per kg of body weight per day. Exacerbation of age-related nephropathy was noted at both dose levels in male rats. The incidence of renal tubular cell hyperplasia and adenomas was also significantly higher in these rats than in untreated controls. A NOEL was not observed in this study.

A teratogenicity study in rats in which α-methylbenzyl alcohol was administered dermally showed a range of teratogenic and embryotoxic effects at the highest dose of 1400 mg per kg of body weight per day. Maternal toxicity was also demonstrated at this dose. Because α-methylbenzyl alcohol was administered dermally, the metabolism and extent of absorption are likely to differ from when it is given by the oral route; hence the comparability of dose levels was uncertain. The NOEL in this study was 430 mg per kg of body weight per day.

α-Methylbenzyl alcohol was mutagenic in eukaryotic cells (mammalian and yeast), but not in prokaryotic cells (bacteria) and induced chromosomal aberrations in mammalian cells *in vitro*.

The Committee noted that α-methylbenzyl alcohol administered by gavage in corn oil was associated with a higher incidence of renal tubular cell adenomas in male rats than in untreated controls, but not in female rats

or in mice, at dose levels at or exceeding the maximum tolerated dose (MTD) and in the presence of factors that exacerbated a high incidence of age-related chronic progressive nephropathy.

The intake of this compound from all sources is extremely low. On the basis of the evidence available, the Committee concluded that the higher incidence of benign neoplasms in the kidney of male rats is not relevant to humans. In view of the limited database, the Committee concluded that the available data could be used to set an ADI by application of a safety factor of 1000 to the minimal-effect level of 93 mg per kg of body weight per day with respect to liver weight increase in the absence of associated pathology in the 13-week study in rats. Accordingly, an ADI of 0–0.1 mg per kg of body weight per day was allocated for α-methylbenzyl alcohol.

A toxicological monograph and new specifications were prepared.

Quinine

Quinine was last reviewed by the Committee at its thirty-ninth meeting (Annex 1, reference *101*), when a clear NOEL with respect to ocular effects in humans of 80 mg of anhydrous quinine hydrochloride per day (equivalent to 72 mg of free base) was observed. At that time, the Committee withdrew the previously established temporary ADI of 0–0.9 mg of quinine per kg of body weight per day and concluded that current levels of use in soft drinks, which the Committee was informed were up to 75 mg/l (as quinine base), were not of toxicological concern.

At its present meeting, the Committee re-assessed the toxicological information in the light of new data on levels of quinine in beverages. The Committee concluded that current levels of use of up to 100 mg/l (as quinine base) in soft drinks were not of toxicological concern. The contribution of other uses of quinine in food and alcoholic beverages to daily intakes was considered to be negligible.

The Committee again noted that certain consumers show an idiosyncratic hyper-reactivity to quinine, and reiterated its recommendation that the consumer should be informed by appropriate means of the presence of quinine in foods and beverages in which it is used.

A toxicological monograph was not prepared. The existing specifications for quinine hydrochloride and quinine sulfate were revised.

3.1.3 *Flavour enhancers*

Disodium 5′-guanylate and disodium 5′-inosinate

The disodium salts of 5′-guanylic acid and 5′-inosinic acid were previously evaluated at the eighteenth meeting of the Committee, when an ADI "not specified" was allocated (Annex 1, reference *35*). At that time, data on metabolism, teratogenicity, and acute, short-term and long-term toxicity of the two substances, as well as data on the reproductive toxicity of inosinic acid and its calcium and sodium salts, were reviewed. At its present

meeting, the Committee reviewed these compounds together, as many of the new toxicological studies had been performed on mixtures of the disodium salts of 5′-guanylate and 5′-inosinate.

These compounds are widely distributed in all animal and plant tissues. Their role in purine metabolism as well as their breakdown to uric acid and to allantoin (in most mammals, but not humans) is well documented. Data presented at the eighteenth meeting as well as new data on the metabolism, reproductive effects, genotoxicity, and short-term and long-term toxicity of guanylate and inosinate were evaluated at the present meeting. No evidence of carcinogenicity, teratogenicity or adverse effects on reproduction has been observed.

Changes in dietary purine intake over the past decade resulting from the use of guanylate and inosinate as flavour enhancers are no greater than those due to variability in the consumption of the major dietary contributors of purines. Exposure to purines as a result of their use as flavour enhancers is low (approximately 4 mg per person per day), compared with the intake of naturally occurring nucleotides in the diet (calculated to be up to 2 g per person per day).

The Committee concluded that, on the basis of the available data, the combined total daily intake of disodium 5′-guanylate and disodium 5′-inosinate is not of toxicological significance and re-confirmed the ADI "not specified" that was previously established. Because exposure to these substances from their use as flavour enhancers is low compared with the daily intake of naturally occurring nucleotides in the diet, the Committee found no reason to recommend that foods to which these substances have been added should be labelled, and withdrew its previous recommendation for labelling.

A consolidated toxicological monograph was prepared. The existing specifications for disodium 5′-guanylate and disodium 5′-inosinate were revised.

3.1.4 *Food colours*

Carotenes from natural sources (algal, vegetable)

Carotenes from natural sources were reviewed at the eighteenth, thirty-first and thirty-fifth meetings of the Committee (Annex 1, references *35*, *77* and *88*). At its thirty-first meeting, the Committee noted that, while there was a substantial toxicological database relating to carotenes and an ADI had been established for synthetic β-carotene, the same ADI was not applicable to natural carotenes as they did not comply with the specifications for β-carotene. At the thirty-fifth meeting, the Committee concluded that there was insufficient evidence to indicate that data relating to one species of *Dunaliella* alga could be applied to others and that the specifications of the test materials were so different from one another that the results of the toxicity tests could not be generalized. There were insufficient data to evaluate any of these materials for the purpose of

establishing an ADI. The Committee concluded that carotene isolated from algal sources would be acceptable for food additive use if it was of sufficient purity to meet the specifications for synthetic β-carotene. Acceptance of algal biomass or crude extracts of carotene from algal sources for use as food additives would be contingent on the provision of evidence of the safety of such materials.

Carotene preparations from algae. At its thirty-fifth meeting, the Committee considered limited short-term toxicological studies on material stated to be derived from three different algal species, namely *Dunaliella bardawil, D. salina and D. kona* (Annex 1, reference *88*). At its present meeting, the Committee was informed that *Dunaliella bardawil, D. kona and D. salina* were identical, and that, according to current nomenclature, the species used commercially was *Dunaliella salina.* Some of the preparations produced from this species were dehydrated powders prepared by lyophilization or spray-drying and others were vegetable oil extracts.

Few new toxicological data have become available since the previous review by the Committee (Annex 1, reference *88*). There were no data from long-term toxicity or teratogenicity studies, although a multigeneration study on dehydrated *Dunaliella bardawil* (= *salina*) in rats did not reveal any adverse effects on reproductive performance or gross fetal morphology. However, a NOEL was not identified in this study, as animals of the F_0-generation maintained on diets containing 5% and 10% algal carotene for one year showed pathological renal changes. In addition, there was focal bronchopneumonia at the higher level. Although the renal changes (metaplastic changes in the pelvic epithelium and nephrocalcinosis) might have been due to nutritional imbalance, this was not clearly established. The focal bronchopneumonia at the higher dose level may have been associated with inhalation of powdered diets, although both low-dose and control rats also received powdered diets without showing similar effects. The Committee considered the available short-term toxicity studies inadequate for establishing an ADI because of the small numbers of animals tested, lack of or inadequate histopathological examination, or inadequate reporting.

There have been few systematic toxicological studies on the oil extract of the alga. Available data on the dried material cannot be extrapolated to the oil extract since the specifications are quite different and lipophilic materials may be concentrated during the oil extraction process.

The Committee considered the data inadequate to establish an ADI for the dehydrated algal carotene preparations or for the vegetable oil extracts of *Dunaliella salina.* There is no history of use of *Dunaliella* algae as food.

The existing specifications for carotenes from *Dunaliella salina* (syn. *D. bardawil* and *D. kona*), the materials on which toxicity studies have been performed, were revised.

Carotene preparations from vegetables. Carotene is also obtained by extraction from vegetables, mainly carrots, alfalfa and vegetable oil.

No relevant toxicological data have been submitted on vegetable extracts. However, the Committee concluded that there was no objection to the use of vegetable extracts as colouring agents, provided that the level of use did not exceed the level normally present in vegetables. Implicit in this conclusion is that the extracts should not be made toxic by virtue of the concentration of toxic compounds (including toxicants naturally occurring in the vegetables) or by the generation of reaction products or residues of a nature or in such amounts as to be toxicologically significant (see section 2.2.1).

The existing specifications for carotenes (vegetable) were revised to include material derived from carrots, alfalfa and palm oil, which are known to be used commercially.

A toxicological monograph on both algal and vegetable preparations was prepared.

3.1.5 *Sweetening agents*

Maltitol and maltitol syrup

Maltitol and maltitol syrup were last evaluated at the thirty-third meeting of the Committee (Annex 1, reference *83*), when new specifications were prepared for maltitol of at least 98% purity and the existing specifications for hydrogenated glucose syrups were revised and retitled "maltitol syrup". At that time, the Committee allocated an ADI "not specified" to maltitol and confirmed that the ADI "not specified" previously allocated to hydrogenated glucose syrups applied to maltitol syrup meeting the revised specifications.

At its present meeting, the Committee reviewed a recently completed long-term toxicity/carcinogenicity study in rats in which a commercial preparation containing approximately 87% maltitol was administered in the diet at levels equal to 0, 0.5, 1.5 or 4.5 g per kg of body weight per day for either 52 weeks (toxicity study) or 106 weeks (carcinogenicity study). No adverse effects were observed in the toxicity study. In the carcinogenicity study, histopathological changes related to treatment were observed in the adrenal gland, which included increased incidences of both benign and malignant phaeochromocytomas in male and female rats in the high-dose group and an increased frequency of slight to moderate adrenal medullary hyperplasia in all treated groups. A slightly increased incidence of mammary gland adenocarcinomas was observed in female rats at 1.5 and 4.5 g per kg of body weight per day. However, the incidence was within the range reported in historical controls in the same laboratory in recent studies. Increased incidences of mammary gland adenomas or fibroadenomas were not observed, and the combined incidences of mammary gland adenocarcinomas and adenomas were not increased. For these reasons, the Committee did not consider the increase in mammary gland adenocarcinomas to be related to treatment.

At its twenty-seventh meeting, the Committee had taken note of the increased incidence of adrenal medullary lesions in rats fed diets containing high levels of poorly absorbed polyols (Annex 1, reference *62*). At its present meeting, in line with earlier conclusions regarding the significance of these lesions, the Committee confirmed the ADI "not specified" for maltitol and maltitol syrup that meet current specifications. The Committee recommended that the information database on adrenal medullary hyperplasia and phaeochromocytomas associated with polyols and other poorly absorbed carbohydrates be reviewed and that the mechanisms of appearance of these lesions and their toxicological significance be assessed at a future meeting.

An addendum to the toxicological monograph was prepared. The existing specifications for maltitol, which applied to maltitol of at least 98% purity, were maintained, while those for maltitol syrup, which specified the content of maltitol as 50–90%, were revised to include products containing 90–98% maltitol.

Saccharin

Saccharin was evaluated by the Committee at its eleventh, eighteenth, twenty-first, twenty-fourth, twenty-sixth and twenty-eighth meetings (Annex 1, references *14*, *35*, *44*, *53*, *59* and *66*). At its twenty-first meeting, the Committee changed the previously unconditional ADI of 0–5 mg per kg of body weight to a temporary ADI of 0–2.5 mg per kg of body weight and withdrew the conditional ADI of 0–15 mg per kg of body weight for dietetic purposes only. This decision was based primarily on results of animal studies which indicated that excessive and long-term ingestion of saccharin might represent a carcinogenic hazard. At the twenty-fourth and twenty-sixth meetings, the temporary ADI of 0–2.5 mg per kg of body weight was extended pending the completion of ongoing investigations, including a long-term feeding study in rats and a large-scale epidemiological study. At the twenty-eighth meeting, the results of a 2-generation feeding study in rats and epidemiological data were reviewed and the temporary ADI was again extended, pending the evaluation of further data on bladder histopathology from the 2-generation study and information to elucidate the mechanism by which the compound produced bladder tumours. These data, along with recent epidemiological studies, were reviewed at the present meeting.

An independent assessment of the data on bladder histopathology from the 2-generation feeding study in rats that was reviewed at the twenty-eighth meeting revealed the presence of transitional cell papillomas and carcinomas in the control group. This assessment reduced concern over setting the NOEL at a dose where tumours were observed and it eradicated the statistical significance of the increase in tumour incidence at the 3% dietary level. Application of a dose-response model to the carcinogenicity data suggested a threshold for carcinogenesis close to 3% saccharin in the diet. This is the dietary level at which saturation of renal tubular secretion occurs in the rat and anaemia and other biochemical

changes occur in weanling rats. In this study, the absolute and relative weights of the urinary bladder of treated male rats were significantly higher than those of controls when sodium saccharin was included in the diet at levels of 3% or higher.

The rat is the only species that has been reported to show an increase in the incidence of bladder tumours at high dietary concentrations of sodium saccharin in a 2-generation study. Apart from mice, studies in other species have not included neonatal exposure to saccharin at levels above the maximum tolerated dose. The Committee concluded from the long-term feeding studies that the dose-related carcinogenic activity of sodium saccharin on the urinary bladder was specific to the male rat and that exposure during the neonatal period was critical for the subsequent development of these tumours in the absence of an initiator or stimulus such as ulceration resulting from freezing. The critical events occurring during the neonatal phase that lead to an increase in the population of initiated cells have not been identified.

The Committee considered the genotoxic potential of saccharin on the basis of its physicochemical properties and results from *in vitro* and *in vivo* assays. At physiological pH, saccharin exists almost exclusively as the anion. As such, the parent compound does not resemble an electrophilic chemical carcinogen that would bind to DNA, nor has it been shown to bind to DNA *in vivo*. Because it is not metabolized, it is not converted to an active metabolite. On the other hand, sodium saccharin has exhibited clastogenic activity in a number of *in vivo* and *in vitro* genotoxicity assays.

Since high concentrations of sodium saccharin were used in these assays, it has been suggested that the clastogenic activity could be attributable to ionic imbalances at the chromosomal level at high concentrations. The clastogenic activity is also in disagreement with the results of the long-term studies and tumour-initiation/promotion studies with sodium saccharin.

The conditions required for the hyperplastic and tumour-promoting activities of high dietary concentrations of saccharin (5% or more) on the urothelium in the male rat are an increased urinary concentration of sodium ion and an elevated pH. The response does not appear to be specific to saccharin, since high dietary concentrations of other organic anions have been shown to promote bladder carcinogenesis and induce urothelial hyperplasia under the same conditions. The differences in tumour-promoting activities observed between organic acids and their sodium salts were unrelated to the urinary concentration of the parent organic molecule.

The Committee was not convinced that the available evidence implicated α_{2u}-globulin in bladder carcinogenesis.

The Committee also noted that a proposed mechanism of action involving enhanced microbial activities in the gut, resulting from excess undigested

carbohydrates and protein in rats administered saccharin in the diet, had been investigated without any conclusive evidence.

The epidemiological studies on saccharin did not show any evidence that saccharin ingestion increases the incidence of bladder cancer in human populations.

The Committee accepted that, on the basis of data reviewed to date, it would be inappropriate to consider the bladder tumours induced in male rats by sodium saccharin to be relevant to the assessment of a toxicological hazard to humans.

In re-assessing the ADI, the Committee considered that the 1% dietary level in the most recent 2-generation long-term feeding study in rats, equivalent to 500 mg per kg of body weight per day, was appropriate for establishing an intake causing no relevant toxicological effect. This was based on the observation that, although dose levels of up to 7.5% sodium saccharin in the diet had no adverse effect on survival, the animals demonstrated a marked disturbance of homoeostasis at levels of 3% and higher. In particular, persistent dose-related decreases in body weight gain in the presence of increased food consumption are indicative of decreased biological performance and were probably related to the inhibitory effects of saccharin on carbohydrate and protein digestion. A NOEL of 500 mg per kg of body weight per day was also observed in a long-term toxicity study in monkeys reviewed at the twenty-sixth meeting (Annex 1, reference *60*).

The Committee allocated a group ADI of 0–5 mg per kg of body weight to saccharin and its calcium, potassium and sodium salts, based on the NOEL of 500 mg per kg of body weight per day in the 2-generation long-term feeding study in rats and a safety factor of 100.

An addendum to the toxicological monograph was prepared. The existing specifications were maintained.

3.1.6 *Thickening agents*

Konjac flour

Konjac flour, often referred to as konjac mannan, is a β-D-(1→4)-linked linear copolymer of glucose and mannose substituted with *O*-acetate every 9–19 sugar units. Konjac flour is derived from the tubers of *Amorphophallus konjac*. It has not been previously evaluated by the Committee. The current evaluation was undertaken because of anticipated new food additive uses of konjac flour as a gelling agent, thickener, emulsifier and stabilizer in such foods as soup, gravy, mayonnaise and jam. Nevertheless, there is a long history of use of konjac (containing approximately 4% konjac flour) in traditional Japanese and Chinese foods; the average consumption of konjac flour from these uses is estimated to be 2–3 g per person per day, and occasionally as high as 4 g per person per day. The anticipated maximum consumption of konjac flour from food additive uses is about 3 g per person per day.

The Committee reviewed data from acute and short-term toxicity studies, as well as studies on embryotoxicity, genotoxicity, nutrient absorption and gastrointestinal effects, anti-carcinogenicity studies, and observations in humans. However, the Committee was concerned about the lack of information on the fate of konjac flour in the gut and the inadequacy of the short-term toxicity studies. The Committee was informed of the existence of a 13-week toxicity study in dogs and a 4-week toxicity study in rats that were not made available for review at the present meeting.

Human studies were conducted for up to 65 days at dose levels of up to 8.6 g of konjac flour per person per day. Volunteers consuming approximately 5.2 g or more of konjac flour per day reported symptoms such as loose stools, flatulence, diarrhoea and abdominal pain or distension. Studies with normal and diabetic volunteers demonstrated that consumption of 7.2–8.6 g of konjac flour per day for 17 days significantly decreased mean fasting serum glucose levels; in addition, a dose of 3.9–5.0 g of konjac flour consumed with a single meal (or administered with glucose) was reported to delay the increase in serum glucose and insulin levels for several hours following the meal, thereby also delaying their return to baseline levels. Consumption of test meals containing 3.9 g of konjac flour appeared to impair vitamin E absorption (up to 30% decrease in peak serum levels) and influenced the pharmacokinetics of the co-administered drug glibenclamide. On the other hand, intestinal absorption of vitamin B_{12} and the drug paracetamol was not affected by consumption of meals containing konjac flour (3.9 g of konjac flour per person for vitamin B_{12} and 5 g of konjac flour per person for paracetamol).

On the basis of the available toxicological data, particularly data from human studies, the long history of use of konjac as a food in China and Japan, and estimates of konjac flour consumption from traditional and anticipated food additive uses, the Committee allocated a temporary ADI "not specified" for konjac flour. The results of additional short-term toxicity studies, which the Committee was informed have been conducted in rats and dogs, together with adequate data on the fate of konjac flour in the gut, are required for review by 1996. In view of the observed impairment of absorption of vitamin E, information on the influence of konjac flour on the bioavailability of fat-soluble vitamins is also required for review by 1996. The Committee noted that consumption of dry konjac flour has been associated with oesophageal obstruction, and recommended that konjac flour be consumed only in the hydrated form.

A toxicological monograph was prepared. New tentative specifications were prepared for the product to be used as a food additive.

Processed Eucheuma seaweed

Processed *Eucheuma* seaweed was previously considered by the Committee at its thirtieth and thirty-ninth meetings (Annex 1, references *73* and *101*), but it could not be evaluated for use in foods because no relevant toxicological data were available. At its present meeting, the

Committee reviewed a 90-day study in rats and a series of genotoxicity studies on processed *Eucheuma* seaweed from *E. cottonii.* Complete details of the 90-day study were not provided.

Analytical data provided on the commercial product and on the material used in the toxicity studies were reported to conform to the specifications that were prepared at the present meeting. The viscosity indicated that the carrageenan component was not degraded. Assays of the relative molecular mass of processed *E. cottonii* showed it to be well above the range of degraded carrageenan and similar to that of traditionally refined carrageenan. Analytical data demonstrated that the acid-insoluble component was similar to cellulose. The crude protein content of the commercial batches ranged from 0.1% to 1.5%, with a mean value of 1%. It was noted that the product did not contain heavy metals at levels of toxicological concern.

In the 90-day study in rats, processed *Eucheuma* seaweed was administered at 0.5%, 1.5% and 5% in the diet, while a comparison group received traditionally refined carrageenan at a level of 5%. The most notable effect from this study was an alteration of stool characteristics with both types of carrageenan at the 5% level, which was more pronounced in the group given traditionally refined carrageenan. This effect is to be expected from this kind of poorly absorbed material and was not considered of toxicological significance. No deposits of metachromatic material were observed in the livers of these rats, and no traces of blood were detected in the faeces, as would have been expected if the carrageenan had been degraded. No effects of toxicological significance were observed.

No genotoxic effects were observed in *in vitro* bacterial assays or an *in vivo* mammalian assay.

The Committee allocated a temporary ADI of 0-20 mg per kg of body weight to processed *Eucheuma* seaweed, based on the application of a 200-fold safety factor to the intake associated with the 5% dose level (equivalent to 3890 mg per kg of body weight per day) in the 90-day study in rats. The ADI was made temporary, pending submission of the complete details from this study, including histopathological data for individual animals. The Committee was informed that additional characterization data on processed *Eucheuma* seaweed existed, and requested that these data and the individual data from the 90-day rat study should be submitted for review by 1995.

A toxicological monograph was prepared.

The Committee re-considered the appropriateness of the name "processed *Eucheuma* seaweed" for the substance evaluated toxicologically and for which revised specifications were prepared. The Committee agreed that the properties and κ-carrageenan content of processed *Eucheuma* seaweed from *E. cottonii* were similar to those of the additive carrageenan. The Committee was unable to decide, however, on an alternative and more

descriptive name that would clearly distinguish processed *Eucheuma* seaweed from carrageenan, for which a separate set of specifications exists. Accordingly, the name "processed *Eucheuma* seaweed" was retained. The specifications were revised and the "tentative" designation was removed.

Propylene glycol alginate

This substance was evaluated at the thirteenth, fifteenth and seventeenth meetings of the Committee (Annex 1, references *19*, *26* and *32*). At the seventeenth meeting, an ADI for propylene glycol alginate of 0–25 mg per kg of body weight was allocated, based on a NOEL of 2500 mg per kg of body weight per day in a long-term toxicity study in rats. At that meeting, the Committee concluded that only the propylene glycol moiety is absorbed and metabolized, the alginate moiety being excreted unchanged in the faeces of rats and mice. Accordingly, the Committee decided that the contribution of propylene glycol alginate to total dietary propylene glycol intake from all sources should be included in the ADI for propylene glycol. The Committee allocated an ADI of 0–25 mg per kg of body weight to propylene glycol (Annex 1, reference *32*).

Alginic acid and its ammonium, calcium, potassium and sodium salts were evaluated by the Committee at its thirty-ninth meeting (Annex 1, reference *101*), when a group ADI "not specified" was allocated.

At its present meeting, the Committee evaluated new data from a 30-day study in rats, genotoxicity assays, a teratogenicity study in rabbits and a study in human volunteers.

An *in vitro* study showed partial hydrolysis of propylene glycol alginate in simulated intestinal juice (25% within 4 hours; 80% within 24 hours). Partial hydrolysis was also observed in an *in vivo* mouse study. Studies on the fate of propylene glycol alginate in the gut in mice showed that unhydrolysed propylene glycol alginate and the alginate moiety were not absorbed. Released propylene glycol was rapidly absorbed and metabolized to lactic and pyruvic acids.

In various short-term and long-term toxicity studies, propylene glycol alginate at levels of 10% or higher in the diet caused reduced growth accompanied by reduced food consumption and loose stools, the common effects in animals fed high doses of bulking agents.

In a long-term toxicity study in mice (12 months), as well as in long-term toxicity studies in rats ($\geq$ 2 years), the NOEL was 5% in the diet. There was no indication of a carcinogenic effect. Propylene glycol alginate did not induce gene mutations in bacteria or in yeast cells or chromosomal aberrations in mammalian cells *in vitro* or *in vivo*.

In addition, in a 2-generation reproduction study in rats, 5% propylene glycol alginate in the diet did not cause any effects. Teratogenicity studies in mice, rats, hamsters and rabbits did not reveal any teratogenic activity of propylene glycol alginate at dose levels of up to 800 mg per kg of body weight per day.

No adverse effects were observed in a recent 23-day study in five human volunteers in which the substance was given orally at a dose of 200 mg per kg of body weight per day.

The Committee noted that effects of reduced growth and loose stool have been observed in animal studies with other poorly absorbed compounds (including modified cellulose, polyalcohols, gums, modified starches and other alginates). The Committee reiterated that the ADI for propylene glycol alginate is limited by the amount of propylene glycol that might be released. Propylene glycol alginate contains up to 36% propylene glycol. On the assumption that all of this amount is hydrolysed, and taking into account the ADI of 0–25 mg per kg of body weight for propylene glycol, the Committee allocated an ADI of 0–70 mg per kg of body weight ($100/36 \times 25$) to propylene glycol alginate.

The Committee was aware of new toxicological studies on propylene glycol, but as the compound was not on the agenda, the data were not reviewed. The Committee recommended that propylene glycol be reviewed at a future meeting.

Because the ADI for propylene glycol alginate is based on the ADI for propylene glycol, the Committee also recommended that the former substance be re-considered at the same meeting.

A toxicological monograph was prepared. The existing specifications were revised and maintained as tentative.

3.1.7 *Miscellaneous substances*

β-Cyclodextrin

β-Cyclodextrin is a cyclic heptamer of glucose units, which forms inclusion complexes with a range of lipophilic compounds of relative molecular mass less than 250. Its proposed applications include direct food additive use as a carrier and stabilizer of food flavours, food colours and some nutrients, and these applications may lead to daily intakes of 1.0–1.4 g per person. Applications such as a processing aid in removing caffeine from coffee and tea and cholesterol from eggs would result in much lower intakes.

The Committee noted that, although β-cyclodextrin is poorly hydrolysed and absorbed in the upper gastrointestinal tract in animals and humans, it is largely utilized following hydrolysis by the microflora in the lower gut. A small proportion of the dose may be absorbed intact.

A number of acute and short-term toxicity studies were reviewed which indicated low toxicity by the oral route, although most of these studies used smaller numbers of animals or more limited histological examination than would normally be appropriate for establishing an ADI. In a well conducted short-term toxicity study in rats, there were no effects of toxicological significance other than caecal enlargement and an increased number of macrophages in intestinal lymph nodes at doses of up to 10%

β-cyclodextrin in the diet; these effects are a common feature of poorly absorbed polysaccharides.

In *in vitro* studies, β-cyclodextrin sequestered cholesterol from erythrocyte membranes and caused haemolysis, but only at concentrations much higher than those seen in the blood of dogs given β-cyclodextrin at a dose level of 10% in the diet. No effects on mucosal cells of the gastrointestinal tract were seen in high-dose oral studies. β-Cyclodextrin was non-genotoxic in a range of tests, and it does not have a structure likely to be associated with such activity. Given its poor bioavailability and lack of genotoxicity, the Committee concluded that a long-term carcinogenicity study was not required for the evaluation of this substance.

When administered parenterally to rats, β-cyclodextrin was nephrotoxic, but no renal toxicity was observed in any of the short-term toxicity studies using oral administration. In dogs, the urinary excretion of unchanged β-cyclodextrin was low, even when the compound was given at a dose level of 10% in the diet, indicating that it is unlikely that systemic levels following oral administration would be high enough to cause renal toxicity.

The Committee was informed that a 1-year oral toxicity study on β-cyclodextrin in dogs was under way, and requested the results of this study to complete the evaluation of this compound.

Despite its low toxicity, the Committee was concerned about the possible sequestering effects of β-cyclodextrin on lipophilic nutrients and drugs. In particular, further data on the effects of β-cyclodextrin on the bio-availability of lipophilic nutrients are required.

The Committee concluded that there were sufficient data to allocate a temporary ADI of 0–6 mg per kg of body weight for β-cyclodextrin, based on a NOEL of 2.5% in the diet (equal to 1230 mg per kg of body weight per day in the study in dogs) and a safety factor of 200.

The results of the 1-year study in dogs and information on the effects of β-cyclodextrin on the bioavailability of lipophilic nutrients are required by 1995.

A toxicological monograph and new tentative specifications were prepared. As β-cyclodextrin is a novel product with a wide range of potential applications, the Committee requested further information on the range of possible production methods that could be used in its manufacture.

Sodium iron EDTA

The Committee was asked to comment on the safety of sodium iron(III) EDTA (ethylenediamine tetraacetate or edetate) as a dietary supplement for use in supervised food fortification programmes in populations in which iron-deficiency anaemia is endemic. The Committee was informed that use of iron in this form would be restricted to this specific application and would be supervised. The Committee was concerned about

over-fortification or misuse of this product and did not recommend its availability for general use by individuals.

The Committee noted that sodium iron EDTA dissociates in the intestine, and that the bioavailability of iron in this form is approximately twice that of iron sulfate. The available studies indicated that only a small fraction, if any, of the iron EDTA chelate is absorbed as such, that EDTA from sodium iron EDTA is only poorly absorbed and that most of the EDTA is excreted in the faeces. The portion that is absorbed (less than 5%) is rapidly excreted in urine. The proposed supplementation programme would result in intakes of iron and EDTA of approximately 0.2 and 1.34 mg per kg of body weight per day, respectively. On the basis of the previous evaluations of both iron and EDTA (Annex 1, references *62* and *32*), and the available bioavailability and metabolism data, the Committee provisionally concluded that use of sodium iron EDTA meeting the tentative specifications prepared at the present meeting would not present a safety problem in supervised food fortification programmes in iron-deficient populations. The Committee requested that additional studies be conducted to assess the site of deposition of iron administered in this form and to assess the metabolic fate of sodium iron EDTA following long-term administration.

The Committee emphasized that its evaluation applies only to the use of sodium iron EDTA as a dietary supplement to be used under supervision, and expressed its concern about the potential for over-fortification of food because of the enhanced bioavailability of iron in this form.

A toxicological monograph was prepared.

The Committee developed new tentative specifications for sodium iron(III) EDTA. In preparing the specifications, the Committee was aware that food-grade sodium iron(III) EDTA is not commercially available. However, as this substance was being evaluated for its usefulness in fortifying the diet in areas of the world where iron-deficiency is endemic, the Committee prepared specifications which it believed would assist in the evaluation. The Committee therefore considered analytical data and other information on fertilizer-grade sodium iron(III) EDTA, which is widely available, together with the existing specifications for disodium EDTA and calcium disodium EDTA. Because further analytical data on the food-grade material and on methods of analysis are still needed, the specifications were designated as "tentative".

Sucrose acetate isobutyrate

Sucrose acetate isobutyrate, which is a mixture of esters of sucrose esterified with acetic and isobutyric acids, was previously evaluated at the nineteenth, twenty-first and twenty-sixth meetings of the Committee (Annex 1, references *38*, *44* and *59*). At its twenty-first meeting, the Committee concluded that a complete toxicological profile was required for the evaluation of this compound, including carcinogenicity/toxicity

studies in two animal species, a 2-year study in dogs with adequate numbers and dose groups to demonstrate a NOEL and to assess the adverse effects of the substance on liver function, and a multigeneration reproduction/teratogenicity study. This information was not yet available when the compound was again reviewed at the twenty-sixth meeting of the Committee, so no ADI was allocated, although a toxicological monograph summarizing the available toxicological data was prepared. With the exception of the 2-year study in dogs, the data required were available for consideration at the present meeting.

Studies on the disposition of sucrose acetate isobutyrate in rats, dogs and humans indicated that absorption from the gastrointestinal tract is delayed for several hours, but that elimination is nearly complete by 4-5 days after ingestion. Extensive metabolism of sucrose acetate isobutyrate occurred in the gastrointestinal tract, mainly in the small intestine, characterized by its de-esterification by non-specific esterases to partially acylated esters and sucrose. Ingested sucrose acetate isobutyrate was partially absorbed from the gut and partially eliminated in the faeces. In all three species, the absorbed dose was largely catabolized to carbon dioxide. Smaller amounts were excreted in the urine and bile. The extent of absorption from the gastrointestinal tract was greater in humans and rats than in dogs in the dosage range of 1-10 mg per kg of body weight. However, at doses approaching 100 mg per kg of body weight per day, the extent of absorption of sucrose acetate isobutyrate in rats was reduced and similar to that found in dogs.

In studies with sucrose octaisobutyrate, the most lipophilic component of sucrose acetate isobutyrate, a dose of 200 mg per kg of body weight administered to rats, dogs and monkeys was almost completely excreted in the faeces, although analysis of faecal metabolites indicated that the extent of hydrolysis in the gastrointestinal tract differed in the three species (rat > dog > monkey). In addition, the small amount of absorbed sucrose octaisobutyrate was preferentially excreted in the bile of dogs and in the expired air of rats. Chromatographic analysis of the urinary and biliary metabolites of sucrose acetate isobutyrate showed that dogs excreted more highly acylated sucrose molecules, whereas humans and rats excreted more polar sucrose esters. Consequently, the dog differs from the rat and human in its disposition of sucrose acetate isobutyrate in that it absorbs less of the total dose of sucrose acetate isobutyrate in the 1-10 mg per kg of body weight range, but it is capable of absorbing more highly acylated sucrose esters and, compared with the rat, excretes a larger proportion of the absorbed dose in the bile. Data on the excretion of sucrose acetate isobutyrate in the bile of humans were not available for comparison.

The results of short-term (up to one year) toxicity studies in mice, rats and monkeys were also available. The conclusions of an earlier 2-year study in rats were not considered to be reliable because of the small numbers of survivors at the end of the study. Sucrose acetate isobutyrate administered at dose levels of up to 10% in the diet for 12 weeks or 2 g per kg of body

weight per day for 52 weeks had no toxicologically significant effect in the rat, nor was any effect evident in the liver as assessed by liver function tests, liver weights and histopathology. In the monkey, sucrose acetate isobutyrate administered by gavage at up to 2.4 g per kg of body weight per day had no apparent adverse effect. In humans, sucrose acetate isobutyrate given orally at up to 20 mg per kg of body weight per day for 14 days was also without effect. In addition, liver function tests conducted in rats, monkeys and humans following oral administration of single or multiple doses of sucrose acetate isobutyrate showed no effect on hepatobiliary excretion.

The available studies clearly showed the liver to be the target organ in the dog. Serum alkaline phosphatase levels were elevated and biliary excretory function was impaired. Liver enlargement was noted in the males and histopathological changes were apparent in the liver of both sexes. All of these changes were reversible within 3 weeks of removal of sucrose acetate isobutyrate from the diet. In addition, histochemical studies revealed increased enzyme activity in the bile canaliculi, but not in the hepatocytes. Liver function tests in the dog showed that biliary excretion was reduced within 4–6 hours of oral administration of a single dose of sucrose acetate isobutyrate. The NOEL for this effect was 5 mg per kg of body weight per day. The authors of the report concluded that this represented a functional rather than a toxic effect of sucrose acetate isobutyrate. Although the effects on the liver of the dog were reversible, no study of longer than 12–13 weeks' duration was available for evaluation. It was not known whether continuous exposure to sucrose acetate isobutyrate for a longer period of time would have resulted in the development of pathological lesions.

The carcinogenic potential of sucrose acetate isobutyrate has been investigated in mice and rats in long-term toxicity studies at doses of up to 2 and 5 g per kg of body weight per day, respectively, with negative results. Sucrose acetate isobutyrate was not genotoxic in *in vitro* point mutation, chromosomal aberration, or unscheduled DNA synthesis assays. A multigeneration reproduction/teratogenicity study in rats and a teratogenicity study in rabbits were also negative.

The NOELs from the long-term studies in mice and rats and from a 1-year study in monkeys were similar (5, 2 and 2.4 g per kg of body weight per day, respectively). However, the NOEL for dogs was much lower (5 mg per kg of body weight per day, based on inhibition of biliary excretory function).

The Committee concluded that a 2-year study in dogs was no longer necessary since the effects of sucrose acetate isobutyrate and its constituent esters on the liver of the dog had been well characterized in liver function tests and 90-day toxicity studies, and a study of longer duration was unlikely to yield new information which would assist in setting an ADI.

Three studies in humans, involving a total of 71 volunteers, were available for consideration by the Committee. The results of these studies

demonstrated that sucrose acetate isobutyrate had no effect on bromosulfophthalein clearance or indicator enzymes of cholestasis in humans when administered orally at a dose of 20 mg per kg of body weight per day, even though a single dose of 25 mg per kg of body weight had been shown to reduce bromosulfophthalein clearance dramatically in the dog. Humans, therefore, did not respond to sucrose acetate isobutyrate in the same way as dogs. The Committee agreed that the data suggested that the dog was an inappropriate species on which to base an ADI, but at the same time noted the absence of data on the mechanism by which cholestasis is induced in the dog.

Taking this into account, the Committee decided to use the NOEL of 2 g per kg of body weight per day for rats, the lowest obtained in long-term toxicity studies, to allocate a temporary ADI of 0–10 mg per kg of body weight, using a safety factor of 200. The submission of information that would clarify the disparate effects of sucrose acetate isobutyrate on hepatobiliary function in the dog compared with other species, in particular the human, is required for review by 1996.

A toxicological monograph was prepared. The existing specifications for sucrose acetate isobutyrate were revised.

Urea

Urea has not been previously evaluated by the Committee.

The Committee considered urea for evaluation only in relation to its use in chewing-gum. Chewing-gum may contain up to 3% urea, and intake from this source could be up to 300 mg of urea per day.

The Committee reviewed biochemical studies, short-term toxicity studies in dogs and several species of ruminants, carcinogenicity studies in rats and mice, mutagenicity studies and studies on effects in human volunteers. It noted that most of the available data were either inadequate or of little relevance for the evaluation of urea as a food additive. As urea is a naturally occurring constituent of the body, the Committee carried out its evaluation in accordance with the principles relating to materials of this type outlined in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*).

Since urea is a natural end-product of amino acid metabolism in humans, and approximately 20 g per day are excreted in the urine in adults (proportionately less in children), the Committee concluded that the use of urea at levels of up to 3% in chewing-gum was of no toxicological concern.

A toxicological monograph and new specifications were prepared.

3.2 Contaminants

3.2.1 *Cadmium*

Cadmium was evaluated at the sixteenth and thirty-third meetings of the Committee (Annex 1, references *30* and *83*). At the sixteenth meeting, the

Committee allocated a Provisional Tolerable Weekly Intake (PTWI) of 400-500 μg of cadmium per person. At the thirty-third meeting, the Committee retained this PTWI, but expressed it in terms of the intake per kg of body weight (7 μg per kg of body weight). In 1992, the International Programme on Chemical Safety (IPCS) produced a monograph on cadmium (*5*), which provides a detailed description of the models on which the PTWI is based and the various assumptions used in their construction.

At its present meeting, the Committee concluded that the models on which the PTWI was based have been conservative. However, the PTWI does not include a safety factor, and the Committee reiterated the statement made in the report of the thirty-third meeting that "there is only a relatively small safety margin between exposure in the normal diet and exposure that produces deleterious effects".

Cadmium has an extremely long biological half-life in humans and is accumulated in body tissues, particularly in the liver and kidney. There are no available chelating agents to enhance cadmium excretion. Cadmium is a nephrotoxin and produces renal tubular dysfunction characterized by increased excretion of low-molecular-weight proteins, particularly β_2-microglobulin, which, together with excreted cadmium, serve as biomarkers measurable in the urine as indicators of toxicity. With continuous exposure to high levels of cadmium, the effects on the kidney become increasingly severe.

Daily intake of cadmium varies in different countries and in different regions within countries. Cadmium is normally present in low concentrations in soil, but is increased from emissions from smelting and refining of ores, waste disposal of cadmium-containing metal products, and application of cadmium-containing fertilizers to agricultural land. It is readily taken up by plants, including foodstuffs, and for non-smokers the major source of human exposure is dietary.

The average dietary intake of cadmium is approximately 10-50 μg per day in areas of normal exposure. The level may be considerably higher in certain countries, however, according to the Joint UNEP/FAO/WHO Food Contamination Monitoring and Assessment Programme (*6*).

The Committee expressed concern about the use of retrospective information for estimating the cadmium intake from the dietary intake of rice and the lack of information regarding the impact of age on the excretion of β_2-microglobulin. It recognized the need to validate the significance of the concentration of cadmium in the renal cortex regarded as critical in the general population (the "population critical concentration"), which should be investigated in new epidemiological studies.

Additional studies should be performed on the relationship of renal glomerular dysfunction to cadmium exposure and on the validity of the mathematical models for estimating the biological half-life of cadmium. An assumption made in using these models is that urinary excretion of

1000 μg of β_2-microglobulin per 24 hours or 1000 μg per g of creatinine is indicative of renal tubular dysfunction. The low-molecular-weight proteinuria associated with long-term cadmium exposure is not likely to be reversible. Epidemiological studies have shown that for people who excrete more than 1000 μg of β_2-microglobulin in the urine per 24 hours, the renal tubular dysfunction either does not improve or worsens within 5 years of reduction of cadmium exposure. The Committee was informed of epidemiological studies in Belgium and the Netherlands that suggest that the current PTWI may not be adequately restrictive to prevent renal tubular dysfunction from cadmium.

A question was raised regarding the relative bioavailability of cadmium from different foods, particularly grains or seeds that are used as food, and foods where cadmium may be bound to metallothionein and other proteins that limit bioavailability. For example, in a study in New Zealand, the serum concentration and urinary excretion of cadmium were found to be surprisingly low in a population with a high dietary intake of New Zealand buff oysters, which contain high levels of cadmium.

The Committee maintained the current PTWI of 7 μg per kg of body weight, pending future research.

In acknowledging the need for research in areas recommended in WHO Environmental Health Criteria, No.134 (*5*), the Committee wished to highlight the following topics:

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

A toxicological monograph was not prepared.

3.2.2 *Chloropropanols*

Certain chlorinated propanols occur as contaminants in hydrolysed vegetable proteins. The two substances considered by the Committee

at its present meeting were 3-chloro-1,2-propanediol and 1,3-dichloro-2-propanol, neither of which has been previously evaluated. Processing of defatted vegetable proteins by traditional hydrochloric acid hydrolysis leads to the formation of significant amounts of 3-chloro-1,2-propanediol and 1,3-dichloro-2-propanol. However, improved manufacturing techniques have reduced the level of 3-chloro-1,2-propanediol to less than 2 mg per kg and 1,3-dichloro-2-propanol to less than 0.02 mg per kg in hydrolysed vegetable proteins.

3-Chloro-1,2-propanediol

3-Chloro-1,2-propanediol increased the relative kidney weights of rats when administered by gavage at 30 mg per kg of body weight per day for 4 weeks or in the drinking-water at 9 mg per kg of body weight per day for 3 months, and absolute kidney weights when given in the drinking-water at 1.1 mg per kg of body weight per day for 2 years. A single subcutaneous injection of 75 mg of 3-chloro-1,2-propanediol per kg of body weight to rats caused renal tubular necrosis and dilatation. A NOEL for the effect on the kidney was not identified.

In monkeys, 3-chloro-1,2-propanediol induced anaemia, leukopenia, and thrombocytopenia following ingestion of 30 mg per kg of body weight per day for 6 weeks.

Data presented to the Committee clearly demonstrated that 3-chloro-1,2-propanediol reversibly reduces fertility in male rats by inhibiting glycolytic enzymes in the epididymis, testicular tissue and spermatozoa, which results in reduced motility of the spermatozoa. No visible morphological changes in the spermatozoa or epididymis were seen at dose levels of 5–10 mg per kg of body weight per day, while a single intraperitoneal injection of 75 mg per kg of body weight caused development of retention cysts or spermatocele of the caput epididymis in rats. In a reproduction study, the NOEL for the reduction in fertility in the male rat was 2 mg per kg of body weight per day, administered orally for 7 days before and during the mating period.

3-Chloro-1,2-propanediol was genotoxic in most *in vitro* assays, but produced negative results in *in vivo* assays. In addition, 3-chloro-1,2-propanediol induced malignant transformation of mouse M_2-fibroblasts in culture.

The results of a recently completed 2-year toxicity/carcinogenicity study in rats administered 3-chloro-1,2-propanediol in drinking-water at dose levels of 1.1, 5.2 or 28 mg per kg of body weight per day indicated a carcinogenic effect. Treatment-related increased incidences of tumours in the kidneys of both sexes and in the testes, mammary gland and preputial gland of male rats were reported. Although it has been suggested that the occurrence of these tumours might be secondary to either a sustained toxic effect on the kidney or hormonal disturbances in the testes and mammary gland, there was no evidence available to support this assumption. The Committee noted that the drinking-water of the control animals contained

low levels of 3-chloro-1,2-propanediol, which may have confounded the quantitative evaluation of the dose-response relationships for carcinogenicity. In addition, significantly increased kidney weights were observed in male rats at the lowest dose level.

1,3-Dichloro-2-propanol

The Committee reviewed studies on biotransformation, acute toxicity and long-term toxicity/carcinogenicity in rats, and *in vitro* genotoxicity of 1,3-dichloro-2-propanol.

The results of a 2-year toxicity/carcinogenicity study in rats given 1,3-dichloro-2-propanol in the drinking-water at dose levels of 2.1, 6.3 or 19 mg per kg of body weight per day indicated a carcinogenic effect. Induction of benign and malignant tumours of the liver, kidney, thyroid gland and oral epithelia/tongue was observed in rats at 6.3 and 19 mg per kg of body weight per day.

1,3-Dichloro-2-propanol was genotoxic in a range of screening assays, including tests for chromosomal effects in mammalian cells in culture and tests for gene mutations in bacteria. In addition, 1,3-dichloro-2-propanol induced malignant transformation of mouse M_2-fibroblasts in culture.

Results from studies on the absorption, distribution or excretion of 1,3-dichloro-2-propanol were not available.

The Committee noted that different rat strains were used in the long-term toxicity/carcinogenicity studies on 3-chloro-1,2-propanediol and on 1,3-dichloro-2-propanol, which precluded a direct comparison of the carcinogenicity of these two compounds.

The Committee concluded that these substances are undesirable contaminants in food and expressed the opinion that their levels in hydrolysed vegetable proteins should be reduced as far as is technically possible.

A toxicological monograph on the two substances was prepared.

3.2.3 *Lead*

The Committee first reviewed lead at its sixteenth meeting (Annex 1, reference *30*), when a PTWI of 3 mg of lead per person, equivalent to 50 µg per kg of body weight, was established. This value was re-confirmed at the twenty-second meeting (Annex 1, reference *47*). At its thirtieth meeting (Annex 1, reference *73*), the Committee assessed the health risks of lead to infants and children and established a PTWI of 25 µg per kg of body weight for this population group. It should be emphasized that these PTWIs apply to lead from all sources. The review of the health effects of lead at the present meeting was based on the recent assessment of lead by an IPCS Task Group, the results of which will be published in the forthcoming Environmental Health Criteria monograph on lead (*7*).

The most significant health effect from lead is the association of lead

exposure with reduced cognitive development and intellectual performance in children. Results of studies on children with blood lead concentrations below 25 μg/dl indicate that, on average, the intelligence quotient (IQ) is reduced by 1–3 points for each 10 μg/dl increment in the blood lead concentration. However, this may not apply to any individual child. In addition, the Committee noted the wide statistical variation in the results.

Existing epidemiological studies do not provide evidence of a threshold. Below the range 10–15 μg/dl, the effect of confounding variables and limits in the precision in analytical and psychometric measurement increase the uncertainty attached to any estimate of effect. If a threshold does exist, it is unlikely to be detected because of these limitations. However, there is some evidence of an association between lead exposure and cognitive deficits even in the 7–8 μg/dl range.

For the purpose of establishing a quantitative relationship between exposure to lead and blood lead concentration, the Committee accepted the conversion factor for infants and children adopted by the IPCS Task Group of 0.16 μg of lead/dl of blood per μg of lead intake per day, to be applied to a 10-kg child. This factor was empirically derived from one study.

When the Committee applied this factor to the current PTWI of 25 μg of lead per kg of body weight for children, it obtained a blood lead concentration of 5.7 μg/dl, which is below the concentration shown to be associated with an effect on intellectual performance.[1]

The Committee also considered the existing PTWI for adults. Although adults are less sensitive than children to lead, the Committee, in considering lead intake from food, took into account the most sensitive population groups and withdrew the separate PTWI for adults. The Committee recognized that the fetus is at least as sensitive as the newborn infant to the potential effects of lead on cognitive development. Lead is readily transported across the placenta from the mother to the fetus; therefore the PTWI for women of child-bearing age should ideally be as low as that for children. Accumulated lead may be mobilized during pregnancy so that lead from prior exposure of women of reproductive age may be available for exposure to the fetus. Furthermore, the blood concentration of lead in adults in the general population throughout the world, including women of reproductive age, is higher than that of children.

A number of specific health effects resulting from exposure to lead have been observed in adults at various blood lead concentrations. Decreased conduction velocity of peripheral nerves has been reported at blood lead concentrations of 30 μg/dl and renal effects and reproductive effects have

[1] For children, the recommended PTWI for lead is 25 μg of lead per kg of body weight per week. Thus, in the case of a 2-year-old child weighing 10 kg, the PTWI is 250 μg of lead per week or 35.7 μg of lead per day. To calculate the resulting blood lead concentration, the PTWI should be multiplied by the conversion factor of 0.16 μg of lead/dl of blood (35.7 × 0.16 = 5.7 μg/dl).

been found at blood lead concentrations of 40 μg/dl. Epidemiological studies have shown an association between exposure to lead in adults and increased systolic and diastolic blood pressure. For each two-fold increase in blood lead, there is an increase of approximately 1 mmHg (0.133 kPa) in systolic blood pressure. The association with diastolic blood pressure is of similar magnitude. However, the IPCS Task Group concluded that there was no clear evidence to suggest that lead has an impact on public health as regards hypertension or risk of cardiovascular disease.

In countries where lead has been removed from petrol, and where there is no specific source of excess lead exposure, blood lead concentrations in children are decreasing and are now approximately 4-6 μg/dl.

A recent report of the Joint UNEP/FAO/WHO Food Contamination Monitoring and Assessment Programme (*6*) identified countries where children's average dietary intake of lead exceeded the PTWI at some time during the past decade. In developed countries, the major sources of lead exposure are environmental and where data are available, the evidence is that lead intakes from food are falling. The decreases are most marked where lead has been removed from petrol. For example, a total diet study conducted by the United States Food and Drug Administration showed that dietary intake of lead by 14-16-year-old males declined from about 85 μg per day in 1978 to less than 10 μg per day in 1990 (*8*). A total diet study carried out in the United Kingdom indicated that during the period 1982-87 average dietary intake of lead was 20-70 μg per day, excluding the contribution from drinking-water (*9*).

The almost complete elimination of lead-soldered side-seams in canned foods in a number of countries has also contributed to the reduction in lead exposure. The Food and Drug Administration reports that the mean level in canned foods in the USA has decreased from 0.20 mg/kg in 1982-83 to 0.01 mg/kg since 1988-89. Most relevant to the concern about infant exposure to lead is that the concentration of lead in canned evaporated milk has decreased from 0.11 mg/kg in 1982-83 to undetectable levels (less than 0.01 mg/kg) since 1985-86 (*8*).

The lead content of drinking-water may be greater than 100 μg/litre where lead pipes or lead solder are used in plumbing systems. The lead content of drinking-water in Canada and the United States is generally below 5 μg/litre and averages 1 or 2 μg/litre. WHO currently recommends that the lead content of drinking-water should not exceed 10 μg/litre (*10*).

The Committee noted that the interpretation of data on lead intakes remains a major problem because of the difficulty of the analysis. A recent survey of the quality of data from analytical studies carried out in the United Kingdom showed, for example, that very few laboratories were able to meet quality assurance criteria (*9*). The Committee therefore emphasized the need for analytical data on lead levels in food to be verified by appropriate quality assurance criteria.

The Committee recognized that steps are now being taken to reduce lead exposure of children with some apparent success in various countries. The Committee recommended that these efforts be extended to countries where petrol containing lead is still being used and to encourage other lead-reduction activities.

There is also a need for continued epidemiological studies on the effects of lead on intellectual development in children. In particular, information is needed on whether a reduction in blood lead concentrations leads to reversal of lead-related intellectual deficits.

The Committee withdrew the previous PTWI of 50 µg per kg of body weight for adults. The existing PTWI of 25 µg per kg of body weight for infants and children was reconfirmed and extended to all age groups.

No toxicological monograph was prepared. Summaries of human health effects and toxicological data on lead will be published in the forthcoming Environmental Health Criteria monograph on lead (*7*).

4. Revision of certain specifications

4.1 General

A total of 25 substances were examined for specifications only (see Annex 2), and the specifications for 18 were revised. The existing specifications for one substance (lecithin, partially hydrolysed), were examined in connection with the specifications for lecithin and were maintained. The existing tentative specifications for the remaining six substances (ethyl hydroxyethyl cellulose, hexane, 2-nitropropane, oxystearin, petroleum jelly and trichloroethylene) were maintained because insufficient information was received to revise them and remove the "tentative" qualification.

For one substance, α-amylase and glucoamylase from *Aspergillus oryzae*, some of the information that had been requested at the thirty-first meeting of the Committee (Annex 1, reference *77*) was not received. The Committee therefore revised the existing tentative specifications, but maintained the "tentative" qualification.

For ammonium polyphosphate and β-glucanase from *Aspergillus niger*, the Committee concluded that sufficient information was available to revise the existing tentative specifications and to delete the "tentative" qualifications.

In view of the close relationship of carmines to cochineal and carminic acid, the Committee decided to revise the specifications for these substances together. At the same time, the specifications for cochineal and carminic acid were retitled "cochineal extract" and the "tentative" qualification was deleted.

4.2 Designation of trichlorogalactosucrose/sucralose

At the thirty-seventh meeting (Annex 1, reference *94*), the Committee was requested to reconsider the specifications title "trichlorogalactosucrose" it had adopted at its thirty-third meeting (Annex 1, reference *83*) and to change it to "sucralose". At the thirty-third meeting, the Committee had established guidelines for designating titles for specifications monographs and had selected the title in accordance with those guidelines.

Upon reconsideration at its thirty-seventh meeting, the Committee concluded that the information submitted in relation to criterion 3 (names established by common usage) was not sufficiently compelling to change the name and reaffirmed its view, based on criterion 4 (available scientific, common or trivial names), that "trichlorogalactosucrose" was appropriate.

At its present meeting, the Committee was again requested to consider the title, this time based on criterion 2 (names established by governmental legislation). The Committee agreed that this criterion has now been satisfied by the approval of the Canadian government. In addition, it was noted that the National Food Authority of Australia had published a notice of intent to amend the food standards code to permit the use of "sucralose" in certain foods. Furthermore, the Codex Committee on Food Additives and Contaminants agreed, at its meeting in March 1992, to add sucralose to the International Numbering System (*2*).

The Committee retitled the specifications as "sucralose". The specifications were also revised.

5. Future work

1. A full review of benzyl alcohol, benzyl acetate, benzaldehyde, benzoic acid and the benzoate salts should be performed in 1995 to determine whether reproduction/teratogenicity and/or other studies are required.
2. In view of the existence of new toxicological studies on propylene glycol, this substance should be reviewed at a future meeting. Because the current ADI for propylene glycol alginate is based upon the ADI for propylene glycol, the former substance should also be considered at the same meeting.
3. The Committee again discussed the issue of the increased incidence of adrenal medullary hyperplasia and phaeochromocytomas observed in long-term studies in rats with polyols and other poorly absorbed carbohydrates. The Committee recommended that the database on this phenomenon be reviewed and that the mechanisms of the appearance and toxicological significance of these lesions be assessed at a future meeting.
4. The Committee recommended that principles for allocating ADIs to substances for which it is only possible to prepare tentative specifications be established at a future meeting.

6. Recommendations

1. In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, the important role that the recommendations of the Committee play in the development 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 should continue to be held at least once yearly to evaluate these substances.
2. The Committee recognized that problems have been encountered in providing adequate funding to hold sufficient meetings for the evaluation of food additives and contaminants. It recommended that FAO and WHO emphasize to governments and industry the significance of the Committee's recommendations and that additional funding mechanisms should be explored.
3. FAO and WHO have procedures in place that are intended to ensure the timely submission of data for review by the Committee. However, data for some substances considered at the present meeting were submitted only shortly before the meeting, which made their full review particularly difficult (see Annex 4). Accordingly, the Committee recommended that special efforts be made by FAO and WHO to ensure that sponsors adhere to the deadlines specified in the requests for data that are circulated before each meeting. Failure to comply with deadlines may mean that the Committee is unable to review the substances on the agenda.
4. In view of the importance of specifications of purity in defining the products being considered in safety assessments, the Committee re-emphasized the need for full purity specifications relating to the materials tested to be submitted to both FAO and WHO. Similar information should be provided when specifications are proposed for revision.
5. Increasingly often, the Committee is requested to evaluate novel substances that may be used at relatively high proportions in the diet. Many of these are proposed for use as replacements for traditional sources of dietary fat or complex carbohydrates or as low-calorie bulking or sweetening agents. The Committee noted that the application of traditional methods of toxicity testing to these products may result in nutritional, physiological or metabolic perturbations which complicate the safety evaluation. Moreover, the Committee was concerned that use of certain of these materials in the diet may lead to alterations in nutritional status because of effects on nutrient utilization. The Committee recommended that a special meeting be held to address these issues, to suggest appropriate methods for the safety evaluation of these types of products, and to recommend procedures for assessing their impact on nutrient utilization.

6. During its assessments of benzyl acetate and propylene glycol alginate at the present meeting, the Committee also considered previous assessments of some of their metabolites. To ensure that assessments are complete, the Committee recommended that, in future, it should evaluate all related compounds at the same meeting, taking into account both the latest information and previously reviewed data, which should be made available.

Acknowledgement

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Annex 1

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

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Annex 2

Acceptable Daily Intakes, other toxicological information, and information on specifications

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg per kg of body weight and other toxicological recommendations
Antioxidants		
Dodecyl gallate	R	0–0.05 (temporary)[b]
Octyl gallate	R	0–0.1 (temporary)[b]
Propyl gallate	R	0–1.4
Flavouring agents		
Benzyl acetate	S	0–5 (group ADI)[b, c]
2-Ethyl-1-hexanol	N	0–0.5
(+)-Limonene	R	Not specified[d]
α-Methylbenzyl alcohol	N	0–0.1
Quinine hydrochloride	R	Current use levels of up to 100 mg/l (as quinine base) in soft drinks not of toxicological concern
Quinine sulfate	R	
Flavour enhancers		
Disodium 5′-guanylate	R	Not specified[d]
Disodium 5′-inosinate	R	
Food colours		
Carotenes (algal)	R	No ADI allocated because of inadequate data
Carotenes (vegetable)	R	Acceptable, provided the level of use does not exceed the level normally found in vegetables
Sweetening agents		
Maltitol	S	Not specified[d]
Maltitol syrup	R	
Saccharin	S	0–5 (group ADI)[e]
Thickening agents		
Konjac flour	N, T[b]	Not specified (temporary)[b, d]
Processed *Eucheuma* seaweed	R	0–20 (temporary)[b]
Propylene glycol alginate	R, T[b]	0–70

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg per kg of body weight and other toxicological recommendations
Miscellaneous substances		
β-Cyclodextrin	N, T[b]	0–6 (temporary)[b]
Sodium iron EDTA	N, T[b]	Provisionally considered to be safe in food fortification programmes[f]
Sucrose acetate isobutyrate	R	0–10 (temporary)[b]
Urea	N	Use at levels of up to 3% in chewing-gum not of toxicological concern

Contaminant	Provisional Tolerable Weekly Intake (PTWI) in μg per kg of body weight
Cadmium	7
Chloropropanols (3-chloro-1,2-propanediol and 1,3-dichloro-2-propanol)	Levels in hydrolysed vegetable proteins should be reduced as far as is technically possible
Lead	25

Substance (considered for specifications only)	Specifications[a]
Alginic acid	R
Ammonium alginate	R
Ammonium polyphosphate	R
α-Amylase from *Bacillus stearothermophilus*	R
α-Amylase from *Bacillus subtilis*	R
α-Amylase and glucoamylase from *Aspergillus oryzae*	R, T[b]
Calcium alginate	R
Carmines	R
Cochineal extract (formerly cochineal and carminic acid)	R
Disodium pyrophosphate	R
Erythrosine	R
Ethyl hydroxyethyl cellulose	S, T[b]
β-Glucanase from *Aspergillus niger*	R

Substance (considered for specifications only)	Specifications[a]
Hexane	S, T[b]
Lecithin	R
Lecithin, partially hydrolysed	S
2-Nitropropane	S, T[b]
Oxystearin	S, T[b]
Petroleum jelly	S, T[b]
Potassium alginate	R
Sodium alginate	R
Sucralose (formerly trichlorogalactosucrose)	R
Tetrasodium pyrophosphate	R
Trichloroethylene	S, T[b]
Xanthan gum	R

Notes to Annex 2

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

[b] See Annex 3.

[c] Group ADI for benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and benzoate salts.

[d] ADI "not specified" means that, on the basis of the available data (chemical, biochemical, toxicological, and other), the total daily intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary.

[e] Group ADI for saccharin and its calcium, potassium and sodium salts.

[f] The Committee provisionally concluded that sodium iron EDTA (ethylene-diamine tetraacetate) meeting the tentative specifications prepared at the meeting would not present a safety problem when used in supervised food fortification programmes in iron-deficient populations.

Annex 3

Further toxicological studies and other information required or desired

Antioxidants

Dodecyl and octyl gallate

Additional studies on the pharmacokinetics and metabolism of dodecyl, octyl and propyl gallate are required for review by 1996.

Flavouring agents

Benzyl acetate

The Committee recommended that a full review of benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and benzoate salts be performed in 1995.

Thickening agents

Konjac flour

The results of short-term toxicity studies known to have been conducted in rats and dogs and data on the fate of konjac flour in the gut are required for review by 1996.

Information on the concentration of lead and the influence of konjac flour on the bioavailability of fat-soluble vitamins is also required for review by 1996.

Processed Eucheuma seaweed

Additional data known to exist on the characterization of the substance and complete details of the recent 90-day study in rats, including histopathological data for individual animals, are required for review by 1995.

Propylene glycol alginate

Information is required on:

- the relative molecular mass;
- the method of assay;
- methods of sample drying prior to analysis of propylene glycol content;
- the method of determination of total and free propylene glycol content.

Miscellaneous substances

β-Cyclodextrin

The results of a 1-year oral toxicity study in dogs that is known to be under way and further data on the effects of β-cyclodextrin on the bioavailability of lipophilic nutrients are required by 1995.

Information is required on:

- the range of production methods used;
- the levels of other cyclodextrins in commercial products;
- solvents used in manufacture, residual levels of solvents, and methods of analysis;
- the sources of α-, β-, and γ-cyclodextrins and their characterization and bioavailability.

Sodium iron EDTA

Additional studies to determine the site of deposition of iron administered as sodium iron EDTA and to assess the metabolic fate of sodium iron EDTA following long-term administration are requested.

Information is required on the characterization of food-grade sodium iron EDTA and methods of analysis for the impurity nitrilotriacetic acid.

Sucrose acetate isobutyrate

Information to clarify the effects of this substance on hepatobiliary function in the dog compared with other species, in particular the human, is required for review by 1996.

Specifications only

α-Amylase and glucoamylase from Aspergillus oryzae

Information is required on the levels of and methods of analysis for the impurities α-cyclopiazonic acid and kojic acid.

Ethyl hydroxyethyl cellulose

Information is required on the limits and methods of analysis for impurities, including ethylene oxides and, where applicable, for ethylene glycols, 1,4-dioxane and ethylene chlorohydrin.

Hexane

Information is required on limits for aromatic hydrocarbons.

2-Nitropropane

Information is required on the refractive index range applicable to commercial products and on the adequacy of the method of assay.

Oxystearin

Information is required on the methods of analysis for epoxides.

Petroleum jelly

Information is required on:

- the actual composition of hydrocarbons;
- the methods for identification of individual hydrocarbons;
- limits and methods of analysis for sulfur, arsenic, lead and other heavy metals;
- the nature of the sulfur compounds.

Trichloroethylene

Information is required on:

- the nature and levels of and methods of analysis for stabilizers in food-grade trichloroethylene;
- the method of assay;
- the methods of analysis for volatile impurities in food-grade trichloroethylene.

Annex 4

Matters of interest arising from the Twenty-fourth Session of the Codex Committee on Food Additives and Contaminants

1. The Expert Committee was informed that the Codex Committee was continuing to develop a Codex General Standard for Food Additives. Antioxidants and preservatives had been included in the draft General Standard. It was expected that many other substances that were covered by the International Numbering System would also be included; therefore those that had not yet been assessed would be placed on the priority list for assessment by the Expert Committee.

2. The Expert Committee was informed that the Codex Committee was elaborating "General principles for contaminants", with a view to developing a Codex General Standard on Contaminants. The Expert Committee was invited to discuss the implications of this at a future meeting.

3. An ad hoc Working Group on Priorities has been re-established to make recommendations to the Codex Committee regarding substances that should be placed on the priority list for assessment by the Expert Committee. The Working Group emphasized that, when a delegation to the Codex Committee makes a proposal, the delegation should ensure that the appropriate data, including individual animal data, are submitted to the Expert Committee. Companies or organizations in other countries are also encouraged to submit information, particularly on specifications, to ensure that the full range of products on the market is considered.

4. The Codex Committee Working Group on Specifications is now considering all specifications prepared by the Expert Committee that have not yet been adopted as Codex Advisory Specifications.

5. The Codex Committee made the following recommendations and statements concerning the conclusions of the thirty-ninth meeting of the Expert Committee:

   - The terms used in the report should be as explicit as possible and statements such as "present uses are not of toxicological concern" were not helpful if the uses were not listed in the report. It was not sufficient for the uses to be listed only in the specifications, because many readers of the report would not have access to the specifications.
   - The statement that lysozyme "may be regarded as food" was not clear.
   - In the light of available information, the Codex Committee did not consider the conclusion of the Expert Committee that "current use levels in soft drinks of up to 75 mg of quinine/l (as quinine base) were not of toxicological concern" to include all current uses, and requested that the Expert Committee re-consider this substance at a future meeting.

In the interest of clarity, the Expert Committee agreed to use quantitative terms as far as possible in its conclusions. With regard to lysozyme, the Expert Committee wished to emphasize that the assessment was consistent with its guidelines for enzyme preparations used in food processing, which state that "enzymes obtained from edible tissues of animals commonly used as foods ... are regarded as foods and, consequently, considered acceptable, provided that satisfactory chemical and microbiological specifications can be established" (Annex 1, reference *76*, Annex II). The Committee reassessed quinine at its present meeting (see section 3.1.2 of the main report).

6. The Expert Committee was informed that an FAO Consultation on Aflatoxin Sampling Plans, which had been requested by the Codex Committee, would be held in Rome in May 1993.

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