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Evaluation of certain food additives and contaminants

Twenty-sixth Report of the
Joint FAO/WHO Expert Committee on
Food Additives



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Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives
FAO Food and Nutrition Paper, No. 25

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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 19-28 April 1982

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Mr D. F. Dodgen, Staff Scientist, Keller and Hackman, Washington, DC, USA
Dr S. W. Gunner, Chief, Division of Chemical Evaluation, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada
Professor K. Kojima, College of Environmental Health, Asabu University, Sagami-hara-Shi, Kanagawa, Japan (*Chairman*)
Dr W. Kroenert, Head, Food Chemistry Division, Federal Health Institute, Berlin (West)
Professor F. J. Pellerin, Faculty of Pharmacy, University of Paris XI, Centre hospitalier Courentin Celton, Issy-les-Moulineaux, France

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Dr H. Blumenthal, Director, Division of Toxicology, Bureau of Food, Food and Drug Administration, Washington, DC, USA (*Vice-Chairman*)
Dr G. Nazario, Department of Food Standards, National Health Council, Rio de Janeiro, Brazil
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Dr A. Zaitsev, Head, Laboratory for the Hygienic Examination of Food Additives, Institute of Nutrition, Academy of Medical Sciences, Moscow, USSR

Observer invited by FAO

- Mr A. Feberwee, Chairman, Codex Committee on Food Additives, c/o Ministry of Agriculture and Fisheries, The Hague, Netherlands

Secretariat

- Dr J. R. P. Cabral, Division of Chemical and Biological Carcinogenesis, International Agency for Research on Cancer, Lyons, France (*WHO Temporary Adviser*)
Mr R. Haigh, Principal Administrator, Commission of the European Communities, Brussels, Belgium (*WHO Temporary Adviser*)
Dr Y. Hayashi, Division of Pathology, Biological Safety Research Centre, National Institute of Hygienic Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr V. L. Kossila, Animal Production Officer, Feed Resources, Animal Production and Health Division, FAO, Rome, Italy

Dr G. D. Kouthon, Nutrition Officer, Food Policy and Nutrition Division, FAO, Rome, Italy (*Joint Secretary*)

Dr L. G. Ladamery, Food Standard Officer, Food Quality and Standard Service, FAO/WHO Food Standards Programme, Food Policy and Nutrition Division, FAO, Rome, Italy

Dr C. Lintas, Istituto Nazionale della Nutrizione, Via Ardeatina 545, Rome, Italy (*WHO Temporary Adviser*)

Dr J. E. Long, Chief, Toxicological Evaluation Division, Food Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Ontario, Canada (*WHO Temporary Adviser*)

Dr R. K. Malik, Senior Officer, Food Quality and Standards Service, Food Policy and Nutrition Division, FAO, Rome, Italy

Professor A. G. Rico, Laboratory of Radioelements and Metabolic Studies (I.N.R.A.), National Veterinary School, Toulouse, France (*WHO Temporary Adviser*)

Dr F. J. C. Roe, Institute of Cancer Research, University of London, London, England (*WHO Temporary Adviser*)

Dr S. I. Shibko, Chief, Contaminants and Natural Toxicants Evaluation Branch, Division of Toxicology, Bureau of Food, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr P. Shubik, Resident Fellow, Green College, University of Oxford, England (*WHO Temporary Adviser*)

Professor R. C. Truhaut, Director, Toxicological Research Centre, René Descartes University, Paris, France (*WHO Temporary Adviser*)

Dr G. Vettorazzi, Toxicologist, International Programme on Chemical Safety, Division of Environmental Health, WHO, Geneva, Switzerland (*Joint Secretary*)

Dr E. Weisenberg, Director, Institute for the Standardisation and Control of Pharmaceuticals, Ministry of Health, Jerusalem, Israel (*WHO Temporary Adviser*)

Mr A. Yamamoto, Office of Health Studies, Department of Environmental Health, Environment Agency, Tokyo, Japan (*WHO Temporary Adviser*)

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Twenty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 19 to 28 April 1982. The meeting was opened by Dr Z.I. Sabry, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Sabry recalled that the Committee was concerned not only with the preparation of specifications for the identity and purity of food additives and with toxicological evaluations, but also, since 1973, with the evaluation of food contaminants. He pointed out that the Committee dealt with matters that were of considerable scientific and practical interest to all Member Governments, and that rapid developments in food technology and toxicology required continuous updating of knowledge about the evaluation of food additives and contaminants.

Dr Sabry stated that the objective and scientific judgments of the Committee were appreciated not only by Member Governments of FAO and WHO, but also by the Codex Alimentarius Commission and the food industry, and he drew attention to the fact that an ever-growing number of countries, both developed and developing, were adopting the recommendations of the Committee, with regard to toxicological evaluations and specifications, in their regulatory food control and consumer protection programmes.

Dr Sabry noted that the increasing body of information on food technology and toxicology, together with estimates of food consumption, was providing further evidence of the safety in use of food additives. The work of the Committee in marshalling information would be facilitated by the recent development of the FAO/WHO

Food Additives Data Bank System located in Rome. This system would greatly aid the two Organizations in responding to requests for information about the status of toxicological evaluations of and specifications for food additives. It would also be useful for retrieval of information about maximum levels recommended by the Codex Alimentarius Commission for use in food commodities.

Dr Sabry concluded by thanking governments, the Codex Committee on Food Additives, the food additives manufacturing industry and various governmental and nongovernmental organizations for the information they supplied; this information was essential to the Committee for the establishment of specifications and for the toxicological evaluation of food additives and food contaminants.

1. INTRODUCTION

As a result of the recommendation of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,¹ there have been 25 previous meetings of the Committee (see Annex 1). The present meeting was convened on the recommendation made at the twenty-fifth meeting (see Annex 1, reference 57). The tasks before the Committee were: (1) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological evaluations of them; (2) to revise specifications for selected food additives; (3) to undertake toxicological re-evaluations of certain food additives; (4) to consider the toxicological implications of the presence in food of some metal contaminants; (5) to consider certain xenobiotic anabolic agents and to evaluate the toxicological significance of their residues, including metabolites, in food; (6) to consider the general principles governing the establishment of specifications for the identity and purity of food additives; (7) to consider the safety aspects of specifications; and (8) to give advice on the operation of the FAO/WHO Food Additive Data Bank System.

¹ FAO Nutrition Meeting Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

Stannous chloride was not on the agenda, but was considered in relation to tin (see section 3.2.1). Insufficient information was available to the Committee for adequate consideration of the food colours capsanthine and capsorubine, the flavouring agents 1,4-heptanolactone and sucrose octa-acetate, or the metals iron and arsenic; therefore, these substances were removed from the agenda. Polydimethylsiloxane was added to the agenda for revision of specifications only.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (see Annex 1) and by a WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives,¹ and a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.² In addition, it reaffirmed the need to take into consideration the recent developments in toxicological techniques, as stated in its seventeenth report (see Annex 1, reference 32).

The Committee noted that guidelines and general principles had been elaborated for evaluation of various groups of food additives (e.g., natural colours, solvents used in food processing, enzymes) by previous meetings. The Committee thought that it would be of assistance to future meetings if these were assembled in consolidated form (see Annex 6).

The Committee decided that the allocation of an ADI value was not appropriate for phosphates since a range of values of an ADI from zero to an upper level is not appropriate for substances that are essential nutrients and unavoidable constituents of food (see section 3.1.6). For such substances, it may be necessary to allocate an upper level of intake, determined from the toxicological evaluation, or a "maximum tolerable daily intake"; in addition, it may be desirable to fix a lower level in terms of recommended daily allowance.

¹ WHO Technical Report Series, No. 348, 1967

² WHO Technical Report Series, No. 546, 1974

2.3 Principles governing the establishment and revision of specifications

The Committee endorsed the statement in the report of the Third Joint FAO/WHO Conference on Food Additives and Contaminants¹ that specifications have three main objectives:

(a) to identify the substance that has been subject to biological testing;

(b) to ensure that the substance is of the quality required for safe use in food;

(c) to reflect and encourage good manufacturing practice.

In addition, the Committee was of the opinion that the establishment of specifications should, whenever feasible, be carried out simultaneously with toxicological evaluations, in order to accomplish the above objectives.

In certain circumstances, however, when the available toxicological data are inadequate or incomplete and do not permit the establishment of full or temporary ADIs, it may none the less be desirable for the Committee to prepare specifications to be available before the completion of the toxicological evaluation of the substances concerned. The Committee considered that if specifications could be available before the completion of the toxicological evaluations they might provide a guide to the scientific workers in the field of toxicology in carrying out the further work required, as is frequently the case for many of the older food additives.

The testing of new food additives raises different considerations. With these, there is a need for clear definition of the compound from the identity and purity points of view before any toxicological work is initiated (see Annex 1, reference 2). The chemical data describing the substance tested, information relating to good manufacturing practice, and other appropriate data, form the basis of the specifications that are prepared.

In certain cases, the Committee may decide to amend existing specifications in order to take into account (a) comments received from the Codex Committee on Food Additives, and (b) technological developments; in either case, the Committee will pay special attention to safety aspects.

¹ Issued by FAO as *Miscellaneous Meeting Report Series* ESN: MMS 74/6 and by WHO as document WHO/FOOD ADD./74.73.

The development of new manufacturing and analytical techniques makes necessary the regular updating of analytical methods contained in the specifications prepared by the Committee. In awareness of this situation, especially in relation to general methods for the analysis of food colours and flavouring substances, the Committee proposed to continue to take account of advances in methodology when specifications are revised (see section 5.4).

2.4 Significance of the occurrence of nephrocalcinosis in the toxicological evaluation of modified starches

In its twentieth report (see Annex 1, reference 40), the Committee considered the toxicological significance of kidney lesions found in long-term studies in rats fed with diets containing 5% to 25% of various chemically modified starches, and recommended that further studies should be carried out to elucidate the pathogenesis of these lesions. It is in this context that it was felt appropriate to include in the present report some general observations on recent research that throw light on the toxicological significance of the pelvic form of nephrocalcinosis in the rat.

Nephrocalcinosis is a common finding in untreated laboratory rodents, particularly rats. Morphologically, nephrocalcinosis has been divided into several types, of which pelvic nephrocalcinosis and corticomedullary nephrocalcinosis are the two kinds most frequently encountered.¹ In the first type, there is mineral deposition beneath, within or attached to the pelvic epithelium. It is this type of nephrocalcinosis that increases in incidence in response to the feeding of some modified starches. In the other main kind of nephrocalcinosis, there is deposition of mineral in the corticomedullary region of the kidney. This latter type has been associated experimentally with magnesium deficiency.^{2,3}

¹ ROE, F.J.C. (1979) *Mineral deposition in the renal pelvis of rats: a brief review* (unpublished study made available to the Committee).

² WHANG, R. & WELT, L.G. (1963) Observations in experimental magnesium depletion. *Journal of clinical investigation*, 42: 305.

³ SCHMEEBERGER, E. E. & MORRISON, A. B. (1965) The nephropathy of experimental magnesium deficiency: light and electron microscopic investigations, *Laboratory investigations*, 14: 674.

There is now experimental evidence that pelvic nephrocalcinosis may arise as a consequence of increased absorption of calcium.¹⁻⁴ This occurs, *inter alia*, with the increased availability of monosaccharides for absorption within the lower bowel. Such increased availability may occur because of dietary overloading, particularly with the more poorly absorbed monosaccharides, or because higher and more complex carbohydrates are not degraded to monosaccharides before the food bolus reaches the caecum. Caecal enlargement commonly accompanies increased calcium absorption in either case. Increased calcium absorption has been observed in feeding studies with sugars, sugar alcohols, and dextrans, as well as with the modified starches.

The physiological influence of carbohydrate intake on mineral metabolism needs to be taken into account in assessing the possible toxicological significance of nephrocalcinosis.

2.5 Food colours extracted from foods

The agenda contained a number of natural food colours for toxicological evaluation and, in some cases, for preparation or revision of specifications. Two of these food colours are normal constituents of recognized foods, namely, anthocyanins and beet red. In evaluating these food colours, the Committee took into account the principles established in its eighth and twenty-first reports (see Annex 1, references 8 and 43). In the case of anthocyanins, the Committee was able to recommend an ADI for one particular type for which specifications were available, namely grape-skin extract. The Committee reiterated the previously expressed principle that this ADI is in addition to the intake of anthocyanins resulting from the consumption of grapes and of food derived from grapes

¹ FOURNIER P. ET AL. (1972) Mechanisms of action of sugars on calcium absorption and retention. *Comptes rendus hebdomodaires des séances de l'Académie des Sciences*, Série D, 275:85.

² VAUGHAN, O. W. & FILER, L. J. (1960) The enhancing action of certain carbohydrates on the intestinal absorption of calcium in the rat, *Journal of nutrition*, 71: 10.

³ HODGKINSON A. ET AL. (1982) A comparison of the effects on mineral metabolism of diets containing waxy maize starch, either of two chemically-modified waxy maize starches, or lactose. *Food & chemical toxicology*, in press.

⁴ BUTTOLPH, M. L. & NEWBERNE, P. M. (1981) Modified food starch ingestion in hamster and rat. In: McHowell, J. et al., ed., *Trace elements*, Canberra, Australian Academy of Science, pp. 158-161.

and from the use of grape-skin extracts to restore colour to normal levels when it has been lost during the processing of foods derived from grapes. The Committee recognized that the colouring principles present in grape-skin extract also occur naturally in other fruits and it is not intended that the consumption of these substances in such fruits should be included within the ADI.

2.6 Phosphates and polyphosphates in food additive use

The Committee was informed that concern had arisen in certain quarters as to the calcium/phosphorus ratio in the diet because of the possibility that the nutritionally sound range of ratios, which it is desirable to maintain, might be perturbed by the increasing use of phosphates and polyphosphates as food additives.

The Committee had data showing that the estimated daily intake of phosphates (expressed as phosphorus) by North Americans was 800–1700 mg for males and 700–1200 mg for females, and that the Ca:P ratio was about 1 : 1.6.¹ This is at variance with a previous recommendation based on animal studies that the ratio should be from 1 : 0.5 to 1 : 1 (see Annex 1, reference 7, pp. 29–32). At present, there is insufficient evidence for resolution of the question of the optimum ratio; therefore, the Committee recommended that further studies should be carried out on the consequences of high dietary intakes of phosphate, with particular reference to the Ca:P ratio and the influence of other minerals on the Ca:P ratio.

2.7 Toxicological evaluation of xenobiotic anabolic agents

In 1981, the twenty-fifth report of the Committee (see Annex 1, reference 57) considered the use of hormones and substances with hormonal activity in animal production. The substances used were divided into two categories, namely:

(a) hormones that are identical to those occurring naturally in food-producing animals and human beings, including the esters of these hormones; and

(b) xenobiotic compounds, such as derivatives of hormones, synthetic compounds with hormonal activity, natural-product hormonally active agents that are not identical with human endogenous hormones, and derivatives of such compounds.

¹ CHINN, H.C. (1981) *Effects of dietary factors on skeletal integrity in adults: calcium, phosphorus, vitamin D and protein*. Bethesda, MD, Federation of American Societies for Experimental Biology.

The twenty-fifth report was more concerned about potential toxicological problems that might arise with xenobiotic compounds than with the former category of substances when used as anabolic agents for animal production.

The present Committee considered that the evaluation for acceptance of the use of xenobiotic anabolic agents in animal food production resembles in many respects the evaluation of pesticides, since the two essential elements required are:

(a) adequate, relevant toxicological data, and

(b) comprehensive data about the kinds and levels of residues when the substances are used according to good animal husbandry practice.

In connexion with good animal husbandry practice, evidence would be required as to the efficacy of the anabolic agents, the amounts used to produce the effect, the residue levels based on field trials, and information about methods of analysis of residue levels that could be used for control or monitoring purposes.

For xenobiotic anabolic agents, the Committee reaffirmed the view expressed in its twenty-fifth report (see Annex 1, reference 57) that the toxicological data should be relevant to the problems of the potential tumorigenic activity of these compounds and the presence of residues or metabolites in animal products that might have endocrinological or toxicological consequences for consumers.

2.8 Metals occurring in foods

Three heavy metal contaminants of food, namely mercury, cadmium and lead, were considered in the Committee's sixteenth report (see Annex 1, reference 30) and provisional weekly tolerable intakes were allocated. The tenth report of the Committee (see Annex 1, reference 12) considered the trace elements arsenic, copper, lead, mercury, tin and zinc. Various other metals have been considered from time to time in reports of the Joint FAO/WHO Expert Committee on Food Additives as food contaminants or in connexion with food additive use.

The following metals were placed on the agenda for consideration by the present meeting as contaminants: arsenic, copper, iron, tin and zinc. Of these, at least copper, iron and zinc are essential nutrients.

Toxicological evaluation of metals in foods calls for carefully balanced consideration of the following factors:

(a) nutritional requirements, including nutritional interactions with other constituents of food¹ in respect of, for instance, absorption, storage in the body and elimination;

(b) the results of epidemiological surveys and formal toxicological studies, including interactions with other constituents of food,¹ information about pharmaceutical and other medicinal uses, and clinical observations on acute and chronic toxicity in human and veterinary practice;

(c) total intake on an appropriate time basis (e.g., daily, weekly, yearly or lifetime) from all sources (food, water, air) of metals as normal constituents of the environment, as environmental contaminants, and as food additives of an adventitious or deliberate nature.

The tentative tolerable daily intakes proposed for certain metals by the Committee (see section 3.2.1) provide a guideline for maximum tolerable exposure. In the case of essential elements, these levels exceed the normal daily requirements, but this should not be construed as an indication of any change in the recommended daily requirements, but as reflecting permissible human exposures to these substances as a result of natural occurrence in foods or various food processing practices, as well as exposure from drinking-water.

It is important that the proposed tolerable intakes are not used as guidelines for fortifying processed food, since the currently accepted values for required daily intake are sufficient to meet the known nutritional requirements.

2.9 Safety aspects of the Expert Committee and Codex specifications

The Committee considered a request by the Codex Alimentarius Commission to indicate precisely those aspects of its specifications that constitute "minimum safety requirements consistent with the toxicological evaluations". The need for this clarification arose from the conclusion of the Commission that, in accepting Codex Standards containing food additive provisions, governments were obliged to avoid the use of food additives that failed to meet the minimum safety requirements included in the specifications.

The Committee was informed about the conclusions of the Codex Committee on Food Additives, at its fourteenth session (1) that food-grade quality is achieved by compliance with the Expert Com-

¹ Including other metals when the interactions are nutritionally or toxicologically relevant.

mittee's specifications as a whole, and (2) that it is not feasible to rank individual criteria in specifications in terms of safety.

Following discussion of the above matters, the Committee agreed that its specifications in their entirety describe substances of a food-grade quality that relate directly to the toxicological evaluations and to good manufacturing practice, and the Committee recognized that there may be differences in specifications because of particular circumstances prevailing in various countries. However, there was no information available to the Committee to indicate that these differences were reflected in any health risk to consumers.

As regard the requests of the Codex Alimentarius Commission to identify criteria in the Committee's specifications which represent "minimum safety requirements", the Committee concluded that this was not practicable. It was understood that it is the prerogative of governments to interpret specifications and that this is done on the basis of expert advice and in the light of the particular circumstances prevailing in their countries.

The Committee experienced difficulty in fully understanding the meaning of the expression "minimum safety requirements". It therefore suggested that this expression should be taken to mean that only food additives of a food-grade quality consistent with the toxicological evaluations should be used. In giving this interpretation and advice to the Commission, the Committee noted that its function was to evaluate scientific and technical information, and that questions of the obligation falling on governments to accept or otherwise apply the conclusions of the Joint FAO/WHO Expert Committee on Food Additives were a matter for governments.

2.10 Food additive computerized data bank

The Committee was informed that a FAO/WHO Food Additive Data Bank System was in the experimental phase of development and the operation of the system was demonstrated to members of the Committee. Data on all the food additives so far considered by the Joint FAO/WHO Expert Committee, amounting to about 500 substances, had been entered in the system and were in the process of being edited. The data consist of name and synonyms, functional class, the status of toxicological evaluations and specifications with references, and the food uses included in standards of the Codex Alimentarius Commission. The software for use with the data bank allows for updating and for retrieval of information by substances,

by classes, and by uses. Further software for manipulation of the data is under development. A copy of the tape on which the data are stored will be made available to WHO as soon as it has been edited by FAO personnel. Decisions concerning such matters as utilization of the data and cooperation with other data banks have yet to be made by FAO and WHO. The Committee strongly urged FAO and WHO to continue with this important enterprise.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

The Committee evaluated a number of food additives and contaminants for the first time and also re-evaluated some substances that had been considered at previous meetings. Information on the allocation of ADIs (or maximum tolerable intakes for certain substances) and specifications is summarized in Annex 2, and the "further work required" for certain substances is shown in Annex 3.

3.1 Specific food additives

3.1.1 *Antioxidants*

Anoxomer

This polymeric antioxidant has not previously been evaluated by the Committee, which was informed that depolymerization of anoxomer was not likely to occur under ordinary conditions of use. There was a considerable amount of toxicological data about anoxomer available to the Committee. A temporary ADI of 0–8 mg/kg of body weight was allocated to anoxomer until 1984. The Committee required further information about the occurrence of senile cataract in rats exposed to high levels of anoxomer in the diet.

A toxicological monograph and new tentative specifications were prepared.

Butylated hydroxyanisole (BHA)

Previous evaluations of this substance were made by the Committee in 1961, 1965, 1973, 1976, and 1980, and toxicological monographs were issued in 1961, 1973, 1976, and 1980. Additional data have become available on the inhibitory effect on neoplasia.

A multigeneration reproduction study in the rat has been requested but the results are not yet available. However, the Committee was informed of the results of a teratological study in pigs in which no BHA-induced effects were observed. The Committee was also informed of a recently completed carcinogenesis study in rats,¹ but there was insufficient detail to allow for evaluation. The Committee requested the submission of the full data for evaluation as soon as possible. Taking into account all the available information, the Committee decided not to change the previous temporary ADI of 0–0.5 mg/kg of body weight allocated to butylated hydroxyanisole, butylated hydroxytoluene (BHT) and tertiary butyl hydroquinone (TBHQ) singly or in combination. The results of the multigeneration study are still required for the full evaluation of butylated hydroxyanisole. The existing specifications were revised. No toxicological monograph was prepared.

3.1.2 *Emulsifying agents*

Sorbitan monolaureate and sorbitan mono-oleate

The toxicological effects of sorbitan monolaureate or mono-oleate observed in feeding studies with high levels of these compounds appear to be due to the fatty acid moieties. A group ADI for sorbitan monoesters of palmitic and stearic acids of 0–25 mg/kg of body weight was allocated by the seventeenth meeting of the Committee (see Annex 1, reference 32).

The present meeting examined the available toxicological data for the sorbitan monoesters of lauric acid and oleic acids and agreed to include them in the group ADI for other sorbitan esters, namely, 0–25 mg/kg of body weight as the sum of the sorbitan esters of lauric, oleic, palmitic, and stearic acids.

A new toxicological monograph on sorbitan esters was prepared. For both the monolaureate and the mono-oleate the existing tentative specifications were revised and the “tentative” qualification was deleted.

Stearyl monoglyceridyl citrate

This compound is formed from monoglycerides, citric acid, and stearyl alcohol. No data on which a toxicological evaluation of the

¹ ITO, N. ET AL. (1982): Induction of squamous cell carcinoma in the fore-stomach of F344 rats treated with butylated hydroxyanisole. *Gann*, (in press).

compound could be based were available to the Committee. No ADI was allocated.

In order to carry out an evaluation of this compound, the Committee would require the results of a 90-day feeding study and data about the extent and rate of hydrolysis.

Not toxicological monograph was prepared. The existing specifications were revised.

Succinylated monoglycerides

The toxicological data available to the Committee were inadequate for evaluation leading to allocation of an ADI. The minimum additional data that would be required for evaluation by a future meeting of the Expert Committee would be the results of a 90-day feeding study and adequate metabolic studies. No toxicological monograph was prepared. The existing specifications were revised.

3.1.3 *Enzymes of microbiological origin used in food processing*

General principles for the toxicological evaluation of enzymes for use in food processing were set out by the Expert Committee in its twenty-first report (see Annex 6). The two enzymes on the agenda were from nonpathogenic microorganisms and were free from antibiotics and mycotoxins, but the normal habitats and presence in food of these organisms were not known to the Committee.

Glucose isomerase (isolated from Streptomyces violaceoniger)

The results of adequate short-term feeding studies were available to the Committee. The enzyme preparation is normally removed from the processed food. The Committee allocated a temporary ADI "not specified" and required information about the occurrence of the microorganism in nature. A new toxicological monograph was prepared. The existing specifications were maintained.

Protease (isolated from Streptomyces fradiae)

The results of limited feeding studies in three species were available to the Committee. The Committee allocated a temporary ADI "not specified". Submission of the results of the feeding study, including histopathological observations, and information about the occurrence of the microorganism in nature were required. A new toxicological monograph and new specifications were prepared.

3.1.4 *Flavouring agents*

Ethyl lactate

This substance is used as a carrier solvent for flavours, in addition to being a flavouring agent in its own right. Ethyl(-)-lactate was last evaluated by the Expert Committee in 1979, when it was allocated a temporary ADI "not specified" under the group ADI for lactic acid. The further work required was available for evaluation by the present meeting. The Committee dealt with ethyl lactate rather than ethyl(-)-lactate. The previous specification was revised accordingly. The temporary status was removed and ethyl lactate was included in the group ADI for lactic acid as "not specified". A new toxicological monograph was prepared.

The Committee considered the establishment of two new specifications, one each for the (-) and (\pm) forms of ethyl lactate. However, because of the toxicological insignificance of the differences between these optical isomers, only one set of specifications was considered necessary. The existing specifications were revised to take into account toxicological considerations.

Eugenol

New information has become available since eugenol was last evaluated (see Annex 1, reference 51, p. 28). A 2-year study in rats led to the conclusion that eugenol was not carcinogenic. However, a study in a hybrid mouse strain provided equivocal evidence for a possible increase in incidence of liver tumours in females, but not males. In another mouse study, in which both eugenol and saffrole were tested, saffrole was carcinogenic but eugenol was not. Mutagenicity tests have given negative results. On the basis of all the available data, the Committee concluded that eugenol does not have carcinogenic potential. The temporary status of the ADI was removed, and an ADI of 0-2.5 mg/kg of body weight was allocated. A new toxicological monograph was prepared. The existing specifications were revised.

α - and β -ionone

These compounds were last considered by the Expert Committee in its twenty-third report (see Annex 1, reference 51, p. 29), where they were each allocated a temporary ADI of 0-0.05 mg/kg of body

weight. The present meeting was informed that the required further work was being carried out and therefore agreed to extend the temporary ADIs of 0–0.05 mg/kg of body weight for α -ionone and 0.05 mg/kg of body weight for β -ionone until 1984, pending submission of the results of the short-term studies that are in progress. No new toxicological monograph was prepared. The specifications for α -ionone and β -ionone were revised.

3.1.5 *Food colours*

Natural food colours

In evaluating the food colours in this class that were on the agenda, the Committee took into account the general principles set out in its twenty-first report (see Annex 6).

Annatto extracts

In its eighteenth report in 1974 (see Annex 1, reference 34), the Expert Committee extended the temporary ADI of 0–1.25 mg/kg of body weight that had been allocated to annatto extracts in its thirteenth report (see Annex 1, reference 19). The results of metabolic studies that had been requested in previous reports were available for evaluation at the present meeting. These and results of some other studies, including an additional long-term feeding study in the rat, were used in the evaluation of annatto extracts. The Committee allocated an ADI to annatto extracts in terms of the carotenoid content expressed as bixin, namely, 0–0.065 mg/kg of body weight. A new toxicological monograph was prepared. The existing specifications were revised.

Anthocyanins (grape-skin extract).¹ These food colouring agents have not previously been considered by the Expert Committee. Information on the metabolism and toxicity of anthocyanins is limited and interpretation is complicated because there are several different, although chemically related anthocyanins, and studies have been done with certain specific anthocyanins as well as with mixtures extracted from fruits. The Committee established new specifications for grape-skin extract. The Committee took into consideration the results of short-term feeding studies with grape-skin

¹ See also section 2.5.

extract in allocating an ADI of 0–2.5 mg/kg of body weight to anthocyanins in grape-skin extract. A new toxicological monograph on anthocyanins, including grape-skin extract, was prepared.

In addition to preparing new specifications for grape-skin extract, the existing specifications for anthocyanins were maintained.

Beet Red. A temporary ADI “not specified” was allocated in the Committee’s eighteenth report (see Annex 1, reference 34) and was extended in the twenty-second report (see Annex 1, reference 48), which concluded that a full toxicological evaluation was required. A limited amount of further information has now become available on the colour-active principle, betanine, which was of particular concern in the twenty-second report. Betanine amounts to about 4% of the commercial product “Beet Red”. The present Committee had no information about the initiation of any of the studies that had been requested in previous reports; therefore, the previously allocated temporary ADI was withdrawn. The existing tentative specifications were revised.

Carmines. These food colours were last considered in the twenty-fifth report of the Expert Committee (see Annex 1, reference 57). The results of further work required by the previous meeting were available for evaluation by the Committee, which allocated an ADI of 0–5.0 mg/kg of body weight as ammonium carmine or the equivalent of calcium, potassium, or sodium salts. A new toxicological monograph was prepared. The existing tentative specifications were revised but the “tentative” qualification was deleted.

Turmeric and curcumin. Turmeric can be considered as a flavouring agent as well as a food colour. Curcumin is the main colour-active principle of turmeric. These compounds were evaluated in the Committee’s twenty-second report (see Annex 1, reference 48) and temporary ADIs were allocated at 0–2.5 mg/kg of body weight for turmeric and 0–0.1 mg/kg of body weight for curcumin. Further data were considered in the twenty-fourth report (see Annex 1, reference 54) and the temporary ADIs were extended. The present Committee reviewed the earlier data, considered still further data, and was informed of other studies in progress that respond to the “further work required” in previous reports. The temporary ADIs were extended again at the same levels, namely 0–2.5 mg/kg of body weight for turmeric and 0–0.1 mg/kg of body weight for curcumin, and further work required by 1986 was specified (see Annex 3). A new toxicological monograph was prepared. The existing specifications for turmeric and curcumin were revised.

Synthetic food colours

Amaranth. This compound was last reviewed by the Expert Committee in 1978 in its twenty-second report (see Annex 1, reference 48). At that time, the previously established temporary ADI of 0–0.75 mg/kg of body weight was extended, pending the evaluation of the data from additional long-term feeding studies which had been required by 1982. These data were not available but the Committee was informed that two such studies were in progress. However, the Committee reviewed some new studies on metabolism and on mutagenicity; no evidence of potential toxicity was revealed by these studies. Therefore, the Committee agreed to continue the temporary ADI of 0–0.75 mg/kg of body weight and required the submission of the data from the long-term feeding studies by 1984. No new toxicological monograph was prepared. The existing specifications were revised and the Committee agreed to delete the “tentative” qualification.

Brown HT (formerly Chocolate Brown HT). This colour was last evaluated by the Expert Committee in its twenty-third and twenty-fifth reports (see Annex 1, references 51 and 57), where a temporary ADI of 0–0.25 mg/kg of body weight was allocated. The results of the required metabolic study were available to the present meeting, and the Committee was informed that the results of a reproduction study would soon be available. Therefore, the temporary ADI of 0–0.25 mg/kg of body weight was extended to 1984. No new toxicological monograph was prepared. The existing specifications were maintained.

Lithol rubine BK. This colour was considered by the Expert Committee in its twenty-first report (see Annex 1, reference 43) but insufficient data were available for evaluation and allocation of an ADI. Although lithol rubine BK was placed on the agenda for the present meeting, only limited further information was provided. The available information is still not sufficient for evaluation. No ADI was allocated. No toxicological monograph was prepared. The existing tentative specifications were revised but the “tentative” qualification was deleted.

Patent Blue V. This food colour had been allocated a temporary ADI by the Expert Committee in 1969, but this was withdrawn at its eighteenth meeting in 1974 (see Annex 1, reference 34) because the results of the required studies had not been submitted. Patent Blue V was again on the agenda for the present meeting, but only

limited further data were available. These were insufficient to allow for allocation of an ADI. The existing tentative specifications were revised and the "tentative" qualification was deleted.

The Committee was informed that further studies were in progress. No new toxicological monograph was prepared.

Quinoline Yellow. This compound was last evaluated by the Expert Committee in 1978 and a temporary ADI was allocated (see Annex 1, reference 48). Some additional toxicological data were available to the present meeting, and the Committee was informed that further major studies were approaching completion. There are two quinoline yellows, the so-called "earlier" and "later" quinoline yellows; the latter is about 30% methylated, whereas the former is non-methylated.

In its nineteenth report (see Annex 1, reference 37) the Committee suggested that data from both compounds could be used for toxicological evaluation of either of the quinoline yellows for food additive use. This view was reiterated at the present meeting.

It was decided, therefore, to extend the temporary ADI of 0-0.5 mg/kg of body weight to 1984. The Committee decided to postpone the preparation of a consolidated toxicological monograph on Quinoline Yellow until the results of the studies in progress were available for evaluation.

Specifications were revised to take account of the proportion of methylated derivatives in the commercial product and maintained as tentative.

Sunset Yellow FCF. This food colour was previously reviewed in the eighth report of the Expert Committee (see Annex 1, reference 8) and allocated an ADI of 0-5.0 mg/kg of body weight, but further work was considered desirable. Some of this has been done and other studies have also been carried out with Sunset Yellow FCF. The Committee reconsidered the earlier studies together with its consideration of the newer studies and decided to allocate a revised ADI of 0-2.5 mg/kg of body weight. The existing specifications were revised. A new toxicological monograph was prepared.

3.1.6 *Inorganic salts and buffering agents*

A number of substances on the agenda that have a variety of functions as food additives could be conveniently assembled under the heading of inorganic salts.

Phosphates and polyphosphates

Many phosphate and polyphosphate salts and phosphoric acid have been previously evaluated by the Expert Committee for acceptable daily intake (see Annex 1, references 6, 7, 8, 11, 19, and 32) and a toxicological monograph was published in 1974 (see Annex 1, reference 33). Some other phosphates and polyphosphates were considered for the first time by the present meeting. The list of compounds and their status in respect of toxicological evaluations and specifications is given in Annex 4.

Aluminium-containing phosphates were considered separately by the Committee. The remaining phosphates and polyphosphates were considered as a group, together with phosphate occurring naturally in food. The Committee noted the need to pay attention to the calcium/phosphorus ratio in the diet in evaluating the use of phosphates and polyphosphates as food additives (see section 2.6). The main toxicological finding in feeding studies with high levels of phosphates is nephrocalcinosis, in which respect the rat is acutely susceptible. The best estimate of the lowest level of dietary intake of phosphates (expressed as phosphorus) that might conceivably cause nephrocalcinosis in man is about 7000 mg per day.

Since phosphorus (as phosphates) is an essential nutrient and an unavoidable constituent of foods, it is neither appropriate nor feasible to give a range of values from zero to a maximum; therefore, the Committee decided to allocate a maximum tolerable daily intake (MTDI) to phosphates, rather than an ADI.

The maximum tolerable daily intake allocated was 70 mg/kg of body weight (expressed as phosphorus), which applies to the sum of phosphates and polyphosphates naturally present in food and the additives listed in Annex 4. This figure applies to diets that are nutritionally adequate in respect of calcium. However, if the calcium intake were abnormally high, the intake of phosphates could be proportionately higher than that stated above, and the reverse relationships would also apply (see also section 6.2). A revised toxicological monograph on phosphates was prepared.

Previously prepared specifications were confirmed except for calcium and potassium polyphosphates, the specifications for which were modified to include limits and a test procedure for cyclic phosphates. The Committee foresaw the need to revise the specifications for the polyphosphates in this respect. The Committee was not aware of any food additive use of ammonium polyphosphate and

requested additional information; meanwhile tentative specifications were established, including limits and a test for cyclic phosphates. The Committee was concerned about the potential levels of fluoride, lead, and other heavy metal contaminants in bone phosphate, and was only able to establish tentative specifications until further information has been obtained.

Sodium aluminium phosphate (acidic and basic)

The main toxicological consideration in relation to these compounds is due to the aluminium component. The particular compounds on the agenda were "sodium aluminium phosphate, basic" and "sodium aluminium phosphate, acidic". Neither has been considered specifically by a previous meeting of the Expert Committee, but both compounds were included in a toxicological monograph on aluminium published in 1977 (see Annex 1, reference 44). Only one recent feeding study with "sodium aluminium phosphate, acidic" was available for consideration; this was a 90-day feeding study in beagles at levels up to 3% in the diet. A temporary ADI of 0-6 mg/kg of body weight was allocated to sodium aluminium phosphate. Further work required is specified in Annex 3. A toxicological monograph on sodium aluminium phosphate was prepared. New specifications were prepared for "sodium aluminium phosphate, basic" and new tentative specifications were prepared for "sodium aluminium phosphate, acidic".

Ammonium carbonate and ammonium hydrogen carbonate (formerly ammonium bicarbonate)

Although only limited toxicological data are available for these ammonium salts, the results of studies with other ammonium salts and other carbonates and bicarbonates provide a basis for evaluation. There is a considerable amount of information on the clinical uses of ammonium chloride and sodium bicarbonate to alter acid-base balance and urinary pH. The evidence from human exposure to relatively high doses suggests that it is without significant toxic effects, except for alteration in acid-base balance. It would appear that this would be less of a problem with ammonium carbonate and bicarbonate.

In assigning the ADI for ammonium carbonate and ammonium hydrogen carbonate as "not specified", the Committee stressed the need to apply all the conditions and restraints that follow from such

a designation (see Annex 1, reference 32). The existing specifications for the two compounds were revised. A toxicological monograph was prepared.

Magnesium silicate

This anti-caking agent was previously considered by the Expert Committee in 1969, 1973, 1976, and 1980 (see Annex 1, references 19, 32, 40, and 54). No additional information was made available to the present meeting. However, the existing tentative specifications have been revised to exclude magnesium trisilicate. Therefore, the Committee considered that the ADI for magnesium silicate should be reallocated at its former level, namely, "not specified". No new toxicological monograph was prepared. The existing specifications were revised and the Committee agreed to delete the "tentative" qualification.

3.1.7 *Sweetening agents*

Sorbitol

This substance was assigned an ADI "not specified" by the Committee in its seventeenth report (see Annex 1, reference 32). However, this was changed to a temporary ADI in 1978 (see Annex 1, reference 48) and confirmed as temporary in 1980 (see Annex 1, reference 54) because of concern about the production of adrenal medullary hyperplasia in rats in a feeding study with 20% of sorbitol in the diet. The present meeting took the view that such a high level of sorbitol produced gross dietary imbalance, which may produce metabolic imbalance, and considered that the adrenal medullary hyperplasia produced by high dietary levels of sorbitol and certain other nutrients might occur as a physiological consequence of the stresses induced in aging rats. Consequently, the Committee removed the temporary status.

The Committee was aware of a multigeneration study in progress and considered that the submission of the results of this study was highly desirable. No new toxicological monograph was prepared. The existing specifications were revised.

Calcium and sodium cyclamates

Cyclamate, calcium and sodium salts, and cyclohexylamine were evaluated in the twenty-first report of the Expert Committee, when a temporary ADI of 0–4 mg/kg of body weight was allocated to

cyclamate, calcium and sodium salts (see Annex 1, reference 43). This was extended in the twenty-fourth report in 1980 (see Annex 1, reference 54) pending the submission of results of studies then in progress. Additional toxicological data had become available and were considered by the present meeting. The totality of the toxicological data before the Committee allowed the allocation of an ADI of 0–11 mg/kg of body weight to cyclamate, calcium and sodium salts, expressed as cyclamic acid. A new toxicological monograph on calcium and sodium cyclamates, including cyclohexamine, was prepared. The existing specifications were maintained.

Saccharin, potassium and sodium salts

In its twenty-first report (see Annex 1, reference 43), the Expert Committee changed the ADI for saccharin from 5 mg/kg of body weight to a temporary ADI of 2.5 mg/kg of body weight and withdrew the conditional ADI of 15 mg/kg of body weight for dietetic purposes only. The temporary ADI was extended in the twenty-fourth report in 1980 (see Annex 1, reference 54) pending the submission of results on ongoing studies that were designed to elucidate the mechanism of induction of bladder tumours in rats by high doses of saccharin.

The present meeting reviewed further findings from epidemiological studies. It was concluded that these studies did not reveal any evidence for a saccharin-associated increase in bladder tumours. The Committee was also informed that an additional large-scale epidemiological study has almost been completed. The Committee decided to extend the temporary ADI of 0–2.5 mg/kg of body weight for saccharin, potassium and sodium salts, to 1984 and required the submission of the results of a long-term feeding study in rats and the epidemiological study, both of which are nearing completion. A revised toxicological monograph was prepared. The existing specifications were revised for saccharin only.

3.1.8 *Thickening agents*

Gum arabic

This substance was previously evaluated in the thirteenth and seventeenth reports of the Expert Committee (1970 and 1974), and a toxicological monograph was last issued in 1974 (see Annex 1, reference 33).

The results of two long-term studies were available for evaluation by the Committee. A new toxicological monograph was prepared incorporating the new data. The Committee allocated an ADI "not specified" (replacing the previous terminology "not limited") to gum arabic. The existing specifications were revised.

Gum ghatti

This gum had previously been evaluated by the Committee in 1980 (see Annex 1, reference 54). It has the typical heteroglycan structure of other gums in food additive use. Notwithstanding this, the Committee considered that there were insufficient data to allow evaluation for food additive use. No toxicological monograph was prepared. The existing specifications were maintained as tentative.

Modified starches

The list of modified starches on the agenda is set out in Annex 5. Many of these modified starches were previously evaluated by the Committee in 1973, and two others were evaluated subsequently. Concern was expressed by the Committee in 1976 about kidney lesions occurring in rats that were fed high levels of modified starches. New information about their etiology and significance for toxicological evaluation is given in section 2.4 of the present report. In the light of this new information, and on the basis of further studies with some of the modified starches that had been previously evaluated, the ADIs were confirmed as "not specified" (replacing the earlier terminology of "not limited"). In addition, this ADI was allocated to a modified starch that had not been evaluated previously (starch sodium octenyl succinate).

In its twentieth report (see Annex 1, reference 40), the Committee requested analytical data about certain chlorohydrin residues in starches. Further information on these was now available.

The Committee was informed that starches modified by the use of the crosslinking agent epichlorohydrin are no longer used as food additives. Therefore no ADIs were allocated for such starches.

When propylene oxide is used in producing various modified starches, residues of propylene chlorohydrin may be present in the product. The Committee has previously considered a number of short-term feeding studies on propylene chlorohydrin. In a recent lifetime study in rats, which were fed 55% hydroxypropyl distarch phosphate containing 4.3 mg/kg of propylene chlorohydrin, no

effects attributable to this residue were observed. The Committee considered that this study provides additional information on the safety of residues of propylene chlorohydrin likely to be encountered in modified starches. New toxicological monographs were prepared on these substances. Annex 5 provides information on specifications.

3.1.9 *Miscellaneous food additives*

Quillaja extracts

Extracts of the bark of *Quillaja* species contain triterpenoid saponins and are used as foaming agents in beverages. *Quillaja* extracts have not previously been evaluated by the Expert Committee. The toxicological data now available to the Committee included the results of adequate life-time studies in mice and rats from which a no-effect level could be derived. No specifications were prepared for quillaja extracts because the available information was inadequate; hence, no ADI could be allocated. A toxicological monograph was prepared.

Sodium hydrogen DL-malate

Salts of malic acid have been considered previously (see Annex 1, reference 51). The Committee agreed to add sodium hydrogen malate to the malic acid salts previously accepted for food additive use. Therefore, the group ADI "not specified" for DL-malic acid and bases now included that salt. No toxicological monograph was prepared. New specifications were prepared for sodium hydrogen DL-malate.

Ammonium acetate

This substance is used in foods for adjustment of pH. It has not previously been evaluated as such, but other ammonium salts and acetates have been allocated group ADIs "not specified". Accordingly, the Committee agreed to include ammonium acetate within the previously accepted groups. No toxicological monograph was prepared. No specifications were prepared.

Sucrose acetate isobutyrate (SAIB)

This density-adjusting agent was previously evaluated by the Committee in 1975 and 1977 (see Annex 1, reference 37 and 43) but no ADI was allocated and further information that would be

required for evaluation was indicated. This information was not yet available; therefore, it was not possible to evaluate sucrose acetate isobutyrate. Although no ADI was allocated, the Committee considered it worth while to prepare a toxicological monograph summarizing the available toxicological data. The existing specifications were revised and designated as "tentative".

Ethyl cellulose

As a food additive, ethyl cellulose is used for micro-encapsulation of flavouring agents. Although only limited data were available on ethyl cellulose, the Committee decided that it could be included with other modified celluloses that were evaluated by the Committee in its seventeenth report, (see Annex 1, reference 32). Accordingly, the group ADI of 0–25 mg/kg of body weight now applies to ethyl cellulose as well as to hydroxypropyl cellulose, methyl cellulose, methyl ethyl cellulose, hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose. No toxicological monograph was prepared. Existing specifications were revised.

3.2 Contaminants

3.2.1 Metals

Arsenic, copper, iron, tin and zinc were on the agenda. The Committee decided not to consider arsenic and iron (see section 2.1). The factors set out in section 2.8 were applied to considerations of copper, tin, and zinc.

Copper

In its tenth report, the Committee arrived at a maximum acceptable daily load for copper of 0.5 mg/kg of body weight. The daily dietary requirement for copper has been estimated to be 0.05 mg/kg of body weight.¹ The Committee reviewed information on dietary intake of copper, the results of toxicological studies, and observations on toxicity in dogs, rats, pigs, sheep and human subjects, including those with a rare disorder of copper metabolism (Wilson's disease). A no-effect level of about 5 mg/kg of body weight in the dog was provided by a 1-year feeding study.

¹ WHO Technical Report Series, No. 532, 1973.

The Committee tentatively confirmed the previous decision for copper and allocated a provisional value for maximum tolerable daily intake from all sources of 0.5 mg/kg of body weight. It recommended that further information be collected about the ranges of daily intakes of copper from all sources by selected human sampling, and that consideration be given to coordinating epidemiological surveys of any high-intake groups that may be detected, in order to determine whether or not there is any evidence of copper-induced ill-health. A new toxicological monograph on copper has been prepared.

Tin

Tin was last considered in the Committee's twenty-second report (see Annex 1, reference 48). The Committee reviewed a considerable amount of information on the absorption, distribution, and excretion of tin, the amounts of tin present in foods (with special reference to canned foods and food additive uses), the results of toxicological studies, and human toxicity data.

The main problem with excessive levels of tin in foods, such as canned fruit-based beverages, takes the form of acute manifestations of gastric irritation. The threshold for this effect appears to occur with concentrations of about 200 mg/kg in food.

The Committee was of the opinion that care should be taken to ensure that the levels of tin in food should be kept as low as practicable; to this end, consumers should be advised not to store food in opened tin-coated cans. The Committee allocated a provisional value for maximum tolerable daily intake of tin of 2 mg/kg of body weight. This value includes the food additive use of stannous chloride; the previously allocated ADI for stannous chloride was withdrawn. A new toxicological monograph on tin and stannous chloride was prepared.

Zinc

Zinc was previously considered by the Committee in its tenth report (see Annex 1, reference 12). No ADI was established. The daily requirement for zinc has been estimated to be 15–22 mg daily.^{1,2} The Committee reviewed the available data on zinc intake,

¹ WHO Technical Report Series, 1973, No. 532, p.13

² US Food and Nutrition Board, Committee on Dietary Allowances (1974) *Recommended dietary allowances*, Washington, DC, National Academy of Sciences.

the results of toxicological studies in experimental animals, including those involving interactions of zinc with copper and iron, as well as reports on the use of clinical studies in man. Clinical studies showed that man can tolerate 200 mg of zinc sulfate per day. The Committee proposed a provisional maximum daily tolerable intake for zinc of 1 mg/kg of body weight. A toxicological monograph was prepared.

3.2.2 *Xenobiotic anabolic agents*

A Working Group on Health Aspects of Residues of Anabolics in Meat met in Bilthoven, Netherlands, on 10–13 November 1981, under the auspices of the WHO Regional Office for Europe.¹

The Working Group recommended that the available data about trenbolone acetate and zeranol should be evaluated for safety in use of these anabolic agents as soon as possible by the appropriate international body—the Joint FAO/WHO Expert Committee on Food Additives. Accordingly, trenbolone acetate and zeranol had been placed on the agenda for the present meeting.

Some of the problems in evaluating xenobiotic agents for acceptance in the raising of animals for food are discussed in section 2.7.

The Committee was supplied with a considerable amount of relevant toxicological data about trenbolone acetate and zeranol. The Committee was also informed that residue levels of these anabolic agents, when used in conformity with good animal husbandry practice, were extremely low. Such low residues would not exert endocrinological effects on human consumers of meat products from treated animals. Furthermore, in the light of this information, the Committee considered that the residues were not likely to pose any significant toxicological hazard of a non-endocrinal nature.

However, the Committee did not have available the necessary documentation on residue levels, good animal husbandry in relation to the use of these agents, or details of methods and analysis; furthermore, the Committee had some slight reservations about the adequacy of the toxicological data. Therefore, the Committee recommended that trenbolone acetate and zeranol should be considered by a future meeting, which would be supplied with adequate documentation for evaluation covering the matters set out in section 2.7. No toxicological monographs were prepared.

¹ *Health aspects of residues of anabolics in meat*. Copenhagen, WHO Regional Office for Europe, 1982 (EURO Reports and Studies 59).

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for a large number of substances, including inorganic salts, buffering agents, salts, emulsifying agents, thickening agents, stabilizers, flavouring agents, food colours, sweetening agents, and miscellaneous food additives (see Annex 2). The Committee also developed new specifications (some tentative) for several additional substances; these specifications related to buffering agents, an antioxidant, a food colour, an enzyme preparation, and a number of phosphate salts.

The Committee was unaware of uses of ammonium polyphosphate as a food additive and requested additional information in this regard.

A number of specifications were recommended by the Codex Committee on Food Additives for adoption by the Commission after editorial correction. The Committee reviewed these specifications with regard to the editorial changes and concurred with the revisions suggested. The compounds were citral, ethyl formate, ethyl heptanoate, linalool, linalyl acetate, nitrogen, potassium nitrate, quinine hydrochloride, quinine sulfate, and turmeric.

Specifications were not developed for ammonium acetate, *Quillaja* extracts, and some modified starches (see Annex 5). The information requested by the Committee in its twenty-fifth report (see Annex 1, reference 57) about actual modified starches used in food was available to the meeting. These data were used to prepare specifications some of which were tentative in the absence of information on contents of hydroxypropyl groups and adipate groups as well as associated methods of analysis.

New tentative specifications were prepared for anoxomer and the Committee requested confirmation of all the proposed analytical methods for that compound.

In the course of the revision of specifications, the name dimethylpolysiloxane was amended to polydimethylsiloxane to reflect its chemical structure more accurately.

5. FUTURE WORK

1. A considerable number of food additives have temporary ADI values. These food additives should be re-evaluated when the expiry date for the temporary ADI is reached, or sooner if the required information becomes available.

2. For many food additives, the specifications are only tentative. As soon as the necessary information is available, full specifications should be prepared.

3. Iron, arsenic, trenbolone acetate, and zeranol should be evaluated as food contaminants at a future meeting of the Committee.

4. In reviewing the specifications for a number of colours and flavouring substances, the Committee revised some of the general methods and added them as an annex to the publication on specifications. The Committee considered it desirable to review, update, and expand the full publication on general methods contained in *Guide to specifications*¹ in order to take into account advances in methodology.

6. RECOMMENDATIONS TO FAO AND WHO

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 at least annually.

2. A group of experts should consider the toxicological consequences of the complex nutritional problems raised by the increasing intake of phosphates and polyphosphates as food additives, and the tendency to replace calcium with magnesium or other cations in other food additive use (see section 2.6).

3. Studies on the range of daily intakes of copper by various populations should be undertaken. Epidemiological surveys should be carried out with high-intake groups to determine whether there is any evidence of copper-induced ill-health.

4. The evaluation of xenobiotic anabolic agents that are proposed for use in animals, subsequently to be used for human food, requires (1) the preparation of full documentation on relevant toxicological data and (2) comprehensive data about the nature and level of residues (see section 2.7). The Committee stressed the necessity for the provision of these data by FAO and WHO.

5. A large number of xenobiotic compounds are used in animal husbandry and veterinary practice and residues of these compounds and their metabolites are present in food products. Such compounds include animal feed additives, growth-promoting agents, drugs for

¹ FAO Food and Nutrition Paper 5, Rome, 1978.

prophylaxis or treatment of infection, and the like. Such xenobiotic contaminants of food should be evaluated along the lines set out above for xenobiotic anabolic agents.

6. In view of the growing concern about the presence in foods of industrial organic contaminants of the environment (e.g., polychlorinated biphenyls), the Committee recommends that FAO and WHO collect relevant data.

7. When a food additive is also either an essential nutrient or an unavoidable constituent of the normal diet, or both, the Committee recommends that a maximum tolerable daily intake should be allocated rather than an ADI. In the case of phosphates, this action was taken at the present meeting (see section 2.6). The Committee recommends the collection of data about the natural levels of such substances in foods and in diets and the revision of the evaluation of ADI levels in terms of maximum tolerable daily intakes.

8. The Committee stressed the urgency of implementing the recommendation made in its twenty-fifth report that "a group of experts be convened, as soon as possible, to study the application of advances in methodology to the toxicological evaluation of food additives and contaminants, and also of pesticide residues".

9. In its twenty-fifth report (see Annex 1, reference 57, section 2.7), the Committee had agreed to request certain data concerning technological and safety aspects of food additives. While those data are not essential to an evaluation, they would greatly facilitate it, and the Committee recommends that those data should continue to be assembled.

Annex 1

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

Documents marked with an asterisk may be obtained on request from: Division of Environmental Health, World Health Organization, 1211 Geneva 27, Switzerland, or from Food Standards and Food Science Service, Food and Agriculture Organization of the United Nations, 00100 Rome, Italy.

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 intentional 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.
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. 25, 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.
- *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.
12. *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.
- *13. *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.
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. *Specification 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. 43A, 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; 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; 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.
33. *Toxicological evaluation of certain food additives including anticaking agents antimicrobials, antioxidants, emulsifiers, and thickening agents.* FAO Nutrition Meetings Report Series, No. 53A; WHO Food Additives Series, No. 5, 1974.
34. *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.
35. *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.
36. *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.
37. *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.
38. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 55A; WHO Food Additives Series, No. 8, 1975.
39. *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.

40. *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.
41. *Toxicological evaluation of certain food additives*. FAO Food and Nutrition Series, No. 1A, 1978; WHO Food Additives Series, No. 10, 1978.
42. *Specifications for the identity and purity of certain food additives*. FAO Food and Nutrition Series, No. 1B, 1977.
43. *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.
44. *Summary of toxicological data of certain food additives*. WHO Food Additives Series, No. 12, 1977.
45. *Specifications for identity and purity of some food additives, including anti-oxidants, food colours, thickeners, and others*. FAO Nutrition Meetings Report Series, No. 57, 1977.
46. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers*. FAO Food and Nutrition Paper, No. 4, 1978.
47. *Guide to specifications – General notices, general methods, identification tests, text solutions, and other reference materials*. FAO Food and Nutrition Paper, No. 5, 1978.
48. *Evaluation of certain food additives* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
49. *Summary of toxicological data of certain food additives and contaminants*. WHO Food Additives Series, No. 13, 1978.
50. *Specifications for the identity and purity of certain food additives*. FAO Food and Nutrition Paper, No. 7, 1978.
51. *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.
52. *Toxicological evaluation of certain food additives*. WHO Food Additives Series, No. 14, 1979.
53. *Specifications for identity and purity of food colours, flavouring agents, and other food additives*. FAO Food and Nutrition Paper, No. 12, 1979.
54. *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.
55. *Toxicological evaluation of certain food additives*. WHO Food Additives Series, No. 15, 1981.
56. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives)*. FAO Food and Nutrition Paper, No. 17, 1980.
57. *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.
58. *Toxicological evaluation of certain food additives*. WHO Food Additives Series, No. 16, 1982.

59. *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.

Annex 2

ACCEPTABLE DAILY INTAKES AND INFORMATION ON SPECIFICATIONS

	Specifications ¹	ADI for man (mg/kg of body weight) [and other toxicological decisions]
A. Specific food additives		
<i>Antioxidants</i>		
anoxomer	NT	0-8 ²
butylated hydroxyanisole (BHA)	R	0-0.5 ^{2,3}
<i>Emulsifying agents</i>		
sorbitan monolaureate	R	0-25 ⁴
sorbitan monooleate	R	0-25 ⁴
stearyl monoglyceridyl citrate	R	No ADI allocated
succinylated monoglycerides	R	No ADI allocated
<i>Enzymes</i>		
glucose isomerase (isolated from <i>Streptomyces violaceoniger</i>)	S	ADI not specified ^{2,5}
protease (isolated from <i>Streptomyces fradiae</i>)	N	ADI not specified ^{2,5}
<i>Flavouring agents</i>		
ethyl lactate	R	ADI not specified ⁵
eugenol	R	0-2.5
α-ionone	R	0-0.05 ²
β-ionone	R	0-0.05 ²

Food colours

Natural food colours

annatto extracts	R	0-0.065 ⁶
anthocyanins	S	ADI not allocated ⁹
anthocyanins (grape-skin extract)	N	0-2.5
Beet Red	RT	ADI withdrawn ⁷
carmines	R	0-5.0 ⁸
curcumin	R	0-0.1 ²
turmeric	R	0-2.5 ²

Synthetic food colours

Amaranth	R	0-0.75 ²
Brown HT (formerly Chocolate Brown HT)	S	0-0.25 ²
Lithol rubine BK	R	ADI not allocated ⁹
Patent Blue V	R	ADI not allocated ⁹
Quinoline Yellow	RT	0-0.5 ²
Sunset Yellow FCF	R	0-2.5 ¹⁰

Inorganic salts and buffering agents

phosphates and polyphosphates ¹¹	R, S, N, NT ¹²	[70] ¹³
sodium aluminium phosphate, acidic	NT	0-6 ²
sodium aluminium phosphate, basic	N	0-6 ²
ammonium carbonate	R	ADI not specified ⁵
ammonium hydrogen carbonate (formerly ammonium bicarbonate)	R	ADI not specified ⁵
magnesium silicate	R	ADI not specified ⁵

Sweetening agents

sorbitol	R	ADI not specified ⁵
calcium and sodium cyclamates	S	0-11 ¹⁴
saccharin, potassium and sodium salts	R	0-2.5 ²

Thickening agents

gum arabic	R	ADI not specified ⁵
gum ghatti	ST	ADI not allocated ⁹
modified starches	O, R, RT, S ¹⁵	ADI not specified ^{5,16}
starch sodium octenyl succinate	R	ADI not specified

Miscellaneous food additives

quillaja extracts	O	ADI not allocated ¹⁷
sodium hydrogen DL-malate	N	ADI not specified ^{5,18}
ammonium acetate	O	ADI not specified ^{5,19}
sucrose acetate isobutyrate (SAIB)	RT	ADI not allocated ⁹
ethyl cellulose	R	0-25 ²⁰

B. Contaminants

Metals

copper	–	[0.05–0.5] ^{21,22}
tin (inorganic; including stannous chloride)	–	[2.0] ^{22,23}
zinc	–	[0.3–1.0] ^{21,22}

Xenobiotic anabolic agents

trenbolone acetate	O	ADI not allocated ²⁴
zeranol	O	ADI not allocated ²⁴

Notes to Annex 2

1. N, new specifications prepared; O, specifications not prepared; R, existing specifications revised; S, specifications exist, revision not considered; T, the existing new, or revised specifications are tentative and comments are invited.
2. Temporary acceptance.
3. Group ADI. As BHA, BHT, TBHQ singly or in combination.
4. Group ADI. As the sum of the sorbitan esters of lauric, oleic, palmitic and stearic acid.
5. The statement “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 this reason, and for the reasons stated in the individual evaluations, the establishment of an acceptable daily intake (ADI) is not deemed necessary.
6. The ADI is in terms of the carotenoid content expressed as bixin.
7. The previous temporary ADI “not specified” allocated in the eighteenth report of the Committee and extended in the twenty-second report has been withdrawn since the additional information requested in the earlier evaluations was not available.
8. The ADI includes ammonium carmine or the equivalent of calcium, potassium or sodium salts.
9. No sufficient toxicological data were available.
10. The previous ADI of 0–5.0 mg/kg of body weight was revised in the light of reconsideration of earlier studies together with newer studies.
11. Aluminium-containing phosphates are not included.
12. See Annex 4.
13. This figure represents the maximum tolerable daily intake (MTDI) of phosphates. It is not an ADI. The MTDI is expressed as phosphorus and it applies to the sum of phosphates naturally present in food and the additives listed in Annex 4. It also applies to diets that are nutritionally adequate in respect of calcium. However, if the calcium intake were high, the intake of phosphate could be proportionately higher, and the reverse relationship would also apply.
14. Expressed as cyclamic acid.

15. See Annex 5.
16. Does not include starches modified by the use of the cross-linking agent epichlorohydrin.
17. No specifications are available on these substances.
18. Group ADI. The Group ADI "not specified" for DL-malic acid and bases now includes sodium and potassium hydrogen DL-malates.
19. Group ADI. Included in the group ADI for other ammonium salts and acetates.
20. Group ADI including ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose.
21. Daily dietary requirement/maximum tolerable daily intake. Expressed in mg/kg of body weight.
22. Provisional.
23. Maximum tolerable daily intake.
24. Necessary documentation on residue levels was not available for full evaluation of this compound.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

Antioxidants

*anoxomer*²

- (1) Further information about the occurrence of senile cataract in rats exposed to high levels of anoxomer in the diet.

butylated hydroxyanisole (BHA)^{1,5}

- (1) A multigeneration reproduction feeding study in Sprague-Dawley rats.
- (2) Receipt and evaluation of a carcinogenic study in the rat.

Emulsifying agents

*stearyl monoglyceridyl citrate*⁴

- (1) 90-day feeding study.
- (2) Data about the extent and rate of hydrolysis.

*succinylated monoglycerides*⁴

- (1) 90-day feeding study.
- (2) Adequate metabolic studies.

Enzymes

glucose isomerase (isolated from *Streptomyces violaceoniger*)²

- (1) Information about the occurrence of *Streptomyces violaceoniger* in nature.

protease (isolated from *Streptomyces fradiae*)²

- (1) Submission of the results of a feeding study, including histopathological observations.
- (2) Information about the occurrence of *Streptomyces fradiae* in nature.

Flavouring agents

α-ionone^{2,5}

- (1) An additional short-term toxicity study (90 days) on a well-characterized sample of α -ionone with one dietary level, comparable to those at which minimum effects were previously observed.
- (2) Metabolic studies.

β-ionone^{2,5}

- (1) A short-term toxicity study (90 days) on a well-characterized sample of β -ionone with one dietary level, comparable to those at which minimum effects were previously observed.

Turmeric and curcumin^{3,5}

Turmeric

- (1) Adequate short-term feeding study in a non-rodent species.

curcumin (using an deoresin of turmeric with a well-defined curcumin content.

- (1) Adequate long-term feeding carcinogenicity study in a rodent species.
- (2) A multigeneration reproduction/teratogenicity study.

Synthetic food colours

Amaranth^{2,5}

- (1) Long-term feeding studies in two species, one study to include exposure *in utero* and through lactation.

Brown HT (formerly Chocolate Brown HT)^{2,5}

- (1) Multigeneration reproduction/teratology study.
- (2) Metabolic studies in several species, preferably including man.

Quinoline yellow^{2,5}

- (1) Metabolic studies in several species, preferably including man.
- (2) An adequate long-term feeding study in a species other than the rat.

Inorganic salts and buffering agents

*Sodium aluminium phosphate (acidic and basic)*³

- (1) Absorption and metabolic studies, preferably in man.
- (2) Short-term feeding study.
- (3) Multigeneration reproduction study.

Sweetening agents

*Sorbitol*⁶

- (1) Submission of the results of a multigeneration study in progress.

*Saccharin, potassium and sodium salts*²

- (1) Submission of the results of a long-term feeding study, currently in progress.
- (2) Submission of the results of the epidemiological study currently in progress.

¹ Information required by 1983.

² Information required by 1984.

³ Information required by 1986.

⁴ Information required before an ADI can be allocated.

⁵ Information required by previous meetings of the Committee.

⁶ Information desirable.

Annex 4

PHOSPHATES AND POLYPHOSPHATES EVALUATED FOR FOOD ADDITIVE USE

phosphoric acid
ammonium phosphate, dibasic^{1,5}
bone phosphate²
calcium phosphate (mono-, di- and tri-basic)
magnesium phosphate (mono-, di-¹ and tri-basic)
sodium phosphate (mono-, di- and tri-basic)
sodium aluminium phosphate, basic¹ } see Section 3.1.6
sodium aluminium phosphate, acidic² }
disodium dihydrogen diphosphate
tetrasodium diphosphate
pentasodium triphosphate
pentapotassium triphosphate³
sodium hexametaphosphate
ammonium polyphosphate^{2,5}
calcium polyphosphate^{1,5}
potassium polyphosphate^{3,5}
sodium polyphosphate
sodium potassium polyphosphate
sodium tripolyphosphate
calcium pyrophosphate^{4,5}
tetrapotassium pyrophosphate⁴

¹New specifications were prepared.

²New "tentative" specifications were prepared.

³The existing specifications were revised.

⁴The existing specifications were maintained.

⁵Evaluated in this report.

Annex 5

MODIFIED STARCHES (including amylose and amylopectin)

acetylated distarch adipate ^{1,6}	(new information, new monograph)
acetylated distarch glycerol ^{4,7}	(new information, new monograph)
acetylated distarch phosphate ^{1,5}	(new information, new monograph)
acid-treated starches ^{1,5}	(new information, new monograph)
alkali-treated starches ^{1,5}	
amylose and amylopectin ¹	
bleached starches ^{1,5}	
dextrins, white and yellow ^{1,5}	(new information, new monograph)
distarch glycerol ^{4,7}	
distarch phosphate ^{1,5}	
enzyme-treated starches ^{1,8}	
hydroxypropyl distarch glycerol ^{4,7}	(new information, new monograph)
hydroxypropyl distarch phosphate ^{2,5}	(new information, new monograph)
hydroxypropyl starch ^{1,5}	(new information, new monograph)
monostarch phosphate ^{1,5}	
oxidized starch ^{2,5}	
phosphated distarch phosphate ^{1,5}	(new information, new monograph)
starch acetate ^{1,5}	(new information, new monograph)
starch sodium octenyl succinate ^{3,5}	(monograph)
starch sodium succinate ^{4,7}	

¹ ADI "not specified" (previously "not limited").

² ADI "not specified".

³ ADI "not specified" (not previously considered).

⁴ No ADI allocated.

⁵ Revised specifications were prepared.

⁶ Revised tentative specifications were prepared.

⁷ The existing tentative specifications were withdrawn.

⁸ The existing tentative specifications were maintained.

Annex 6

GUIDELINES FOR THE EVALUATION OF VARIOUS GROUPS OF FOOD ADDITIVES AND CONTAMINANTS

1. Enzyme preparations used in food processing

(a) *Toxicological evaluation*¹

For the purpose of toxicological evaluation, enzyme preparations used in food processing may be grouped into five major classes:

- (1) Enzymes obtained from edible tissues of animals commonly used as foods. These are regarded as foods and consequently considered acceptable provided satisfactory chemical and microbiological specifications can be established.
- (2) Enzymes obtained from edible portions of plants. These are also regarded as foods and consequently considered acceptable provided that satisfactory chemical and microbiological specifications can be established.
- (3) Enzymes derived from microorganisms that are traditionally accepted as constituents of foods or are normally used in the preparation of foods. These products are regarded as foods and consequently acceptable provided satisfactory chemical and microbiological specifications can be established.
- (4) Enzymes derived from nonpathogenic microorganisms commonly found as contaminants of foods. These materials are not considered as foods. It is necessary to establish chemical and microbiological specifications and to conduct short-term toxicity experiments to ensure the absence of toxicity. Each preparation must be evaluated individually and an ADI must be established.
- (5) Enzymes derived from microorganisms that are less well known. These materials also require chemical and microbiological specifications and more extensive toxicological studies, including a long-term study in a rodent species.

(b) *Specifications for identity and purity*²

Prior to revising existing specifications and developing new specifications for enzyme preparations for food processing, the following data are necessary:

- (1) A comprehensive description of the main enzymatic activity (or activities), including the Enzyme Commission number(s) if any.
- (2) A list of the subsidiary enzymatic activities, whether they perform a useful function or not.
- (3) A clear description of the source.
- (4) A list of non-enzymatic substances derived from the source material(s), with limits where appropriate.
- (5) A list of added co-factors, with limits where appropriate.
- (6) A list of carriers and diluents, with limits where appropriate.
- (7) A list of preservatives present from manufacture or deliberately added, with limits where appropriate.

¹ From WHO Technical Report Series, No. 617, 1978, pp. 8–9 (slightly modified).

² From WHO Technical Report Series, No. 631, 1978, pp. 9–10 (slightly modified).

2. Natural and synthetic food colours¹

For toxicological evaluation, natural colours should be considered as falling within three main groups:

- (1) A colour isolated in a chemically unmodified form from a recognized foodstuff and used in the foodstuff from which it is extracted at levels normally found in that food. This product could be accepted in the same manner as the food itself with no requirement for toxicological data.
- (2) A colour isolated in a chemically unmodified form from a recognized foodstuff but used at levels in excess of those normally found in that food or used in foods other than that from which it is extracted. This product might require the toxicological data usually demanded to assess the toxicity of synthetic colours.
- (3) A colour isolated from a food source and chemically modified during its production or a natural colour isolated from a non-food source. These products would also require a toxicological evaluation similar to that carried out for a synthetic colour.

It is recognized that natural colours may be reproduced by chemical synthesis but it is noted that "nature-identical" colours produced by chemical synthesis may contain impurities warranting toxicological evaluation similar to that required for a synthetically produced food colour.

The toxicological evaluation of synthetic food colours would require the following minimum data:

- (1) Metabolism studies in several species, preferably including man. These studies should include absorption, distributions, biotransformation, and elimination, and an attempt should be made to identify the metabolic products in each of these steps.
- (2) Short-term feeding studies in a non-rodent mammalian species.
- (3) Multigeneration reproduction/teratogenicity studies.
- (4) Long-term carcinogenicity/toxicity studies in two species.

3. Solvents used in food processing²

Extraction solvents are used *inter alia* in the extraction of fats and oils (including flavouring oils and oleoresins), defatting fish and other meals, and in decaffeinating coffee and tea. They are chosen mainly for their ability to dissolve the desired food constituents selectively and for their volatility, which enables them to separate easily from the extracted material with minimum damage. The points raised by their use relate to:

- toxicity of their residues;
- toxicity of any impurities in them;
- toxicity of substances such as solvent stabilizers and impurities that may be left behind after the solvent is removed; and
- toxicity of any substances produced as a result of a reaction between the solvent and food ingredients.

Before any extraction solvent can be evaluated, information is required on:

- (1) identity and amount of impurities in the solvent (including those that are

¹From WHO Technical Report Series, No. 617, 1978, pp. 6-8 (slightly modified).

²From WHO Technical Report Series, No. 648, 1980, pp. 10-12 (slightly modified).

- formed, acquired, or concentrated owing to continuous reuse of the solvent);
- (2) identity and amount of stabilizers and other additives; and
- (3) toxicity of residues of solvents, additives, and impurities.

Impurities are particularly important because there are wide differences in the purities of the food grade and industrial grade of solvents. The food use of extraction solvents is frequently much less than the industrial use, and hence their food-grade requirements may receive insufficient consideration both in food use and in toxicological testing. Furthermore, the impurities or stabilizers may not have the same volatility as the solvent itself, and as a result, these may be left behind in the food after the solvent is removed. Finally, the possibility of any solvent, impurity, stabilizer, or additive reacting with food ingredients should be checked.

When biological and toxicological data raise doubts about a substance's safety, two approaches are possible: (1) to set an ADI for the substance or (2) to discourage its use altogether. When data indicate a wide margin of safety for a substance, or when there is a paucity of toxicological data on the substance but no problems concerning the impurities, residues, and any chemical reaction with food ingredients, it would be appropriate to limit the use of the substance to the minimum possible level.

When the data on a substance indicate the presence of certain impurities in the tested material, considerable problems arise in its evaluation. This is especially true if industrial-grade rather than food-grade material has been used in the toxicological study. For example, when evaluating the solvent 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene, it has been noted that the toxicological data indicated the presence of certain known toxic and carcinogenic substances. The interpretation of these data became extremely difficult because the studies had used industrial-grade material. Only food-grade material should be used in toxicological studies and the impurities in the material should be fully identified.

Carrier solvents raise somewhat different issues. They are used for dissolving and dispersing nutrients, flavours, antioxidants, emulsifiers, and a wide variety of other food ingredients and additives. With the exception of carrier solvents for flavours, they tend to occur at higher levels in food than extraction solvents, mainly because frequently no attempt is made to remove them, and because some of them are relatively nonvolatile. Since carrier solvents are intentional additives and are often not removed from the processed food, it is important to evaluate their own safety along with the safety of any additives or stabilizers in them.

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