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Evaluation of certain food additives and contaminants

Thirty-fifth Report of the
Joint FAO/WHO Expert Committee on
Food Additives

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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 29 May–7 June 1989

Members invited by FAO

Mr J.F. Howlett, Head, Risk Assessment and Management Branch, Food Science Division, Ministry of Agriculture, Fisheries and Food, London, England

Mrs D.C. Kirkpatrick, Director, Bureau of Chemical Safety, Health Protection Branch, Health and Welfare Canada, Ottawa, Canada (*Joint Rapporteur*)

Professor K. Kojima, College of Environmental Health, Azabu University, Sagamihara-shi, Japan (*Chairman*)

Dr P.M. Kuznesof, Division of Food Chemistry and Technology, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA

Mrs I. Meyland, Scientific Officer, National Food Agency, Ministry of Health, Søborg, Denmark

Members invited by WHO

Dr H. Blumenthal, Silver Spring, MD, USA

Professor K. Odusote, Associate Professor of Medicine, Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria

Professor M.J. Rand, Department of Pharmacology, University of Melbourne, Melbourne, Victoria, Australia (*Vice-Chairman*)

Professor F.G. Reyes, Professor of Food Toxicology, Department of Food Science, State University of Campinas, Campinas, São Paulo, Brazil (*Joint Rapporteur*)

Professor A. Somogyi, Director, Max von Pettenkofer Institute of the Federal Health Office, Berlin (West)

Dr J.H. Steadman, Senior Principal Medical Officer, Division of Toxicology and Environmental Protection, Department of Health, London, England

Secretariat

Dr G. Burin, Toxicologist, Health Effects Division, Office of Pesticide Programs, Environmental Protection Agency, Washington, DC, USA (*WHO Consultant*)

Dr G.J. van Esch, Bilthoven, Netherlands (*WHO Temporary Adviser*)

Professor C.L. Galli, Professor of Toxicology, Institute of Pharmacological Sciences, University of Milan, Milan, Italy (*WHO Temporary Adviser*)

Mr T. Hallas-Moller, Commission of the European Communities, Brussels, Belgium (*WHO Temporary Adviser*)

Dr Y. Hayashi, Chief, Division of Pathology, National Institute of Hygienic Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr J.L. Herrman, Scientist, International Programme on Chemical Safety, Division of Environmental Health, WHO, Geneva, Switzerland (*Joint Secretary*)

Dr H. Irausquin, Division of Toxicological Review and Evaluation, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr T. Kemeny, Head, Food Chemicals Section, Toxicological Evaluation Division, Bureau of Chemical Safety, Health and Welfare Canada, Ottawa, Canada (*WHO Temporary Adviser*)

Dr N. Rao Maturu, Food Standards Officer, Joint FAO/WHO Food Standards Programme, FAO, Rome, Italy

Dr P. Shubik, Senior Research Fellow, Green College, Oxford, England (*WHO Temporary Adviser*)

Mr R. Top, Vice-Chairman, Codex Committee on Food Additives and Contaminants, Ministry of Agriculture and Fisheries, The Hague, Netherlands (*WHO Temporary Adviser*)

Professor R. Walker, Professor of Food Science, Department of Biochemistry, University of Surrey, Guildford, England (*WHO Temporary Adviser*)

Dr J. Weatherwax, Food Quality and Consumer Protection Group, Food Quality and Standards Service, Food Policy and Nutrition Division, FAO, Rome, Italy (*Joint Secretary*)

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. 26, in press.

Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives. (To be published as an FAO Food and Nutrition Paper.)

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.

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Thirty-fifth Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 29 May to 7 June 1989. The meeting was opened by Dr P. Lunven, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Lunven noted that the work of the Joint FAO/WHO Committee on Food Additives in providing scientific assessments was invaluable to WHO, FAO, and Member States and, in particular, to the work of the Codex Alimentarius Commission. The Commission had been recognized as one of the key elements in removing barriers to trade and was expanding its work on food additives to provide uniform and comprehensive recommendations to governments. Dr Lunven also noted that a comprehensive compilation of specifications for the identity and purity of food additives was in preparation for publication.[1]

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been 34 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the thirty-third meeting (Annex 1, reference *83*).

The tasks before the Committee were: (*a*) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological evaluations of them; (*b*) to review specifications for selected food additives; and (*c*) to undertake toxicological evaluations of certain food additives and the contaminants polychlorinated biphenyls and patulin.

[1] *Specifications for the identity and purity of food additives* (being prepared by FAO).

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

The issue of the safety of certain fungal enzyme preparations used in food was added to the agenda.

Four flavouring agents, dihydrocoumarin, ethyl vanillin, fumaric acid, and quinine hydrochloride, were placed on the agenda on the basis of application of the first three steps of the method for setting priorities for the safety review of food flavouring ingredients, which is summarized in the report of the thirty-third meeting (Annex 1, reference *83*).

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 *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). This publication, developed in response to repeated recommendations by the Committee, embraces the major observations, comments, and recommendations on the safety assessment of food additives and contaminants contained in the previous 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 *Enzyme preparations*

In conjunction with the revision of general specifications for enzyme preparations (section 4.2), the Committee briefly reviewed the guidelines for evaluating enzyme preparations used in food processing that are given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*).

It concluded that these guidelines provide a logical hierarchical procedure for determining the amount and kind of data required to establish the safety in use of enzyme preparations. The Committee stressed the advisory nature of the guidelines and recommended that

they and others given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) be reviewed at a future meeting.

2.2.2 *Flavouring agents*

Flavouring agents have been the subject of general comments in several previous reports of the Committee and in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). The view has repeatedly been expressed that, although flavouring agents should ideally be toxicologically evaluated in the same way as other food additives, special considerations dictate a degree of flexibility.

Although minimum requirements for the safety evaluation of flavouring agents have not been specified, any such evaluation should, in general, include at least a short-term feeding study, relevant metabolism studies, and mutagenicity studies.

The Committee had before it a number of flavouring agents for evaluation. In many instances, however, as is evident from section 3.1.3, the Committee had difficulty in carrying out an evaluation since data were lacking.

The Committee recognized the special problems involved in the safety evaluation of flavouring agents. However, it emphasized that a minimum amount of data was necessary to permit the development of a flexible procedure for evaluating these substances.

2.2.3 *Group ADIs for compounds that have a laxative effect*

In allocating a group acceptable daily intake (ADI) "not specified" to modified celluloses (section 3.1.5) and drawing attention to the laxative effect of an excessive intake of these substances, the Committee noted that similar considerations applied to polyols and that some gums and modified starches might also cause laxative effects at high intakes. At the Committee's twenty-seventh meeting (Annex 1, reference *62*), it was recommended that controls should be introduced to limit the consumption of polyols from all sources. At its present meeting, the Committee considered that other groups of thickeners and stabilizers that have laxative effects should also be subject to these controls since their effects are likely to be additive.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *General*

The Committee reaffirmed the importance of specifications for identity and purity in the evaluation and safe use of food additives, as set out in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). Material subjected to toxicological testing should always be adequately defined. The Committee stressed that information on methods of manufacture, raw materials, and potential impurities should be assessed on a regular basis so that specifications can be drawn up that are both appropriate to the material used in food and consistent with the composition of the material toxicologically tested or evaluated.

In updating existing specifications, the Committee recognized the need, in certain instances, to change the terms "molecular weight" and "relative molecular mass" to "formula weight" in order to conform to accepted chemical principles (*2*). The Committee considered the term formula weight, which represents the mass corresponding to the simplest or empirical formula of a chemical compound, to be the correct term both for salts and for other chemicals that do not exist in nature as discrete molecules. Specifications reviewed at the present meeting were revised, where necessary, in accordance with this principle.

2.3.2 *Enzyme preparations*

Enzyme preparations were considered at the present meeting in response to a recommendation made at the Committee's thirty-first meeting. Questions had arisen from a discussion of the need to define the non-enzymic components of enzyme preparations and how information on such components might be taken into account from the point of view of the definition and safety of the products. The Committee concluded that a complete definition of all the components of an enzyme preparation can rarely, if ever, be achieved and that the identity and purity of preparations can therefore best be ensured by defining the processes by which they are produced and establishing criteria limiting the presence of contaminants and possible toxic metabolites derived from the source material or contaminating organisms.

The uncertainty as to the nature of the non-enzymic components mainly concerns the components that are derived in association with the active enzyme from the source material. In the case of enzymes derived from microbial sources, the potential for variability is related to both the identity of the organism concerned and the conditions under which it is cultured during the production of the enzyme. The Committee considered that it would be desirable, in specifications for microbial enzyme preparations, to define the source organism in terms not only of the species concerned but also of the strain or variant and to ensure that the culture conditions employed during the production of any particular preparation were the same as those under which the preparation subjected to toxicological testing was produced. Differences in either the strain of source organism or the conditions under which it was cultured would imply a change in the identity of the preparation and therefore require its re-evaluation. The Committee reiterated the principle already incorporated in the existing general specifications for enzyme preparations used in food processing (Annex 1, reference *69*) that non-enzymic components added for technological reasons (stabilizers, diluents, preservatives, etc.) and as immobilizing agents should be acceptable and appropriate for the intended uses of the enzyme preparations in food and food processing.

The Committee recognized that it may be inappropriate to impose limits on named mycotoxins in all microbial enzyme preparations regardless of source organism. It considered that, as individual specifications for enzymes are reviewed, the limits on named mycotoxins in the general specifications should be transferred, where relevant, to the individual source organisms. The Committee remained concerned, however, about the possibility of the production of as yet unidentified toxic metabolites. It considered that an appropriate battery of tests to screen for such potentially toxic metabolites should be developed for inclusion in the general specifications for enzyme preparations from microbial sources.

2.3.3 *Naturally occurring substances*

Substances of natural origin (e.g., spice oleoresins) may be introduced into commerce in forms that vary widely in composition. This variation is attributable to a number of factors, including the existence of different cultivars, the effects of climate and geography, the use of different extraction solvents and procedures, and the use

of diluents. Because of such compositional variation, specifications have tended to be broad and therefore not necessarily relevant to the substance for which a toxicological evaluation may be available. The Committee believed that specifications that simply state, for example, the content of the principal component (e.g., flavouring principle, colour principle) as "not less than declared on the label", while suitable for ensuring honesty in trade, could be inadequate for purposes of safety. It therefore recognized the need to continue exploring new principles for establishing adequate specifications for substances of natural origin that are both appropriate to the material used in food and consistent with the composition of the toxicologically evaluated material.

2.3.4 *Solvent residues*

During its deliberations on specifications for spice oleoresins, the Committee expressed the opinion that the use of dichloromethane and 1,2-dichloroethane as extraction solvents should be discouraged because of toxicological concerns. Because these and other solvents have not been recently evaluated and new data are now available, the Committee concluded that an overall review of solvents used in food processing would be appropriate.

In future reviews of existing specifications where provision has been made for the use of solvents, the Committee intends to request the user industry to provide justification for their use in addition to more specific data on typical levels of residues resulting from such use.

The Committee further stressed that levels of residues resulting from the use of any solvent should be the minimum technically achievable and toxicologically insignificant. Research leading to the development of new solvent systems of lower toxic potential is to be encouraged.

2.4 Methodology for analysing chemical contaminants in food

For assessing the health implications of dietary exposure to chemical contaminants, reliable information on the intake of such substances is needed. In particular, data are required on the actual levels of the substances of interest in various foods, and it is necessary to ensure that the analytical procedures employed to generate these data are both reliable and of adequate accuracy.

In connection with the chemical contaminants evaluated at its present meeting, the Committee was aware of the difficulties that could be encountered in the analysis of polychlorinated biphenyls (PCBs) in food and, in particular, in PCB isomer-specific analysis. It was informed of the ongoing activities of the WHO Regional Office for Europe related to PCBs (as well as other chlorinated hydrocarbons, including polychlorinated dibenzodioxins and polychlorinated dibenzofurans) and the assessment of health risks to infants associated with contamination of mothers' milk. Part of this project involves interlaboratory quality-control studies on levels of PCBs in human milk, and the results of the first round of such studies, which involved 12 laboratories, have been published (*3*). Planning of the second round of quality-control studies has already begun, and additional laboratories are expected to participate. The Committee expressed its support for studies of this type.

In the case of patulin, the results of numerous surveys of fruit products have been published over the last two decades. However, in many of the older surveys, the methods used were not sufficiently sensitive, and patulin was not positively identified. The Committee's evaluation of this mycotoxin took account of these facts.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS[1]

The Committee evaluated a number of food additives and contaminants for the first time and re-evaluated several substances considered at previous meetings. Information on the evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and of other information required or desired for certain substances are given in Annex 3.

3.1 Specific food additives

3.1.1 *Emulsifiers*

Polyglycerol esters of fatty acids

At the Committee's seventeenth meeting (see Annex 1, reference *32*), polyglycerol esters of fatty acids were evaluated and the

[1] Bibliographical references to toxicological studies are included in this section only for substances for which toxicological monographs (which would normally list such references) have not been prepared.

Committee agreed to convert the former conditional ADI to an ADI of 0–25 mg per kg of body weight.

At its thirty-first meeting (see Annex 1, reference *77*), the Committee revised the specifications but was unable to accept the request to increase the range of average polyglycerol chain lengths permitted from three to ten glycerol units without a review of the toxicological data on these substances. Since the data requested were not forthcoming, the Committee at its present meeting maintained the previous ADI of 0–25 mg per kg of body weight for polyglycerol esters of fatty acids having an average chain length of up to three glycerol units.

A toxicological monograph was not prepared.

The existing specifications for polyglycerol esters of fatty acids were maintained.

Sucrose esters of fatty acids and sucroglycerides

Sucrose esters of fatty acids are the mono-, di-, and triesters of sucrose with edible fatty acids. They may be prepared from sucrose and the methyl and ethyl esters of edible fatty acids, usually in the presence of a solvent. "Sucroglycerides" (a mixture of sucrose esters of fatty acids and mono- and diglycerides) are produced by reaction of edible fats or oils with sucrose; this reaction is also usually carried out in the presence of a solvent.

These substances were evaluated for the purpose of establishing an ADI at the Committee's thirteenth, seventeenth, twentieth, and twenty-fourth meetings (Annex 1, references *19, 32, 41,* and *53*). Separate toxicological monographs were prepared on each occasion for sucrose monoesters of individual fatty acids and for palm-oil sucrose esters and lard and tallow sucrose esters.

At its present meeting, the Committee was asked to consider the consequences of modifying the specifications for these substances when manufactured by a process in which dimethylsulfoxide, isobutanol, ethyl methyl ketone, or a combination of these is used as solvent. It was noted that an ADI (or provisional intake) had not been established for these solvents but that dimethylsulfoxide and isobutanol occur naturally in the diet and ethyl methyl ketone has been identified as a product of intermediary metabolism. The Committee concluded that, in foods as consumed, the levels of these solvents arising from residues in sucrose esters of fatty acids that comply with the specifications (as revised at the present meeting) are

insignificant relative to naturally occurring levels in the diet, and there is no reason to suppose that they present a hazard.

The Committee also reviewed new toxicological studies on a palm-oil sucroglyceride, including a long-term carcinogenicity study in rats and short-term studies in rats and dogs.

It was concluded that, both for sucrose esters of fatty acids manufactured by a process using dimethylsulfoxide, isobutanol, ethyl methyl ketone, or a combination of these as solvent, and for the palm-oil sucroglyceride, the previously established group ADI of 0–10 mg per kg of body weight for sucrose esters of fatty acids and sucroglycerides would apply.

An addendum to the toxicological monograph was prepared.

The specifications for sucrose esters of fatty acids were revised to include considerations on the use of the above-mentioned solvents.

The existing specifications for sucroglycerides were maintained.

3.1.2 *Enzyme preparations*

Enzyme preparations derived from Aspergillus niger

As a consequence of its review of general specifications for enzyme preparations, the Committee reconsidered the evaluation of enzymes derived from *Aspergillus niger* made at the thirty-first meeting (Annex 1, reference 77). At that meeting, the Committee established a single ADI for several separate enzyme preparations derived from *Aspergillus niger* of 0–1 mg of total organic solids per kg of body weight. The enzyme preparations for which this ADI was established were carbohydrases, amyloglucosidases (EC 3.2.1.3), endo-1,3(4)-β-glucanase (EC 3.2.1.6), hemi-cellulase, pectinases (EC 3.1.1.11; 4.2.2.10; 3.2.1.15), and protease.

In view of the fact that *Aspergillus niger* is a common organism in food, that many strains have had a long history of use as an enzyme source, and that the numerous studies of various preparations from various strains have demonstrated no hazard to human health, the numerical ADI that was earlier established for each of the above-listed enzyme preparations from *Aspergillus niger* was changed to an ADI "not specified".

A toxicological monograph was not prepared.

None of the existing specifications for enzyme preparations derived from *Aspergillus niger* were reviewed.

3.1.3 *Flavouring agents*

Benzyl acetate

This compound was previously reviewed at the eleventh, twenty-seventh, twenty-ninth, and thirty-first meetings of the Committee (Annex 1, references *14, 62, 70,* and *77*).

At the thirty-first meeting, the Committee extended the temporary ADI of 0–5 mg per kg of body weight pending the evaluation of lifetime gavage studies with benzyl alcohol, a normal metabolite of benzyl acetate. These studies did not show an increased incidence of either hepatocellular or forestomach tumours in mice or pancreatic tumours in rats, although such effects had previously been observed in studies with benzyl acetate. However, there are difficulties in interpreting the results of the carcinogenicity studies with benzyl acetate since the compound was given by gavage. Since new long-term studies are under way with benzyl acetate incorporated into the diet of rats and mice, the Committee decided to extend the temporary ADI of 0–5 mg per kg of body weight until 1993 pending the evaluation of the results of these studies.

In view of a report of a positive result in an *in vitro* mutagenicity test on benzyl acetate, the Committee concluded that it would be desirable to ascertain whether the results of an existing *in vivo* study that demonstrated the absence of the induction of unscheduled DNA synthesis could be confirmed by an *in vivo* test for chromosome damage in bone marrow.

A toxicological monograph was prepared.

The existing specifications for benzyl acetate were maintained.

Cinnamaldehyde

Cinnamaldehyde was evaluated at the eleventh, twenty-third, twenty-fifth, and twenty-eighth meetings of the Committee (Annex 1, references *14, 50, 56,* and *66*).

At its twenty-third meeting, the Committee converted the previously established conditional ADI of 0–1.25 mg per kg of body weight into a temporary ADI of 0–0.07 mg per kg of body weight (Annex 1, reference *50*) because of inadequacies in the toxicity data. At the twenty-eighth meeting, the temporary ADI was extended and an extensive series of studies was requested.

Because the required data were not forthcoming, the Committee was unable to extend the temporary ADI at its present meeting. However, the Committee concluded that, of the information

requested at the twenty-eighth meeting, the results of the short-term feeding study in a non-rodent mammalian species and of adequate metabolic studies might be sufficient to make re-evaluation possible.

A toxicological monograph was not prepared.

The existing specifications for cinnamaldehyde were maintained.

Dihydrocoumarin

The safety of this substance was evaluated for the first time by the Committee at its present meeting.

Metabolites of dihydrocoumarin identified in rabbit urine include umbelliferone, 3-hydroxycoumarin, coumarin, *o*-coumaric acid, melilotic acid, melilotoylglycine, and *o*-coumaroylglycine (*4*). There is some evidence that the gut flora is responsible for the conversion to melilotic acid (*5*).

The toxicological information available was derived from acute toxicity tests in mice (*6*), rats (*7, 8*), and guinea-pigs (*7*), a 14-week study in rats in which loss of test compound in the diet mixture during storage precluded estimation of exact exposure levels (*9*), a short-term study in rats (90 days), in which a single dose level was used (*10*), and a study in which three dogs were treated at one of two dose levels of dihydrocoumarin for two years but for which there was no control group (*9*). Although no adverse effects were reported in these studies, the Committee considered the data inadequate for toxicological evaluation and was therefore unable to allocate an ADI for dihydrocoumarin. The Committee stated that, for a re-evaluation of this substance, the results of a short-term study in a rodent species and metabolic studies to investigate the extent of conversion to coumarin would be needed.

A toxicological monograph was not prepared.

New specifications were prepared for dihydrocoumarin and were designated as tentative. Further information is required (see Annex 3).

Ethyl vanillin

Ethyl vanillin was previously evaluated at the eleventh meeting of the Committee (Annex 1, reference *14*), when an ADI of 0–10 mg per kg of body weight was allocated to this compound on the basis of a long-term study in rats. Although the Committee had then considered it possible to allocate an ADI, it had noted that few metabolic studies were available and concluded that further studies of that type were desirable.

Ethyl vanillin was placed on the agenda of the present meeting on the basis of partial application of the method for setting priorities for the safety review of food flavouring ingredients (see section 2.1).

The Committee noted that none of the previously evaluated long-term or carcinogenicity studies met modern standards in that fewer animals per group had been used than would be the present norm.

Accordingly, it reduced the previous ADI to 0–5 mg per kg of body weight, and made it temporary. The Committee requested submission, by 1992, of the results of an adequate short-term study in rats and metabolic studies in rats.

A toxicological monograph was prepared.

The existing specifications for ethyl vanillin were revised.

Fumaric acid

Fumaric acid and sodium fumarate were evaluated for the purpose of establishing an ADI by the Committee at its tenth, eighteenth, and twenty-third meetings (Annex 1, references *13, 35,* and *50*). At the eighteenth meeting, the previous unconditional ADI for fumaric acid was confirmed as an ADI of 0–6 mg per kg of body weight. At the twenty-third meeting, the Committee decided to establish a group ADI for fumaric acid and its salts of 0–6 mg per kg of body weight.

Fumaric acid was placed on the agenda of the present meeting on the basis of partial application of the method for setting priorities for the safety review of food flavouring ingredients (see section 2.1).

Because fumaric acid is a normal constituent of tissues and is metabolized by the body, the Committee decided to change the previous group ADI to a group ADI "not specified" for fumaric acid and its salts, in agreement with the guidelines laid down in section 5.2.3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*).

A toxicological monograph was not prepared.

The existing specifications for fumaric acid were revised.

Quinine hydrochloride

The safety of this substance was evaluated for the first time by the Committee at its present meeting. Specifications had been developed at the twenty-fourth and twenty-sixth meetings (Annex 1, references *53* and *59*).

Biochemical studies, short-term studies in rats, teratogenicity studies in rats, and mutagenicity studies were reviewed. In these

studies, no-effect levels ranged from 40 to 100 mg per kg of body weight per day. Mutagenicity studies gave negative results.

Varied complaints including headaches and transient visual problems were reported in human volunteers given doses of 100 mg of quinine hydrochloride per person per day. These findings were not confirmed in a second, controlled study using 120 mg per person per day. A third study showed electronystagmographic changes in stressed subjects for which a no-effect level of 52.5 mg of quinine per person per day was determined. The Committee concluded that an evaluation could be made on the basis of the human data. Since the toxic effects of concern were acute and reversible, and there is extensive experience of human consumption of quinine without reports of acute toxicity, except very rarely in hypersensitive individuals, the Committee saw no need to require a margin of safety. It established an acceptable intake of 52.5 mg of quinine per person per day, equivalent to an ADI of 0–0.9 mg of quinine per kg of body weight per day. However, the Committee considered that data from more extensive human studies should be submitted and therefore made the ADI temporary.

The Committee requested submission of the results of an adequate human study by 1992.

A toxicological monograph was prepared.

The existing specifications for quinine hydrochloride were revised.

3.1.4 *Food colours*

Canthaxanthin

This substance was last evaluated by the Committee at its thirty-first meeting (Annex 1, reference *77*), when it was noted that ingestion of canthaxanthin could, in some circumstances, lead to deposits of crystals in the human retina. At that time, the Committee reduced the previously allocated ADI to 0–0.5 mg per kg of body weight and made it temporary. In addition, it required: (*a*) further details of long-term studies in rats and mice; (*b*) clarification of the factors that influence deposition in the eye, including the establishment of the threshold dose, information on the influence of dose and duration of exposure and on the reversibility of pigment accumulation, and the investigation of potential animal models; and (*c*) clarification of whether pigment deposition is causally related to impaired visual function.

Canthaxanthin is used both as a direct food additive and as a feed additive for colouring salmonid fish and chicken egg yolks. Although there is some metabolic transformation to other carotenoids in egg yolks, the parent compound is present in the products derived from animals to which it has been given as a feed additive, so the present evaluation also covers its use for this purpose.

Since the previous evaluation, substantial amounts of new data have become available and these were reviewed by the Committee.

The Committee noted that the results of two long-term carcinogenicity studies in mice and rats did not provide evidence of carcinogenicity. However, at high dose levels, canthaxanthin produced liver damage in rats (with a non-dose-related increased incidence of benign nodules in female rats); mice appeared to be less sensitive to hepatic injury. It was concluded that, in addition to the eye, the liver was a target organ for canthaxanthin.

In the long-term studies in rats, it was not possible to establish a no-effect level. However, the Committee was informed that another long-term study in rats was in progress aimed at establishing a no-effect level in respect of pathological changes in the liver.

While distribution studies with radiolabelled canthaxanthin showed that relatively high concentrations accumulated in the eye in all the mammalian species studied, crystal deposition has, to date, been observed only in the human retina. The animal species studied have therefore not provided a suitable model for the study of the pathogenesis and reversibility of this phenomenon. However, the changes noted in electroretinograms in humans were reproduced in the electroretinograms of pigmented rabbits after canthaxanthin treatment.

The Committee concluded that the long-term toxicity of canthaxanthin in rats indicated potential hepatotoxicity in humans; this matter may be resolved by obtaining clinical data from human subjects showing retinal pigment deposition. However, the Committee considered that the primary problem associated with canthaxanthin was the deposition of crystals in the human retina.

In view of the irreversibility or very slow reversibility of the retinal crystal deposition, the significance of which is not known, the Committee was unable to establish an ADI for canthaxanthin when used as a food additive or animal feed additive. The previous temporary ADI was therefore not extended.

A toxicological monograph was prepared.

The existing specifications for canthaxanthin were maintained.

Carotene preparations from natural sources

These substances were reviewed at the eighteenth and thirty-first meetings of the Committee (Annex 1, references *35* and *77*). At the latter meeting, the Committee noted that, while there was a substantial toxicological data base 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 its present meeting, the Committee considered limited biochemical, acute, and short-term toxicological studies on material derived from three different algal species, namely *Dunaliella bardawil, D. salina,* and *D. kona.* Some of the preparations produced from these species were dried concentrates produced by lyophilization or spray-drying; another product was a vegetable oil extract.

The Committee concluded that there was insufficient evidence to indicate that data relating to one species of *Dunaliella* could be applied to others. It also decided 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 considered 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.

A toxicological monograph was not prepared.

The existing tentative specifications for carotenes (algae) were revised. The Committee was aware that three different species of *Dunaliella* are used as sources of carotene, and recognized the need for further information regarding the differences between both the species and the resulting products, and the influence of the method of manufacture, such as spray-drying, on the quality. The Committee was also informed that carbon dioxide is not used for the extraction and it saw no need to test for urethane which might have resulted from such use. The existing tentative specifications for carotenes (vegetable) were also revised. The "tentative"

qualifications for both were maintained and certain further information is required (see Annex 3).

Curcumin and turmeric oleoresin

Turmeric and curcumin (the main colouring component of turmeric) were considered at the thirteenth, eighteenth, twenty-second, twenty-sixth, and thirtieth meetings of the Committee (Annex 1, references *19, 35, 47, 59,* and *73*). Toxicological monographs were prepared on each of these occasions (Annex 1, references *20, 36, 48, 60,* and *74*). At the thirtieth meeting, the Committee concluded that turmeric is often regarded as a food rather than as a food additive, and it is therefore not appropriate to allocate an ADI to this substance. The temporary ADI for curcumin was extended, and a temporary ADI was allocated to turmeric oleoresin at that meeting.

Curcumin. When the temporary ADI of 0–0.1 mg per kg of body weight was extended at the Committee's thirtieth meeting, the submission of the results of a carcinogenicity study and a reproduction/teratogenicity study was requested. The results of these studies were not made available at the present meeting, but the Committee was informed that the results of carcinogenicity studies, including fertility assessment phases, in B6C3F1 mice and F344 rats given turmeric oleoresin containing a high concentration of curcuminoids should be available in 1990. The Committee therefore extended the temporary ADI until 1992, with the requirement that the results of the above-mentioned studies should be made available for review at that time. Since a reproduction phase is included in the ongoing carcinogenicity studies, the Committee would wish to review these studies before deciding whether the reproduction/teratogenicity study requested earlier was still needed.

A toxicological monograph was not prepared.

The existing specifications for curcumin were maintained.

Turmeric oleoresin. At the thirtieth meeting, when the Committee established the temporary ADI of 0–0.3 mg per kg of body weight for turmeric oleoresin, it requested the results of an additional short-term study in pigs or another suitable non-rodent species in order to establish a clear no-effect level for effects on the thyroid gland, which had been observed in a study in pigs. The results of such a study were

not made available at the present meeting of the Committee and the temporary ADI was therefore not extended.

A toxicological monograph was not prepared.

The Committee reviewed the specifications for turmeric oleoresin and turmeric colour as recommended at the thirtieth meeting. The Committee, at that meeting, had suggested that the specifications for turmeric oleoresin be revised to bring them into line with those for turmeric colour. However, at its present meeting, the Committee concluded that specifications for turmeric colour were contained in those for the oleoresin, and therefore deleted the existing separate specifications for the former. The specifications for turmeric oleoresin were revised to emphasize the principal colouring components of the oleoresin and to incorporate the method of assay for content of total colouring matter that was previously part of the turmeric colour specifications.

The Committee pointed out that the revised specifications for turmeric oleoresin cover a range of products, some of which are used as colours and some as flavourings; components other than pure colouring principles (e.g., the volatile oils) should therefore be taken into account, as necessary, when such products are evaluated.

Paprika oleoresin

Paprika oleoresin was evaluated at the fourteenth meeting of the Committee (Annex 1, reference *22*), when no ADI was established because it was recognized that the use of this spice extract is self-limiting for technological and organoleptic reasons.

The Committee was informed that the extraction solvent 1,2-dichloroethane is being used to produce paprika oleoresin. At both the thirty-first meeting (Annex 1, reference *77*) and the present one, the Committee revised the specifications for paprika oleoresin but decided not to include 1,2-dichloroethane as an additional processing solvent. The toxicological data on 1,2-dichloroethane were therefore not reviewed, and a toxicological monograph was not prepared.

In addition to 1,2-dichloroethane, two other chlorinated hydrocarbons are among the solvents currently listed for use in paprika oleoresin production. The Committee expressed its general opinion that levels of residues resulting from the use of any solvent should be both the minimum technically feasible and of no toxicological concern.

In future reviews of the specifications for paprika oleoresin and other oleoresins, justification by the industry for the use of chlorinated hydrocarbon solvents will be sought, together with specific information on actual residues resulting from their use.

3.1.5 *Thickening agents*

Gum arabic

This substance was last evaluated at the twenty-sixth meeting of the Committee (Annex 1, reference *59*) and an ADI "not specified" was allocated.

At its present meeting the Committee reviewed further findings from teratogenicity and biochemical studies, and concluded that the results of these studies gave no reason to modify the previous evaluation. The Committee therefore confirmed the ADI "not specified". An addendum to the existing toxicological monograph was prepared.

The Committee's attention was drawn to the fact that products were being sold as gum arabic that were derived from species other than *Acacia senegal* (L) Willdenow and closely related species hitherto recognized as the source species of gum arabic. It was informed that all these gums would be covered by the existing specifications for gum arabic.

However, the Committee was also informed of extensive studies on the chemical composition of individual gums. These studies clearly showed that, while the composition of gums from *Acacia senegal* and closely related species originating from various geographical regions varied only slightly, there were significant differences in the composition of gums from other species, for example in the carbohydrate content and ratios of different amino acids.

The existing specifications were therefore revised to reflect more closely the gums that have been toxicologically evaluated.

Modified celluloses

Modified celluloses were reviewed at the fifth, seventh, tenth, thirteenth, seventeenth, twenty-sixth, twenty-seventh, and thirtieth meetings of the Committee (Annex 1, references *5, 7, 13, 19, 32, 59, 62,* and *73*). At the seventeenth meeting, a group ADI of 0–25 mg per kg of body weight was allocated for the five modified celluloses previously reviewed (methyl cellulose, methyl ethyl cellulose,

hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and sodium carboxymethyl cellulose). A toxicological monograph on these five compounds was prepared (Annex 1, reference *33*).

At the twenty-sixth and twenty-seventh meetings of the Committee, ethyl cellulose and ethyl hydroxyethyl cellulose, respectively, were reviewed and it was decided that the group ADI of 0–25 mg per kg of body weight should also apply to them. A toxicological monograph on ethyl hydroxyethyl cellulose was prepared (Annex 1, reference *74*).

Since the previous evaluation, additional data have become available, including data from studies in rats on caecal enlargement and changes in caecal flora, teratogenicity, and development, and from *in vitro* mutagenicity studies on methyl cellulose and carboxymethyl cellulose. These studies confirmed the conclusion reached at the earlier meetings of the Committee that modified celluloses are of low toxicity.

In long-term/carcinogenicity studies on hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose in rats and mice, no evidence of mutagenicity or carcinogenicity was observed. In addition, in reproduction and teratogenicity studies in mice, rats, and rabbits, the consumption of hydroxypropyl cellulose, methyl cellulose, or sodium carboxymethyl cellulose did not interfere with the reproductive process, and no embryotoxic or developmental effects were observed.

A new substantial body of human data was available on the laxative effects of modified celluloses, which are seen in some subjects at levels as low as 5 g per person per day. At higher doses, diarrhoea was reported in some subjects, but in others constipation developed. The amounts ingested in studies in humans did not exceed 30 g per person per day, which has been recommended by the United States National Research Council as the upper safe level of dietary fibre in general (*11*).

The Committee allocated a group ADI "not specified" to these modified celluloses, and pointed out that their laxative properties should be taken into account when they are used as food additives (see section 2.2.3).

A toxicological monograph was prepared.

None of the existing specifications for modified celluloses were reviewed.

3.1.6 *Miscellaneous food additives*

Ferrous lactate

Ferrous lactate, a colour adjunct, was considered for the first time by the Committee.

At the seventeenth meeting, the Committee evaluated lactic acid and its ammonium, calcium, potassium, and sodium salts (Annex 1, reference *32*). Since lactic acid is a normal constituent of food and a normal intermediary metabolite in humans, the Committee decided at that meeting to establish a "not limited" ADI.

Iron was evaluated at the twenty-seventh meeting of the Committee and, on the basis of the data available, a provisional maximum tolerable daily intake (PMTDI) of 0.8 mg per kg of body weight was allocated (Annex 1, reference *62*). It was pointed out that the tolerable daily intake should not be used as a guideline in the fortifying of processed food (Annex 1, reference *60*, section 2.8).

At its present meeting, the Committee concluded that, because the iron in ferrous lactate is bioavailable, the amount of iron resulting from the use of ferrous lactate should be included with that from all other sources, and the total should not exceed the PMTDI for iron of 0.8 mg per kg of body weight.

A toxicological monograph was not prepared.

New specifications for ferrous lactate were prepared.

2-Nitropropane

2-Nitropropane was considered by the Committee at the twenty-third, twenty-fifth, and twenty-eighth meetings (Annex 1, references *50, 56*, and *66*). Toxicological monographs were prepared after each meeting (Annex 1, references *51, 57,* and *67*). At the twenty-eighth meeting, 2-nitropropane was considered to be temporarily acceptable for use as a fractionating solvent in the production of fats and oils, as long as its use continued to be limited and residue levels were kept to the lowest technically attainable.

The Committee noted that fractionated fats and oils have physical properties that limit their application and that present procedures for the processing of fats and oils with 2-nitropropane do not lead to detectable levels of this substance in the finished product. On the assumption that such treated fats and oils may contain 2-nitropropane at the limit of detection, namely, 10 µg/kg, and on the basis of a maximum projected intake of this substance in processed oils in the United States, the maximum intake of 2-nitropropane was

estimated to be 0.13 ng per kg of body weight per day. The Committee recognized that this was a worst-case intake estimate and that actual intakes of 2-nitropropane were probably lower.

The Committee reviewed a new inhalation study in which mice were exposed to 2-nitropropane; nodular hyperplasia of the liver was observed in females. A carcinogenic effect had previously been noted in rats after inhalational exposure to relatively high concentrations (100–800 mg/m^3) of 2-nitropropane (Annex 1, reference *66*). In addition, the Committee reviewed a new study in which all rats dosed by gavage with 2-nitropropane at a level of 89 mg per kg of body weight for 16 weeks (three days per week) developed hepatocarcinomas.

On the basis of these studies, 2-nitropropane was considered to be a potent liver carcinogen in rats, and the temporary acceptance of this substance for use as a fractionating solvent in the production of fats and oils was therefore not extended. However, if the technological need for this solvent could be demonstrated and if data were provided that could be used for establishing a safe level of intake of 2-nitropropane, the Committee would reconsider it at a future meeting.

A toxicological monograph was prepared.

The existing specifications for 2-nitropropane were revised, but maintained as tentative (see Annex 3).

Tannic acid

Tannic acid was reviewed at the fifth, tenth, fourteenth, and thirty-first meetings of the Committee (Annex 1, references *5, 13, 22,* and *77*).

At the thirty-first meeting (Annex 1, reference *77*), the previous temporary ADI was changed to a temporary ADI "not specified" for tannic acid used as a filtering aid. Further data were requested on the composition of tannic acid from different sources.

Information was provided to the Committee at its present meeting that permitted revision of the specifications so as to require a high degree of purity for tannic acid used as a filtering aid where the application of good manufacturing practice ensures that it is removed from food after use. An ADI "not specified" for this use was therefore established.

As detailed information on the composition of tannic acid from different botanical sources was not forthcoming and no new

toxicological data were available, it was not possible to consider its use as a direct food additive.

A toxicological monograph was not prepared.

The Committee received updated information on the manufacture of tannic acid and, as stated above, was in a position to revise the existing tentative specifications. It maintained the "tentative" qualification and renewed the request for data on the composition of tannic acid from different botanical sources. Data on actual uses and levels of use of tannic acid as a flavouring agent were also requested (see Annex 3).

Lactoperoxidase/thiocyanate/hydrogen peroxide system

At the twenty-ninth meeting (Annex 1, reference *70*), the Committee considered the practice of adding sodium thiocyanate and hydrogen peroxide (the lactoperoxidase/thiocyanate/hydrogen peroxide system) to raw milk to maintain its quality. Since then, the Joint FAO/WHO Committee of Government Experts on the Code of Principles concerning Milk and Milk Products has produced draft guidelines for the preservation of raw milk by use of the lactoperoxidase system in circumstances where refrigeration is virtually impossible. The underlying principles and application of the lactoperoxidase system have been further elaborated in the "Code of practice for the preservation of raw milk by the lactoperoxidase system" (*12*).

The lactoperoxidase system consists of three components: lactoperoxidase naturally present in bovine and buffalo milks; added sodium thiocyanate; and an added source of hydrogen peroxide.

The Committee reviewed the draft guidelines, and noted that milk preserved by this method would contain an amount of sodium thiocyanate greater by up to 14 mg/l than that naturally present in milk.

The Committee recognized that the potential major toxic effect of thiocyanate ion is interference with iodine uptake by the thyroid gland. Thiocyanate occurs normally in blood and urine as a result of ingestion of precursors in the diet. Epidemiological studies indicate that there is no significant toxicity from chronic dietary consumption of thiocyanate provided that iodine intake is adequate.

The Committee noted that the levels of hydrogen peroxide that would be introduced into milk through the use of sodium percarbonate, a hydrogen peroxide adduct of sodium carbonate ($2Na_2CO_3.3H_2O_2$), as the source of hydrogen peroxide in the

lactoperoxidase system were lower than those considered acceptable at the twenty-fourth meeting of the Committee (Annex 1, reference *53*) and therefore were not considered to be a cause for concern. Application of the lactoperoxidase system to raw milk requires a hydrogen peroxide concentration of approximately 10 mg per litre. This is significantly lower than the concentration of hydrogen peroxide required (300–800 mg/kg) when that substance is used alone for the preservation of raw milk.

The Committee recognized that the use of the lactoperoxidase system would increase total thiocyanate exposure but considered that that would not pose any toxicological problem provided that iodine intake was adequate. It concluded that, when used according to the draft guidelines, the lactoperoxidase system does not present a toxicological hazard and, furthermore, that the system should be used in preference to hydrogen peroxide alone for the preservation of raw milk, though only where absolutely necessary, i.e., in the absence of adequate refrigeration facilities.

A toxicological monograph was not prepared.

The existing specifications for sodium thiocyanate were maintained. New specifications for sodium percarbonate were prepared.

3.2 Contaminants

3.2.1 *Patulin*

Patulin has not been previously evaluated by the Committee. The Committee noted that fungi of several different genera, including *Penicillium, Aspergillus,* and *Byssochlamys*, are capable of producing patulin. The natural occurrence of this mycotoxin has been largely associated with *Penicillium expansum*, a common spoilage microorganism in apples.

The Committee reviewed studies on the biochemistry and toxicology of patulin as well as very limited information on observations in humans when patulin was tested as an antibiotic for treatment of the common cold.

In rats, most of the administered dose was eliminated within 48 hours, in faeces and urine, less than 2% being expired as carbon dioxide. No other metabolites have been identified. About 2% of the administered dose was still present after seven days, associated primarily with erythrocytes.

Patulin has a strong affinity for sulfhydryl groups, which explains why it inhibits the activity of many enzymes. Patulin adducts formed with cysteine were less toxic than the unmodified compound in acute toxicity, teratogenicity, and mutagenicity studies.

In acute and short-term studies, patulin caused gastrointestinal hyperaemia, distension, haemorrhage, and ulceration. Pigtail monkeys tolerated patulin consumption of up to 0.5 mg per kg of body weight per day for four weeks without adverse effects.

The results of two reproduction studies in rats were available. No reproductive or teratogenic effects were noted at levels of up to 1.5 mg per kg of body weight per day, but there was an increase in the frequency of fetal resorptions at that level.

The results of a carcinogenicity study in rats, with orally administered patulin, were negative. Short-term *in vitro* genotoxicity studies indicate that patulin is not mutagenic, but it has clastogenic activity in some test systems.

The Committee set a provisional tolerable weekly intake (PTWI) for patulin of 7 µg per kg of body weight based on a no-effect level of 0.1 mg per kg of body weight per day in a combined reproduction/long-term/carcinogenicity study in rats. An additional long-term/carcinogenicity study in a rodent species other than the rat is recommended for further evaluation of the toxicity of patulin.

The Committee had before it data on patulin levels in apple juice, which is often consumed by children. On the basis of surveys in limited areas of the world, a maximum intake by children of 0.26 µg per kg of body weight per day has been estimated. However, apple juice can occasionally be heavily contaminated and the Committee therefore considered that efforts should be made to avoid unnecessary exposure to this mycotoxin by adherence to good manufacturing practices whereby rotted or mouldy fruit is not used. This should reduce dietary exposure to levels below the PTWI. The Committee urged the application of such practices.

A toxicological monograph was prepared.

3.2.2 *Polychlorinated biphenyls (PCBs)*

Polychlorinated biphenyls (PCBs) have not been previously evaluated by the Committee.

PCBs are a class of stable chlorinated hydrocarbons which, prior to the 1970s, had been used extensively in a wide range of industrial

applications. About 50–60 different PCBs, with different degrees of chlorination and thus differing physical properties, are still found in industrial products. The higher the chlorine content of PCBs, the more resistant they are to biodegradation. When PCBs are ingested, the less highly chlorinated biphenyls are metabolized in the liver, primarily to hydroxylated compounds, which are rapidly excreted. The more highly chlorinated biphenyls are more metabolically stable and accumulate in body fat.

The Committee had before it data from a large number of toxicity studies, of varying merit, most of which were carried out with commercial mixtures of PCBs. The evaluation of these studies is both difficult and complicated since the PCB mixtures tested were ill-defined and many were contaminated with polychlorinated dibenzofurans and other related chlorinated compounds. The presence of these contaminants is thought to be at least partly responsible for a number of effects seen in the animal experiments. The Committee nevertheless concluded that sufficient data were available to enable some general conclusions regarding the effects of PCBs to be reached.

Some of the PCB mixtures were hepatocarcinogenic in rodent bioassays. However, human experience from long-term accidental exposures and from epidemiological studies of workers exposed occupationally is inconclusive in respect of an association between PCB exposure and increased cancer mortality.

From a comparison of data from animal studies and symptoms observed in accidentally exposed human populations, the monkey appears to be the most appropriate animal for use in studies on PCBs. The Committee concluded, on the basis of the available studies with monkeys, that 0.04 mg per kg of body weight per day was a no-effect level; only minor effects were observed at 0.1 mg per kg of body weight per day.

Because of the limitations of the available data and the ill-defined nature of the materials that were used in feeding studies, the Committee concluded that it was impossible to establish a precise numerical value for a tolerable intake for humans. In particular, the PCB mixtures used in the monkey studies cited above were not entirely the same as those to which humans are exposed in the diet. However, there is no reason to believe that humans would be more sensitive than monkeys to the effects of PCBs, and some indication of safe exposure levels can therefore be obtained from the no-effect level observed in the monkey studies.

The major foods in which contamination with PCBs is possible are fish, milk and other dairy products, and meat. Median levels in fish reported in various countries are of the order of 100 μg/kg compared with less than 20 μg/kg for other foods. An important exception is human milk, in which PCB median levels ranging from 15 to 100 μg/kg on a whole milk basis have been reported.

The dietary intake of PCBs by various populations has been estimated to range from 0.005 to 0.2 μg per kg of body weight per day. Such a wide variation in intakes can be explained not only by the type and amount of food consumed but also by the method used to estimate the dietary PCB intake. In the case of breast-fed infants, PCB intakes can be calculated to range from 2 to 12 μg per kg of body weight per day on the basis of the median levels noted previously and an average milk intake of 120 ml per kg of body weight.

In foods that contain higher levels of PCBs and/or contribute significantly to the total dietary PCB intake, preliminary studies have identified ten specific PCBs as predominant. In human breast milk, six of them account for approximately 70% of the total PCB content.

The Committee paid particular attention to the possible health consequences of the intake of PCBs by the suckling infant, but did not anticipate that adverse health effects would occur as a result of consuming breast milk. It should be kept in mind that the infant consumes breast milk for only a short period (1–2% of the total life span). In addition, the numerous benefits of breast milk, including its nutritional, immunological, and other properties, and the psychological advantages of breast-feeding should not be discounted; the disadvantages of breast milk substitutes, including potential contamination by infective agents and the consequences of incorrect preparation and inadequate hygiene, have been amply documented (*13, 14*). For these reasons, the Committee considered that the advantages to the infant of breast-feeding outweighed any potential hazards due to the PCB content of breast milk, and advised that there was absolutely no justification for discouraging this practice.

The Committee was reassured by the observation that the production of PCBs has largely ceased. It is expected, therefore, that levels of PCBs in the environment and food, and consequently in breast milk, will decrease with time.

The Committee suggested that further investigations be conducted to identify the PCBs most commonly present in foods and that safety studies be carried out on them, and particularly on the more highly chlorinated ones, in order to determine their toxicological potential. Furthermore, specific studies on the impact of these PCBs on the fetus and neonate were considered to be of great importance.

The Committee considered that the intake of PCBs should be kept as low as possible. In foods in which PCBs occur, and that are nutritionally essential, attempts should be made to set limits on PCBs, in particular for the most highly contaminated products. However, the Committee concluded that the consumption of PCBs at the dietary levels described above did not involve any long-term hazard. Finally, the Committee pointed out that good public health practices would require that a long-term goal should be the reduction of PCBs in the diet to a minimum.

An early draft of a document on PCBs that is being prepared for publication by WHO in the Environmental Health Criteria series was made available to the Committee. The working paper on which the Committee relied for its evaluation reproduced the discussion of the metabolism and toxicity studies contained in this draft document. In order to avoid duplication within WHO, a toxicological monograph was not prepared.

4. REVISION OF CERTAIN SPECIFICATIONS

4.1 General

Four substances were evaluated for specifications only (see Annex 2), and the specifications for all of them were revised.

The Committee revised the specification for carob bean gum so as to include the use of two solvents, ethanol and isopropanol, in a washing process used to purify the substance.

The previous specifications for citric and fatty acid esters of glycerol (Annex 1, reference *75*) had been designated as "tentative" because a suitable assay method and data on the amounts of individual components were lacking. The Committee revised the tentative specifications by including analytical methods and by specifying total citric acid, total fatty acids, and total glycerol. Consideration was also given to the sum of these components,

but the Committee decided not to specify it. The "tentative" qualification was deleted.

The existing specifications for iron oxides used as food colours were revised.

The specifications for modified starches (Annex 1, reference *79*) had been designated "tentative" as analytical methods were needed for carboxyl groups in oxidized starch and free adipic acid in acetylated distarch adipate. The Committee revised the specifications to include analytical methods for both and removed the "tentative" qualification.

4.2 General specifications for enzymes used in food processing

The existing general specifications for enzyme preparations used in food processing (Annex 1, reference *69*) were revised. The Committee recommended that, as and when enzyme preparations are reconsidered, or when new enzyme preparations are submitted for evaluation, their individual specifications should be reviewed to ensure they are consistent with the principles on which the new general specifications are based.

5. FUTURE WORK

1. The guidelines for the evaluation of various groups of food additives and contaminants that have been developed by the Committee and are given in Annex 3 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) should be reviewed at a future meeting (see section 2.2.1).

2. Individual specifications for enzyme preparations used in food processing should be reviewed to take account of the principles set out in the revised general specifications (see section 4.2).

3. In view of the decision not to include the use of 1,2-dichloroethane as an extraction solvent in the specifications for paprika oleoresin despite its current listing for other spice oleoresins, the Committee should re-evaluate the toxicological basis for the listing of 1,2-dichloroethane in other specifications. Such a re-examination should be expanded to include a consideration of all solvent uses of chlorinated hydrocarbons.

4. A number of the specifications reviewed at the present meeting make reference to the general methods section of the *Guide to*

specifications (Annex 1, reference *65*). The Committee reiterated the need expressed at its thirtieth and thirty-third meetings to update the general methods and to include with them in a single publication the additional general methods adopted since the last revision of this compendium.

5. During its evaluation of specifications, the Committee noted that some of them had stood for a number of years without review or revision. All such long-standing specifications should be reviewed to ensure that they reflect current practices in the additive-manufacturing and food-processing industries, and that the methods of analysis remain appropriate in the light of modern developments in analytical techniques.

6. During the evaluation of specifications for several naturally occurring substances, the Committee recognized that many of them tended to be too broad to provide an effective basis for toxicological evaluation. It therefore recognized the need to develop new principles for establishing adequate specifications that would address this problem (see section 2.3.3).

7. In a number of specifications, gas chromatography using headspace sampling is given as the method of analysis. As this technique is not included in the general methods section of the *Guide to specifications* (Annex 1, reference *65*), the Committee should develop an appropriate general method.

8. General methods should be established for laying down microbiological criteria in specifications for food additives.

6. RECOMMENDATIONS

1. In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, meetings of the Joint FAO/WHO Expert Committee on Food Additives should continue to be held regularly.

2. *Patulin*

(*a*) In many of the older studies on patulin levels in fruit and fruit products, methods were used that were of inadequate sensitivity and patulin was not positively identified. There is a need to expand the current limited data base on patulin levels in such products. In particular, to ensure that reliable data on levels of patulin in apple juice and other fruit products are available for

the assessment of dietary exposure, the Committee urged the application of appropriate analytical procedures that include confirmatory techniques.

(*b*) In view of the well established association between patulin occurrence and rotted fruit:

—the sorting out of rotted apples in accordance with good manufacturing practices should be emphasized in the industrial processing of apples; and

—educational programmes for consumers should highlight the need to remove visibly damaged parts of fruit prior to consumption and to avoid consuming visibly mouldy homogeneous products such as fruit jam.

3. *Polychlorinated biphenyls (PCBs)*

(*a*) There is a need to continue monitoring PCB levels in foods and, in particular, to determine the specific PCB isomers of individual congeners. To ensure the adequacy of analytical procedures and thus the availability of more reliable data on dietary exposure for risk assessment purposes, interlaboratory check-sample programmes are considered desirable. In the light of ongoing activities related to PCBs in human milk (see section 2.4), additional efforts should be made to determine the contribution of other important foods to the dietary intake of PCBs.

(*b*) Because of advances in the analytical determination of PCBs, it is now possible to ascertain which PCB isomers of individual congeners are most prevalent in the media being examined. Once the toxicity of these PCB isomers is known, a better assessment of their human health significance will be possible. In view of the foregoing:

—Future analytical studies should be aimed at identifying and quantifying the specific isomers that are major contributors to the overall dietary intake of PCBs.

—Safety studies should be carried out on the PCBs predominantly present in foods, and particularly on the more highly chlorinated ones, in order to determine their precise toxicological potential. Furthermore, specific studies on the impact of these PCBs on the fetus and neonate are considered to be of great importance.

4. To facilitate its review of solvent specifications, as suggested at its thirtieth meeting, the Committee recommends that the relevant

industries should be requested to provide justification for the use of solvents, together with data on typical levels of residues resulting from their use. Emphasis should be placed initially on chlorinated hydrocarbon solvents.

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12. Code of practice for the preservation of raw milk by the lactoperoxidase system. *Bulletin of the International Dairy Federation,* **234** (1988).
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14. *Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach.* Geneva, World Health Organization, 1986 (Environmental Health Criteria, No. 59).

Annex 1

REPORTS AND OTHER DOCUMENTS RESULTING FROM PREVIOUS MEETINGS OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

1. *General principles governing the use of food additives* (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of international food additives to establish their safety for use* (Second report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants)* (Third report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. I. *Antimicrobial preservatives and antioxidants*. Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. *Specifications for identity and purity of food additives (food colours)* (Fourth report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. II. *Food colours*. Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. *Evaluation of the carcinogenic hazards of food additives* (Fifth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. *Evaluation of the toxicity of a number of antimicrobials and antioxidants* (Sixth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. *Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents* (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. *Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants* (Eighth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants*. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).
10. *Specifications for identity and purity and toxicological evaluation of food colours*. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.
11. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases* (Ninth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases.* FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29, 1967.
13. *Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances* (Tenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.
14. *Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents* (Eleventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.
15. *Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
16. *Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
17. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics* (Twelfth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
18. *Specifications for the identity and purity of some antibiotics.* FAO Nutrition Meetings Report Series, No. 45A, 1969; WHO/Food Add/69.34.
19. *Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances* (Thirteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.
20. *Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.
21. *Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.
22. *Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents* (Fourteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.
23. *Toxicological evaluation of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.
24. *Specifications for the identity and purity of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.
25. *A review of the technological efficacy of some antimicrobial agents.* FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.
26. *Evaluation of food additives: some enzymes. modified starches, and certain other substances: toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants* (Fifteenth report of the Expert

Committee). FAO Nutrition Meetings Report Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. *Toxicological evaluation of some enzymes, modified starches, and certain other substances.* FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.
28. *Specifications for the identity and purity of some enzymes and certain other substances.* FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.
29. *A review of the technological efficacy of some antioxidants and synergists.* FAO Nutrition Meetings Report series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.
30. *Evaluation of certain food additives and the contaminants mercury, lead, and cadmium* (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
31. *Evaluation of mercury, lead, cadmium, and the food additives amaranth, diethylpyrocarbonate, and octyl gallate.* FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.
32. *Toxicological evaluation of certain food additives with a review of general principles and of specifications* (Seventeenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).
33. *Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents.* FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5. 1974.
34. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers.* FAO Food and Nutrition Paper, No. 4, 1978.
35. *Evaluation of certain food additives* (Eighteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.
36. *Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.
37. *Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents, and certain food additives.* FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.
38. *Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances* (Nineteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.
39. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.
40. *Specifications for the identity and purity of certain food additives.* FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.

41. *Evaluation of certain food additives* (Twentieth report of the Expert Committee). FAO Food and Nutrition Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.
42. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 10, 1976.
43. *Specifications for the identity and purity of some food additives.* FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additives Series, No. 11, 1977.
44. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.
45. *Summary of toxicological data of certain food additives.* WHO Food Additives Series, No. 12, 1977.
46. *Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.
47. *Evaluation of certain food additives and contaminants* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
48. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series, No. 13, 1978.
49. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 7, 1978.
50. *Evaluation of certain food additives* (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980, and corrigenda.
51. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1980.
52. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.
53. *Evaluation of certain food additives* (Twenty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 653, 1980.
54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.
55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.
56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.
57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1981.
58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.
59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.
60. *Toxicological evaluation of food additives.* WHO Food Additives Series, No. 17, 1982.

61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.
62. *Evaluation of certain food additives and contaminants* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.
63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.
64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.
65. *Guide to specifications—General notices, general methods, identification tests, test solutions and other reference materials.* FAO Food and Nutrition Paper, No. 5, Rev. 1, 1983.
66. *Evaluation of certain food additives and contaminants* (Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 710, 1984, and corrigendum.
67. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 19, 1984.
68. *Specifications for the identity and purity of food colours.* FAO Food and Nutrition Paper, No. 31/1, 1984.
69. *Specifications for the identity and purity of food additives.* FAO Food and Nutrition Paper, No. 31/2, 1984.
70. *Evaluation of certain food additives and contaminants* (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 733, 1986, and corrigendum.
71. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 34, 1986.
72. *Toxicological evaluation of certain food additives and contaminants.* Cambridge, Cambridge University Press, 1987 (WHO Food Additives Series, No. 20).
73. *Evaluation of certain food additives and contaminants* (Thirtieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 751, 1987.
74. *Toxicological evaluation of certain food additives and contaminants.* Cambridge, Cambridge University Press, 1987 (WHO Food Additives Series, No. 21).
75. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 37, 1986.
76. *Principles for the safety assessment of food additives and contaminants in food.* Geneva, World Health Organization, 1987 (WHO Environmental Health Criteria, No. 70).
77. *Evaluation of certain food additives and contaminants* (Thirty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 759, 1987, and corrigendum.
78. *Toxicological evaluation of certain food additives.* Cambridge, Cambridge University Press, 1988 (WHO Food Additives Series, No. 22).
79. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 38, 1988.
80. *Evaluation of certain veterinary drug residues in food.* (Thirty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 763, 1988.
81. *Toxicological evaluation of certain veterinary drug residues in food.* Cambridge, Cambridge University Press, 1988 (WHO Food Additives Series, No. 23).

82. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, No. 41, 1988.
83. *Evaluation of certain food additives and contaminants* (Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 776, 1989.
84. *Toxicological evaluation of certain food additives and contaminants*. Cambridge, Cambridge University Press, 1989 (WHO Food Additives Series, No. 24).
85. *Evaluation of certain veterinary drug residues in food* (Thirty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 788, 1989.
86. *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 25, in press.
87. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, in press.

Annex 2

ACCEPTABLE DAILY INTAKES, OTHER TOXICOLOGICAL INFORMATION, AND INFORMATION ON SPECIFICATIONS

Substance	Specifications[1]	Acceptable daily intake (ADI) for humans and other toxicological recommendations
A. Food additives		
Emulsifiers		
Polyglycerol esters of fatty acids	S	0–25 mg/kg of body weight[2]
Sucrose esters of fatty acids	R	0–10 mg/kg of body weight[3]
Sucroglycerides	S	0–10 mg/kg of body weight[3]
Enzyme preparations		
Enzymes derived from *Aspergillus niger*	S	ADI "not specified"[4]
Flavouring agents		
Benzyl acetate	S	0–5 mg/kg of body weight[5]
Cinnamaldehyde	S	No ADI allocated[6]
Dihydrocoumarin	N, T	No ADI allocated[7]
Ethyl vanillin	R	0–5 mg/kg of body weight[5]
Fumaric acid	R	ADI "not specified"[4, 8]
Quinine	R	0–0.9 mg/kg of body weight[5]
Food colours		
Canthaxanthin	S	No ADI allocated[9]
Carotene preparations from natural sources	R, T[10]	No ADI allocated[11]
Curcumin	S	0–0.1 mg/kg of body weight[5]
Paprika oleoresin	R	No ADI allocated[12]
Turmeric oleoresin	R	No ADI allocated[9]
Thickening agents		
Gum arabic	R	ADI "not specified"[4]
Modified celluloses	S	ADI "not specified"[4, 13]
Miscellaneous food additives		
Ferrous lactate	N	[0.8 mg/kg of body weight[14]]
2-Nitropropane	R, T	No ADI allocated[15]
Tannic acid	R, T	ADI "not specified"[4, 16]
Lactoperoxidase/thiocyanate/hydrogen peroxide system for milk preservation	[17]	Acceptable[18]

Substance	Provisional tolerable weekly intake (PTWI) for humans
B. Contaminants	
Patulin	7 µg/kg of body weight
Polychlorinated biphenyls (PCBs)	PTWI not established[19]

Substance	Specifications[1]
C. Food additives (specifications only)	
Carob bean gum	R
Citric and fatty acid esters of glycerol	R
Iron oxides used as food colours	R
Modified starches	R

Notes to Annex 2

1. 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 (see Annex 3).
2. Applies to polyglycerol esters of fatty acids having an average chain length of up to three glycerol units.
3. Group ADI for sucrose esters of fatty acids and sucroglycerides.
4. 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.
5. Temporary acceptance (see Annex 3).
6. The previous temporary ADI was not extended (see Annex 3).
7. See Annex 3.
8. Group ADI for fumaric acid and its salts.
9. The previous temporary ADI was not extended.
10. Specifications apply to carotenes from algal and vegetable sources (see Annex 3).
11. Insufficient information was available on toxicity and/or chemical composition to permit establishment of an ADI.
12. Self-limiting as a spice extract.
13. Group ADI for ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose. The ability of modified celluloses to produce laxative effects should be taken into account when they are used as food additives.
14. Provisional maximum tolerable daily intake for iron from all sources.

15. The previous temporary acceptance of 2-nitropropane as a fractionating solvent in the production of fats and oils was not extended.
16. For use as a filtering aid where the application of good manufacturing practice ensures that it is removed from food after use.
17. Existing specifications for sodium thiocyanate were maintained. New specifications for sodium percarbonate were prepared.
18. When used according to the draft guidelines produced by the Joint FAO/WHO Committee of Government Experts on the Code of Principles concerning Milk and Milk Products, this system does not present a toxicological hazard.
19. The Committee concluded that the no-effect level in studies with monkeys was 40 µg per kg of body weight per day. Because of the limitations of the available data and the ill-defined nature of the materials that were used in the feeding studies, it was impossible to establish a precise numerical value for a tolerable intake for humans. In particular, the PCB mixtures that were used in the studies with monkeys were not entirely the same as those to which humans are exposed in the diet. However, there is no reason to believe that humans would be more sensitive than monkeys to the effects of PCBs, and some indication of safe exposure levels can therefore be obtained from the no-effect level observed in the studies with monkeys.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND OTHER INFORMATION REQUIRED OR DESIRED

Flavouring agents

Benzyl acetate

Submission is required by 1993 of the results of long-term studies, already in progress, in which benzyl acetate is incorporated into the diet of mice and rats.

An *in vivo* test for chromosome damage in bone marrow is desirable.

Cinnamaldehyde

Submission of the results of a short-term feeding study in a non-rodent mammalian species and of adequate metabolic studies might be sufficient to make re-evaluation of this substance possible.

Dihydrocoumarin

The results of a short-term study in a rodent species and metabolic studies to investigate the extent of conversion to coumarin would be needed for re-evaluation of this substance.

In addition, information is required on the method of manufacture, with respect to the possible presence of residues of catalysts in the final product, and on the refractive index measured at 25 °C.

Ethyl vanillin

Submission of the results of an adequate short-term study in rats and metabolic studies in rats is required by 1992.

Quinine hydrochloride

Submission of the results of an adequate human study is required by 1992.

Food colours

Carotenes (algae)

Information is required on the source algae (e.g., on the different species used and the differences in the composition of the resulting

products), the influence of the manufacturing process, such as spray-drying, on the quality of finished powder preparations, and the technological justification for the presence of ethanol residues of up to 10%.

Carotenes (vegetable)

Information is required on the composition of commercial products and method(s) of distinguishing between carotenes (vegetable) and synthetic colours.

Curcumin

Submission is required by 1992 of the results of carcinogenicity studies, already in progress, with mice and rats given turmeric oleoresin containing a high concentration of curcuminoids.

Miscellaneous

2-Nitropropane

Information is required on the range of refractive indices of the commercial product. Confirmation is also required of the adequacy of the method of assay.

Tannic acid

Information is required on the composition of tannic acid from different botanical sources, on a test to show that condensed tannins are absent, and on actual use and levels of use of tannic acid as a flavouring agent.