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Evaluation of certain food additives and contaminants

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

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World Health Organization, Geneva 1986

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

Toxicological evaluation of certain food additives
WHO Food Additive Series, No. 20

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. 34

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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

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

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Geneva, 3–12 June 1985

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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 3 to 12 June 1985. The meeting was opened by Dr J. Hamon, Assistant Director-General, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations, and of the World Health Organization. Dr Hamon briefly reviewed the history and the achievements of the Committee during its 29 years of activity. He pointed out that, since 1956, meetings of the Joint FAO/WHO Expert Committee had carried out systematic evaluations of food additives and contaminants. In addition to this task the Expert Committee had also made comments and issued recommendations on principles and methodology for testing and assessing chemicals in food. In so doing, the Committee had taken into account specific recommendations made by other WHO Scientific Groups.

Dr Hamon said that, at the present meeting, the Committee was requested to give comments and recommendations on a draft document on updating the principles of methodology for testing and assessing chemicals in food. This document outlined the project undertaken by the International Programme on Chemical Safety (IPCS) to implement the recommendations to study the "application of advances in methodology to the toxicological evaluation of food additives and contaminants" made in the twenty-fifth, twenty-sixth, and twenty-seventh reports of the Expert Committee. It was hoped that this project would clarify many of the issues that food regulatory authorities, in both developing and developed countries, faced when deciding about the safety of chemicals added to, and found in, food.

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,[1] there have been 28 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the twenty-eighth meeting (Annex 1, reference *66*). The tasks before the Committee were: (*a*) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological evaluations of them; (*b*) to review specifications for selected food additives; (*c*) to undertake toxicological evaluations and re-evaluations of certain food additives and contaminants; (*d*) to consider the methodology for testing and assessing chemicals in food; and (*e*) to discuss and provide advice on matters arising from the report of the seventeenth session of the Codex Committee on Food Additives.[2]

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

Mannitol was added to the agenda for toxicological evaluation only.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (Annex 1) and those established by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives[3] and the WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.[4] In addition, the Committee reaffirmed the need to take

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[1] *Joint FAO/WHO Conference on Food Additives.* FAO Nutrition Meetings Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

[2] CODEX ALIMENTARIUS COMMISSION. *Report of the Seventeenth Session of the Codex Committee on Food Additives, The Hague, 10–16 April 1984.* Rome, Food and Agriculture Organization of the United Nations. FAO document ALINORM 85/12 (1985), p. 119.

[3] WHO Technical Report Series, No. 348, 1967.

[4] WHO Technical Report Series, No. 546, 1974.

into consideration recent developments in toxicological techniques, as stated in its seventeenth report (Annex 1, reference *32*). The Committee also reviewed a draft document produced by the International Programme on Chemical Safety in response to the Committee's repeated recommendations (Annex 1, references *56, 59,* and *62*) to study "the application of advances in methodology to the toxicological evaluation of food additives and contaminants". When finalized this document would update several of the principles established at previous meetings of the Joint FAO/WHO Expert Committee on Food Additives (see section 5).

2.2.1 *Enzyme preparations*

Most of the microbial enzymes that were submitted to the Committee for evaluation are used in their immobilized form. The Committee therefore considered it appropriate to develop general principles for evaluating enzymes in their immobilized state, recognizing that consideration had to be given to the enzyme itself, the immobilizing agent, and the combination of the two.

After reviewing the principles developed previously for establishing the safety of microbial enzymes (Annex 1, references *26, 44, 47,* and *59*), the Committee endorsed the principles for dealing with microbial enzymes that are added directly to the substrate (Annex 1, reference *59,* page 49), but which are normally removed during subsequent processing of the product if good manufacturing practice is followed. Manufacturing processes that use immobilized enzyme systems are designed to prevent, as far as possible, the loss of enzyme into the substrate. Thus, when the Committee considered the type of safety data required for enzyme preparations, it took into account the low enzyme levels likely to be found in treated food. The setting of acceptable daily intakes (ADIs) for both the free and immobilized forms of an enzyme was also considered.

Testing requirements

In the case of an immobilized enzyme used in compliance with good manufacturing practice, the testing requirements may be less stringent than those required for the free enzyme because of the low residues that normally occur in food. Nevertheless, there should be adequate chemical and microbiological specifications that encompass non-viability and lack of toxin production for all immobilized enzymes. It would be acceptable to perform toxicity

studies on the immobilized enzyme preparation to assess the safety of the enzyme component, but studies would also be needed to establish the safety of the immobilizing agent.

Evaluation of microbial enzyme preparations

The Committee recognized that three separate situations must be considered with respect to the enzymes described in categories 4 and 5 of the guidelines for evaluating the toxicity of enzymes.[1] These situations are as follows:

(*a*) enzyme preparations added directly to the food but not removed;

(*b*) enzyme preparations added to the food but removed from the final product according to good manufacturing practice; and

(*c*) immobilized enzyme preparations that are in contact with food only during processing.

For (*a*) above, the Committee concluded that an acceptable daily intake (ADI) should be established to ensure that levels of the enzyme preparation present in food are safe. For (*b*), the Committee concluded that an ADI "not specified" may be established, provided that there is a large margin of safety between possible residues and their acceptable intake. For (*c*), the Committee concluded that it may not be necessary to set an ADI for enzyme residues that might occur in food as a result of using the immobilized form of the enzyme. The Committee endorsed the concept that immobilized enzymes are acceptable for use in food processing.

The Committee was aware that new techniques in genetic engineering could be used in the production of some enzyme preparations that are used in food processing. Evaluation of preparations containing enzymes produced by modified gene

[1] Full guidelines for evaluating enzyme preparations used in food processing are given in the twenty-sixth report of the Joint FAO/WHO Expert Committee (Annex 1, reference *59*, p. 49). Categories 4 and 5 of the guidelines for toxicological evaluation are reproduced below for ease of reference:

(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.

complexes might entail an expansion of some of the principles enunciated by the Committee in its twenty-sixth report. New guidelines will be developed as such enzyme preparations are brought to the attention of the Committee.

Immobilizing agents

The Committee was informed that a number of procedures involving different chemical substances are used to immobilize enzymes. These procedures include microencapsulation (e.g., entrapment in gelatin), addition of glutaraldehyde, entrapment in a porous ceramic carrier, and formation of complexes with agents such as diethylaminoethyl cellulose or polyethylenimine. Several agents may be used in the immobilizing process.

Substances derived from the immobilizing agent may be found in the final food product if it contains impurities or if the immobilized enzyme system breaks down, but the levels of residue are normally extremely low.

Safety data will be required for the immobilizing agent, the type of data depending on the chemical nature of the substance. Some of the substances used to prepare immobilized enzyme systems are extremely toxic. The levels of these substances, or their toxic contaminants, permitted in the final product should be as low as technically feasible, and must be below levels that cause toxicological concern. ADIs will not be established for immobilizing agents.

2.2.2 *Inorganic and organic acids and their salts*

The Committee evaluated a list of food salts referred to it by the Codex Committee on Food Additives (see section 3.4. for details).

The Committee had in the past evaluated a large number of food acids and salts, and was of the opinion that ADIs for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions (Annex 1, references *11* and *50*). Therefore, in order to aid future evaluations of ionizable salts, the Committee prepared Table 1, which gives acceptable daily intakes for a large number of combinations of cations and anions.

The ADIs listed in Table 1 are indicative of the general level of safety of the main classes of salts. Evaluations of specific salts may result in ADIs that differ from those listed in the table. In such cases, the results of evaluations of the individual salts supersede the ADIs

Table 1. Acceptable daily intake for various anions and cations[1]

Cations	Anions	Acceptable daily intake (ADI)	References
Aluminium (*59*)[a]	Acetate[g]	Not specified	*11, 32*
Ammonium (*11,50*)[b]	Adipate[g]	0–5 mg/kg body wt	*11, 44*
Calcium (*11,50*)[c,d]	Caprate	Not specified	
Iron (*62*)[e]	Caprylate	Not specified	
Magnesium (*11,50*)[f]	Carbonate	Not specified	*11, 59*
Potassium (*11,50*)[b]	Chloride[d,g]	Not specified	*11, 50*
Sodium (*11,50*)[b,d]	Citrate[g]	Not specified	*7, 13, 32*
	Fumarate[g]	0–6 mg/kg body wt	*11, 35*
	Gluconate[g]	0–50 mg/kg body wt	*13, 35, 50*
	Guanylate[g]	Not specified	*35*
	Hydrogen carbonate	Not specified	*11, 50, 59*
	Inosinate[g]	Not specified	*35*
	Laurate	Not specified	
	D,L-malate[g,h]	Not specified	*11, 13, 50*
	Myristate	Not specified	*19, 32*
	Oleate	Not specified	
	Palmitate	Not specified	*19, 32*
	Phosphate[d,g]	70 mg/kg body wt[e]	*59*
	Silicate[g]	Not specified[i]	*19, 32*
	Sorbate[g]	0–25 mg/kg body wt	*32*
	Stearate	Not specified	*19, 32*
	Succinate	Not specified	
	Sulfate[f]	Not specified	*47*
	Sulfite[j]	0–0.7 mg/kg body wt	*32, 62*

[1] This table consolidates information presented in a previous report (Annex 1, reference *50*) as well as information about compounds referred to the present Committee; the table applies only to the compounds for which the Committee has developed specifications.

[a] Temporary ADI of 0–6 mg/kg of body weight for sodium aluminium phosphate should be expanded to include all added aluminium salts and the ADI should be based on the aluminium content (0–0.6 mg/kg).

[b] No restriction provided that the contribution made to food is assessed and considered acceptable.

[c] Maximum tolerable daily intake allocated was 70 mg/kg of body weight (expressed as phosphorus) which applies to the sum of phosphates and polyphosphates in food. In the case of calcium salts, the Expert Committee had previously expressed concern about the calcium/phosphorus ratio in the diet and the desirability of maintaining nutritionally sound ratios (Annex 1, reference *59*).

[d] For use in infant foods (Annex 1, reference *26*, sections 3.4 and 5.4 in Annex 3).

[e] Provisional maximum tolerable intake for iron of 0.8 mg/kg of body weight per day applies to iron from all sources except for iron oxides used as colouring agents, supplemental iron taken during pregnancy and lactation, and supplemental iron for specific clinical requirements.

[f] Intake limited by laxative action.

[g] Also includes the free acids.

[h] Not to be added to the diet of very young infants.

[i] See recommendations on sulfite given in the seventeenth and twenty-seventh reports of the Committee (Annex 1, references *32* and *62*, respectively).

[j] An ADI was not specified because these salts are insoluble in water and are not expected to provide a significant level of available silicate to the diet. Asbestiform fibres would be subject to special consideration (Annex 1, reference *41*).

for the main classes of salt. For example, no information was available to the present Committee to indicate whether certain salts that were under review are being manufactured or used as food-grade materials and therefore, even though ADIs have been

allocated to the classes of salt to which these chemicals belong (as indicated in Table 1), no ADIs could be allocated to the specific salts.

With respect to the cations ammonium, calcium, potassium, and sodium, the Committee concurred with the ninth report (Annex 1, reference *11*) in placing no restrictions on their use, provided that their contribution to the diet is assessed and considered acceptable. In the case of calcium salts, the desirability of maintaining nutritionally sound ratios of calcium and phosphorous in the diet was stressed in accordance with the twenty-sixth report (Annex 1, reference *59*). The Committee agreed with the recommendations concerning the use of sodium chloride and calcium phosphate salts in infant foods given in the fifteenth report (Annex 1, reference *26*).

The Committee had specific reservations about the use of aluminium and magnesium salts, as discussed below.

(a) Cations

Aluminium. The Committee has previously expressed concern about the use of aluminium salts (Annex 1, reference *59*). These were that there was (*a*) insufficient information on the aluminium content of the diet, and (*b*) a need for additional safety data including absorption and metabolic studies in man, short-term feeding studies, and a multigeneration reproduction study. The Committee was informed that information on levels of aluminium in the diet is limited. Reported levels range from a few mg to 100 mg/day. However, with the refinement of analytical methods, more meaningful data are being obtained.

Limited new information was presented on the absorption of ingested aluminium. In one recent study in man, in which the levels of dietary aluminium were of the same order as that reported in food, some absorption occurred which resulted in a very slight increase in serum aluminium levels and increased excretion in the urine. No accumulation in tissue was reported, since all the administered aluminium was recovered in the urine and faeces. The Committee noted that (*a*) accumulation of aluminium ions is increased in individuals with chronic renal diseases and that their intake of aluminium should therefore be reduced; (*b*) aluminium has been implicated in the etiology of certain neurotoxic disorders, but definitive studies relating diet to these conditions are lacking; and (*c*) other dietary factors, such as citrate, phosphate, and fluoride, affect

the absorption of aluminium. The studies requested by the Committee in 1982 (Annex 1, reference *59*) had not been submitted. The Committee concluded that the temporary ADI of 0–6 mg/kg of body weight (equivalent to 0–0.6 mg/kg of body weight expressed as aluminium) allocated to sodium aluminium phosphate until its review in 1986 should be used for all aluminium salts added to food. The Committee also recommended that aluminium be subjected to a detailed review at a future meeting.

Magnesium. Magnesium is an essential ion that occurs in a wide range of foods. The estimated daily intake ranges from 180 to 480 mg/day. The recommended daily dietary requirement is 50–250 mg/day for infants, and 200–350 mg/day for adults.[1,2]

The Committee was concerned that the use of magnesium salts as food additives may have a laxative effect. The effect may be caused by osmotic absorption of water into the intestinal lumen or, more likely, by release of the gastrointestinal hormone cholecystokinin-pancreozymin, which stimulates motor and secretory activity in the gastrointestinal tract. The minimum effective dose is approximately 1000 mg of the magnesium moiety in the magnesium salt; however, the laxative effect is observed only when the magnesium salt is administered as a single dose. It is not known whether lower doses have other effects on hormonal activity. It was also noted that infants are particularly sensitive to the sedative effects of magnesium salts, and that individuals with chronic renal impairment retained 15–30% of administered magnesium, which could cause toxicity problems. The Committee concluded that the use of magnesium salts as food additives is acceptable provided that the above caveats are taken into consideration.

Iron. Iron compounds were considered by the Committee in 1983 (Annex 1, reference *62*), when a provisional maximum tolerable daily intake of 0.8 mg iron/kg of body weight was established. The Committee reiterated its view that "this evaluation applies to iron from all sources except for iron oxides and hydrated iron oxides used as colouring agents and iron supplements taken during pregnancy

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[1] *Recommended dietary allowances,* revised edition. Washington, DC, National Academy of Sciences, 1980.

[2] *Handbook of human nutritional requirements.* Geneva, World Health Organization, 1974 (Monograph series, No. 61).

and lactation or for specific clinical requirements" (Annex 1, reference *62*).

(b) Anions (acids)

Fatty acids. The Committee has previously established ADIs "not specified" for myristic, palmitic, and stearic acids. The Committee extended the list of acceptable fatty acids to include capric, caprylic, lauric, and oleic acids. Their safety is based on their occurrence in edible fats and oils that have a long history of use as foods or food components. In addition, the even-chain fatty acids from C_4 to C_{18} have been shown to undergo oxidation to give acetoacetic acid and ketone bodies. The metabolic products are utilized and excreted.

Succinates. Succinic acid is a natural constituent of plants and animals that are commonly used as food. Experimental animals can tolerate high dietary concentrations of succinic acid. Succinic acid does not represent a hazard at the levels at which it is likely to be used as a food additive because of its normal role in metabolism. An ADI "not specified" was established for the succinate moiety.

Sulfates. Sulfates are natural constituents of food and are products of sulfur metabolism in animals. There is no information to suggest that their use as food additives has any toxic effects at normal dietary exposure. An ADI "not specified" was established for the sulfate moiety.

The other acids in Table 1 have been previously considered and ADIs established. The Committee concluded that their use would be safe, based on the information provided in Table 1.

2.2.3 *Limitation of the ADI imposed by lack of observed toxicity*

A number of food additives do not produce adverse effects in feeding studies, even when the maximum possible amount that is consistent with reasonable nutrition is added to the diet; the only effects arise from the physical properties of the additives, such as their bulk and hydrophilic properties. In such cases, the application of the conventional safety factor of 100 to the no-effect level obtained from a feeding study provides an ADI that underestimates the amount of additive that could be safety ingested by human consumers.

The Committee suggested that information on the following should be considered when evaluating such food additives: (*a*) the chemical nature of the compound and its impurities; (*b*) its absorption, distribution in tissues, metabolism, and elimination; (*c*) the nature of any biological effects that it exerts; (*d*) previous uses, particularly those pertaining to oral ingestion in food or its use as a drug; and (*e*) proposed patterns of use as a food additive. Human studies, which should be performed only if extensive safety tests in animals suggest that it is safe to do so, may permit the use of a lower safety factor than that used for data obtained from animal experiments.

As a first step to encourage additional studies, the Committee could approve a temporary ADI at a higher level than that obtained by the application of the usual safety factor, with the understanding that work will be undertaken to provide additional information. However, the application of this principle should not result in the unrestricted use and abuse of such materials in food.

The Committee understood that the above issues would be considered in more detail in a monograph on the principles for assessing the safety of chemicals in food being prepared following previous recommendations of the Committee (see section 5).

2.2.4 *Vegetable gums*

The Committee noted that vegetable gums such as gum ghatti and dammar gum are produced in many developing countries. Though these gums have many uses as food additives, for example as thickening agents, not all of them have been toxicologically cleared, principally because of the lack of adequate information.

The Committee recommended that international organizations should seek ways and means of assisting developing countries to generate the information needed to evaluate these substances.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *The need for sufficient data*

The Committee had on its agenda substances for which the Codex Committee on Food Additives, at its seventeenth session, had requested a review. The Committee reviewed these substances but,

because of inadequate information, was unable to establish specifications for those listed below.

— Substances for which no specifications exist and for which no information was submitted regarding their manufacture as food grade materials.

Ammonium succinate	Magnesium succinate
Calcium adipate	Monomagnesium phosphate
Calcium fumarate	Oat gum
Calcium hydrogen carbonate	Potassium aluminosilicate
Calcium oleate	Potassium fumarate
Calcium succinate	Potassium succinate
Magnesium acetate	Sodium aluminium polyphosphate
Magnesium adipate	Sodium sorbate[1]
Magnesium citrate	

— Substances for which specifications exist but which have no known food use.

Aluminium salts of fatty acids	Potassium caprate
Ammonium polyphosphates	Potassium caprylate
Calcium aluminium silicate	Potassium laurate
Calcium caprate	Potassium oleate
Calcium caprylate	Sodium caprate
Calcium laurate	Sodium caprylate
Calcium polyphosphates	Sodium laurate
Diethyleneglycol mono(methyl ether)	Sodium oleate
Magnesium salts of fatty acids	

[1] See also section 3.4

3. COMMENTS ON SPECIFIC FOOD ADDITIVES

3.1 Enzyme preparations and enzyme immobilizing agents

Carbohydrase (a-amylase) from Bacillus licheniformis

The enzyme preparation derived from *Bacillus licheniformis* is added directly to the food to be processed and then removed from the final product by filtration. The preparation showed no significant toxicological effects in short-term feeding studies in rats (at levels of up to 40 g/kg of feed) and in dogs (at levels of up to 20 g/kg of feed). No teratogenic effects were noted in a study in rats. The preparation was also inactive in dominant lethal tests in rats and mice. An ADI "not specified" was established in accordance with the principles

stated in section 2.2.1. A toxicological monograph was prepared. The existing specifications were revised.

Glucose isomerase (immobilized) from Actinoplanes missouriensis

This enzyme preparation consists of whole non-viable cells that are entrapped in gelatin and cross-linked with glutaraldehyde to form an immobilized complex. A short-term study in rats that included a single-generation reproduction study, and a short-term study in dogs, showed that the non-immobilized preparation had no significant toxicological effects at a level of 10 g/kg of feed. The Committee was not aware of the use of the non-immobilized preparation in food processing; however, since the use of gelatin as an entrapping agent does not present a toxicological problem, the Committee concluded that the studies on the non-immobilized form are appropriate for evaluating the immobilized form. The release of free glutaraldehyde from the enzyme preparation is controlled by the specifications for the preparation established by the Committee. On the basis of these considerations, the Committee concluded that this enzyme preparation is acceptable for use in food processing when used in an immobilized system in accordance with the principles stated in section 2.2.1. A toxicological monograph was prepared. The existing specifications were maintained.

Glucose isomerase from Bacillus coagulans

Non-immobilized enzyme. This enzyme preparation consists of whole non-viable cells. The preparation showed no toxicological effects in short-term feeding studies in rats and dogs at levels of 50 g/kg of feed. The available toxicity data meet the requirements for evaluation as stated in section 2.2.1. However, the Committee was informed that no information was available on the use of this enzyme, so an ADI was not established. No toxicological monograph was prepared. Existing specifications were maintained.

Immobilized enzyme. This enzyme preparation consists of whole non-viable cells that have been immobilized with glutaraldehyde; calcined alumina may be added to adjust the physical properties of the material. Short-term feeding studies of the immobilized enzyme have been carried out in rats and dogs, as well as teratogenicity studies in rats and rabbits, and reproduction and dominant lethal tests in rats. No toxicological effects were seen in rats and dogs at

levels of 50 g/kg of feed. The release of free glutaraldehyde from the enzyme preparation is controlled by the specifications for the preparation established by the Committee. The Committee concluded that this enzyme is acceptable for use in food processing when used in an immobilized system in accordance with the principles stated in section 2.2.1. A toxicological monograph was prepared. The existing specifications were maintained.

Glucose isomerase (immobilized) from Streptomyces olivaceus

This enzyme preparation consists of cells immobilized by the addition of glutaraldehyde to the culture broth. Reproduction and short-term feeding studies in rats and a short-term feeding study in dogs showed no compound-related effects at levels of up to 60 g of immobilized enzyme per kg of feed. The release of free glutaraldehyde from the enzyme preparation is controlled by the specifications for the preparation established by the Committee. The Committee concluded that this enzyme is acceptable for use in food processing when used in an immobilized system in accordance with the principles stated in section 2.2.1. A toxicological monograph was prepared. The existing specifications were maintained.

Glucose isomerase (immobilized) from Streptomyces olivochromogenes

This semi-purified enzyme preparation is immobilized by entrapment in a porous ceramic carrier. Toxicity studies were carried out with non-immobilized whole cells harvested after the addition of Perlite (fused sodium potassium aluminium silicate) to the culture medium. Control studies of Perlite were also carried out. No treatment-related changes were reported when rats were maintained for 90 days on diets containing up to 100 g of the cell preparation per kg of feed. In a study in dogs (90 days) using the same cell preparation at the same dietary levels, there was a significant reduction in the body weight of animals maintained on the highest dietary level of the preparation (100 g/kg of feed); no treatment-related changes were reported at levels of 30 g/kg of feed. The Committee concluded that this enzyme is acceptable for use in food processing when used in an immobilized system in accordance with the principles stated in section 2.2.1. A toxicological monograph was prepared. The existing specifications were maintained.

Glucose isomerase from Streptomyces rubiginosus

Non-immobilized enzyme. The results of short-term studies in rats and dogs, a reproduction and teratogenicity study in rats, and a teratogenicity study in rabbits were available for the Committee to review. In all these studies the free enzyme was incorporated into the diet. The no-effect level of the enzyme was 20 g/kg of feed in rats and dogs. The available data meet the requirements for setting an ADI as stated in section 2.2.1. However, the Committee was informed that no information was available on the use of the free enzyme, so no ADI was established. A toxicological monograph was prepared. Existing specifications were revised.

Immobilized enzyme. The enzyme is complexed with diethylaminoethyl cellulose to produce the immobilized form. The results of short-term studies in rats and dogs, a reproduction and teratogenicity study in rats, and a teratogenicity study in rabbits were available. No significant compound-related effects were noted in any of these studies at levels of 12.5 g/kg of feed. The Committee concluded that this enzyme is acceptable for use in food processing when used in an immobilized system in accordance with the principles stated in section 2.2.1. A toxicological monograph was prepared. Existing specifications were revised.

Polyethylenimine and ethylenimine

Polyethylenimine is produced by the acid-catalysed homopolymerization of ethylenimine. It is used as an immobilizing agent for the production of enzyme preparations used in food processing, and may enter the food supply as a result of leaching. In addition, polyethylenimine may contain residues of ethylenimine which can enter the food during processing. Ethylenimine is also used in the manufacture of food packaging materials and can migrate from packages into food.

The Committee reviewed short-term studies in rats and dogs maintained for approximately 9 months on a diet containing up to 1.0 g of polyethylenimine per kg of body weight. No adverse effects were observed in rats, but in dogs compound-related changes were observed in the kidney and liver at all dose levels tested, although these were minimal in the animals receiving low doses of polyethylenimine (0.25 g/kg body weight). Polyethylenimine that was claimed to be free of ethylenimine was not mutagenic in the

Ames test, with or without activation. However, samples containing measurable amounts of ethylenimine showed mutagenic activity.

The Committee also reviewed studies of ethylenimine. Ethylenimine was shown to be mutagenic in *Drosophila, Neurospora,* and *Salmonella,* and chromosomal aberrations occurred in cultured mammalian cells. It was carcinogenic in two strains of mice, the liver and lung being the major target organs in both sexes of both strains. Subcutaneous administration to rats and mice produced sarcomas, particularly at the injection site. Ethylenimine was also nephrotoxic in rabbits, dogs, and rats.

The Committee was informed that the risk of human dietary exposure to either polyethylenimine or ethylenimine is extremely low. The Committee did not establish an ADI for either polyethylenimine or ethylenimine. The Committee considered polyethylenimine to be a suitable substance for use as an immobilizing agent in the production of immobilized-enzyme preparations. In keeping with previous recommendations on carcinogenic substances migrating from packaging into foods (Annex 1, reference *66*), as well as the present consideration of immobilized enzyme preparations, the Committee accepted the use of polyethylenimine as an immobilizing agent on condition that the amount of ethylenimine migrating into food from immobilized enzyme preparations is reduced to the lowest level technically possible. A toxicological monograph was prepared on both compounds. The Committee prepared a new general method of analysis that can be used to ensure that there is no more than 0.1 mg/kg of ethylenimine in immobilized enzyme preparations.

3.2 Flavouring agents

Benzyl acetate

This compound was previously reviewed at the twenty-seventh meeting of the Expert Committee in 1983 (Annex 1, reference *62*). The Committee considered new information on the metabolism of benzyl acetate in rats and mice, as well as revised data on the occurrence of tumours in lifetime studies in the same species in which the substance was administered by gavage. The Committee was unable to come to a decision on this compound using the available information. The Committee was aware that the results of lifetime studies with benzyl alcohol (a normal metabolite of benzyl acetate)

will be available in 1987, and that a new study of benzyl acetate incorporated into the diet of rats and mice is planned. The Committee extended the temporary ADI of 0–5 mg/kg of body weight until 1987, pending evaluation of the benzyl alcohol study. No toxicological monograph was prepared. The existing specifications were maintained.

3.3 Flour treatment agents

Chlorine

Chlorine, as a flour treatment agent for special-purpose flours, was reviewed at the ninth meeting of the Committee (Annex 1, reference *11*) but an acceptable level of use was not established. At this earlier review, it was concluded that "long-term studies using appropriate products made from flour treated with chlorine at various levels will be needed". Since that time the results of further studies have become available in which large amounts of chlorinated flour, or cakes made from such flour, were included in the diet of test animals. These studies included four long-term studies (two in mice and two in rats) and a multigeneration reproduction/teratogenicity study.

In the long-term and reproduction studies, 75–79% of the diet consisted of dried cakes made from flour chlorinated at levels of up to 25 g/kg. No carcinogenic, teratogenic, or other toxic effects attributable to chlorination were seen.

The Committee concluded that, when restricted to use in cake flour, the use of chlorine at levels of up to 2.5 g/kg flour would be acceptable. A toxicological monograph was prepared. The existing specifications for chlorine were maintained.

3.4 Food acids and their salts

Aluminium ammonium sulfate

Aluminium salts were previously reviewed by the Committee in 1982 (Annex 1, reference *59*). The Committee reviewed the limited information available on the levels of aluminium in the diet and the data on absorption of ingested aluminium. It was noted that aluminium has been implicated in certain neurological disorders in man, but definitive studies relating diet to these disorders are

lacking. It was pointed out that the ADI did not take into account the fact that individuals with renal impairment should restrict their intake of aluminium. In 1982 the Committee established a temporary ADI of 0–0.6 mg of aluminium per kg of body weight, pending the assessment of sodium ammonium sulfate to be completed by 1986. The total intake of aluminium from aluminium salts should not exceed this figure. No toxicological monograph was prepared. New specifications were prepared.

Aluminium, calcium, magnesium, potassium, and sodium salts of capric, caprylic, lauric, myristic, oleic, palmitic, and stearic acids

The Committee noted that fatty acids are normal constituents of coconut oil, butter, and other edible oils, and that the use of calcium, potassium, and sodium salts of capric, caprylic, lauric, and oleic acids does not represent a toxicological problem. The toxicological problems relating to aluminium and magnesium salts of these fatty acids were considered (see section 2.2.2). The Committee had no information about the manufacture or use of the food-grade materials. Thus, no ADIs were established. Table 1 in section 2.2.2 provides information for assessing acceptable daily intakes for these salts. No toxicological monograph was prepared.

The Committee had previously established tentative specifications for all the fatty acids given in the above heading at its twenty-eighth meeting (Annex 1, reference *66*). However, no further information has been received since then by which the Committee could establish full specifications. The Committee revised the tentative specifications for the calcium, potassium, and sodium salts of myristic, palmitic, and stearic acids and deleted the "tentative" qualification. The specifications for aluminium, calcium, magnesium, potassium, and sodium salts of capric, caprylic, lauric, and oleic acids were withdrawn. Specifications were not prepared for aluminium and magnesium salts of myristic, palmitic, and stearic acids.

Ammonium, calcium, magnesium, and potassium salts of succinic acid

Succinic acid is a natural constituent of plants and animals used as food. The biological role of succinic acid as an intermediary metabolite indicates that the levels at which it is likely to be used in food would not represent a hazard. The Committee had no

information about the manufacture or use of the food-grade materials. Thus, no ADIs were established. Table 1 in section 2.2.2 provides information for assessing acceptable daily intakes for these salts. No toxicological monograph was prepared. No specifications were prepared.

Calcium and magnesium salts of adipic acid

The Committee noted that adipic acid had been previously evaluated and an ADI of 0–5 mg/kg of body weight (based on the free acid) established (Annex 1, references *11* and *44*). The Committee had no information about the manufacture or use of the food-grade materials. Thus, no ADIs were established. Table 1 provides information for assessing acceptable daily intakes. No toxicological monograph was prepared. No specifications were prepared.

Calcium aluminium silicate

The Committee had on its agenda aluminium calcium silicate, but was informed that this substance is properly known as calcium aluminium silicate. This compound was previously evaluated at the seventeenth meeting of the Committee (Annex 1, reference *32*). The present Committee took into account the insolubility of this compound when evaluating its safety. The previous ADI "not limited" for certain silicates (aluminium, calcium, and sodium aluminosilicate) was changed to ADI "not specified". No toxicological monograph was prepared. The existing specifications were maintained.

Calcium and potassium salts of fumaric acid

Fumaric acid was previously evaluated by the Committee at its eighteenth meeting, when an ADI of 0–6 mg/kg of body weight was established (Annex 1, reference *35*). Its safe use is based on its occurrence as a natural metabolite, as well as on the results of lifetime feeding studies in rats. The Committee had no information about the manufacture or use of the food-grade materials. Thus, no ADIs were established. Table 1 in section 2.2.2 provides information for assessing acceptable intakes. No toxicological monograph was prepared. No specifications were prepared.

Calcium hydrogen carbonate

The Committee considered available information on other calcium and hydrogen carbonate salts and agreed that these moieties do not pose a toxicological hazard. The Committee had no information about the manufacture of calcium hydrogen carbonate or use of the food-grade material. Thus, no ADI was established. Table 1 in section 2.2.2 provides information for assessing an acceptable daily intake. No toxicological monograph was prepared. No specifications were prepared.

Ferric ammonium citrate

The evaluation is based on information provided in Table 1 in section 2.2.2 and takes into account the provisional maximum tolerable intake of iron of 0.8 mg/kg of body weight per day and the recommended daily intake of iron for man of 10–20 mg/day (Annex 1, reference *62*). The use of ferric ammonium citrate should be encompassed within the maximum tolerable intake of iron salts. No toxicological monograph was prepared. The existing specifications were maintained.

Guanylic acid, inosinic acid, and their dipotassium salts

Calcium and disodium salts of guanylic acid and inosinic acid were previously evaluated at the eighteenth meeting of the Expert Committee (Annex 1, reference *35*), when an ADI "not specified" was established for each salt. The use of the free acids or their dipotassium salts instead of the calcium or disodium salts does not introduce any new toxicological problems (Table 1). The group ADIs "not specified" were extended to cover the free acids and their dipotassium salts. No toxicological monograph was prepared. New specifications were prepared for each substance.

Magnesium acetate and magnesium citrate

The Committee had no information about the manufacture or use of the food-grade materials. Thus, no ADIs were established. Table 1 provides information for assessing an acceptable daily intake for these salts. No toxicological monograph was prepared. No specifications were prepared.

Monomagnesium phosphate

The Committee had no information about the manufacture or use of the food-grade material. Thus, no ADI was established. Table 1 provides information for assessing an acceptable daily intake. No toxicological monograph was prepared. No specifications were prepared.

Potassium aluminosilicate

Sodium aluminosilicate was evaluated at the seventeenth meeting of the Committee (Annex 1, reference *32*). The previously established ADI "not limited" was changed by the present Committee to ADI "not specified". The use of the potassium salt instead of the sodium salt does not introduce any new toxicological problems. The Committee had no information about the manufacture or use of the food-grade material. Thus, no ADI was established. Table 1 provides information for assessing an acceptable daily intake. No toxicological monograph was prepared. No specifications were prepared.

Potassium sulfate

Sulfates are natural constituents of food and are end-products of sulfur metabolism. There is no information to suggest any toxic effects at normal dietary exposure. The use of the potassium salt instead of the sodium salt does not introduce any new toxicological problems (Table 1). The Committee established an ADI "not specified". No toxicological monograph was prepared. New specifications were prepared.

Potassium sulfite

The use of the potassium salt instead of the sodium salt does not introduce any new toxicological problems (Table 1). The Committee was aware that some asthmatic individuals have been shown to be sensitive to sulfite. However, there is little evidence of non-asthmatics showing sulfite sensitivity after ingesting food treated with sulfiting agents. Thus, for the majority of the population, there does not appear to be any hazard. The problem of allergenicity of food additives was previously considered at the seventeenth and twenty-seventh meetings of the Expert Committee (Annex I, references *32* and *62*). The Committee recommended that potassium

sulfite should be included in the list of sulfiting agents, for which a group ADI of 0–0.7 mg/kg of body weight expressed as sulfur dioxide has been previously established (Annex I, references *32* and *62*). No toxicological monograph was prepared. New specifications were prepared.

Sodium aluminium polyphosphate

The Committee had no information about the manufacture or use of the food-grade material. Thus, no ADI was established. Table 1 provides information for assessing an acceptable daily intake. No toxicological monograph was prepared. No specifications were prepared.

Sodium sorbate

The Committee evaluated sorbic acid at its seventeenth meeting (Annex 1, reference *32*) and allocated a group ADI of 0–25 mg/kg of body weight for sorbic acid and its calcium and potassium salts. The use of the sodium salt instead of the calcium or potassium salts does not introduce any new toxicological problems. The Committee had no information on the commercial manufacture of food-grade sodium sorbate, but was aware that solutions of sorbic acid neutralized with sodium alkali are prepared (using food-grade raw materials) by food producers for use *in situ*. The group ADI for sorbic acid and its calcium and potassium salts was extended to cover the sodium salt. No toxicological monograph was prepared. No specifications were prepared.

3.5 Food colours

Brown FK

Brown FK was evaluated and a monograph prepared at the twenty-first meeting of the Committee (Annex 1, reference *44*). At that time it was noted that, in long-term studies in mice, the colour produced hepatic nodules and tissue pigmentation, and that some of its metabolites were myotoxic. The reproduction/teratogenicity studies were inadequate and no ADI could be established.

The Committee considered new data, including a long-term carcinogenicity study and multigeneration reproduction/teratogenicity studies in rats. The carcinogenicity study did not

reveal any increase in the incidence of tumours. The myopathy seen in rats given high doses of Brown FK in short-term studies affects all striated muscle, is accompanied by pigment deposition, and is dose-dependent with a high threshold. In long-term studies in rats there was no compound-specific myopathy and there was no pigmentation in animals in the low-dose group or the controls. However, the Committee considered that the histopathological examination of the low and intermediate dose groups was inadequate to evaluate possible toxic effects of Brown FK.

The reproduction/teratogenicity studies did not reveal any adverse effects on reproductive function.

On the basis of pigment accumulation in the tissues, a temporary ADI of 0–0.075 mg/kg of body weight was allocated to Brown FK until 1986. The Committee requested that the results of a complete histological examination of the low and intermediate dose groups in the long-term study be made available. A new toxicological monograph was prepared. New specifications were prepared.

Caramel colours

In the period since 1972, when the fifteenth report of the Committee was published (Annex I, reference *26*), caramel colours have been classified into four classes which differ in their methods of manufacture, composition, functional properties, and application.

— Caramel colour I (synonyms: plain caramel, caustic caramel, and spirit caramel); this class is prepared by the controlled heat treatment of carbohydrates with alkali or acid.
— Caramel colour II (synonym: caustic sulfite process caramel); this class is prepared by the controlled heat treatment of carbohydrates with sulfite-containing compounds.
— Caramel colour III (synonyms: ammonia caramel and beer caramel); this class is prepared by the controlled heat treatment of carbohydrates with ammonium compounds.
— Caramel colour IV (synonyms: ammonia sulfite caramel and soft-drink caramel); this class is prepared by the controlled heat treatment of carbohydrates with ammonium-containing and sulfite-containing compounds.

Caramel colour I. Caramel was evaluated at the thirteenth and fifteenth meetings of the Committee (Annex 1, references *19* and *26*),

when it was concluded that "with the exception of those caramels prepared by using ammonia or ammonium salts, caramel and caramel colours are natural constituents of the diet and are acceptable as additives"; an ADI "not limited" was allocated.

The present Committee was informed that some materials now classified as caramel colour I may contain sulfur compounds at levels which would not be expected to arise from the carbohydrate starting materials. However, the Committee allocated an ADI "not specified" to caramel colour I, provided that it complies with the revised tentative specifications. The existing specifications were revised and maintained as tentative.

Caramel colour II. The Committee concluded that caramel colour II was sufficiently different from other classes of caramel to warrant a separate evaluation, but that there were insufficient data on its toxicology and chemical composition to do so. No ADI was established. New tentative specifications were prepared.

Caramel colour III. Ammonia caramel was last evaluated at the twenty-first meeting of the Committee (Annex 1, reference *44*), when the principal toxic effect was found to be a depression of circulating lymphocytes. As a no-effect level for this could not be established, the previous temporary ADI was revoked. Since the previous evaluation further studies have been carried out and were considered by the present Committee.

The lymphocyte depression caused by caramel colour III has been shown to be due largely, if not solely, to a minor component, 2-acetyl-4(5)-tetrahydroxybutylimidazole (THI). Comparisons of the lymphocyte-depressing activity of pure THI with that of a batch of caramel colour III containing a known level of THI indicated that other components of the colouring had little effect. The lymphocyte depression caused by caramel colour III was shown to be ameliorated by dietary pyridoxine since it was not seen in animals given caramel colour III containing THI at levels of 10 mg/kg (15 mg/kg on a solids basis) if the dietary levels of pyridoxine were adequate (some of the earlier studies had been performed on diets low in pyridoxine). However, since the low THI caramel colours had not been assayed in animals fed diets low in pyridoxine direct comparisons with some earlier studies were not possible. Studies

with caramel colour III containing a range of THI levels and lower levels of dietary pyridoxine to confirm that THI is the sole agent responsible for depressing lymphocyte counts and to establish a no-effect level for THI are considered desirable.

Mutagenicity tests were negative or equivocal, and the long-term carcinogenicity studies in rats and mice indicated that caramel colour III is not carcinogenic at dose levels of up to 40 g/litre of drinking-water, which was also the no-toxic-effect level.

Because it was not possible to assess caramel colour III at levels higher than 40 g/litre of drinking-water in long-term studies and because the effect of most concern, i.e., lymphocytopenia, could best be evaluated from short-term studies, the Committee based its evaluation on the no-effect level of 20 g/kg of body weight (the highest level tested) in a 90-day study of rats given caramel colour III that contained about 10 mg/kg THI (15 mg/kg on a solids basis). An ADI of 0–200 mg/kg of body weight (0–150 mg/kg of body weight on a solids basis) was allocated to caramel colour III which complies with the revised tentative specifications. Existing specifications were revised, but maintained as tentative.

Caramel colour IV. Ammonia sulfite caramel was evaluated at the twenty-first meeting of the Committee (Annex 1, reference *44*), when the temporary ADI of 0–100 mg/kg of body weight was retained pending adequate carcinogenicity/teratogenicity studies. At that time 4-methylimidazole, a contaminant of ammoniated caramel colourings, was considered. The report stated that "Although 4-methylimidazole is no longer considered to be a concern and the introduction of chemical specifications had limited its concentration, the Committee decided to maintain the limit for this substance in specifications to indicate good manufacturing practice". At the twenty-fourth meeting (Annex 1, reference *53*), the Committee drew attention to the need for adequate specifications for caramel colour IV and for a long-term study of carcinogenicity. The temporary ADI was extended pending the results of long-term toxicity studies. Since then, further studies have been performed and were evaluated by the present Committee.

Carcinogenicity studies have been conducted in rats and mice, and no treatment-related neoplastic changes were observed. In the most recent long-term toxicity/carcinogenicity studies the no-effect level, in both rats and mice, was 10 g caramel colour IV/kg of body weight per day (when administered in drinking-water). Higher

no-effect levels were observed in short-term studies of up to 127 days duration. Human studies demonstrated no adverse effects other than laxation at levels of up to 18 g/day.

The Committee based its evaluation of caramel colour IV on the no-effect level found in the long-term toxicity/carcinogenicity study to which, in view of the ancillary human data, a safety factor of 50 was applied. An ADI of 0–200 mg/kg of body weight (0–150 mg/kg of body weight on a solids basis) was therefore allocated to class IV caramel colours that comply with the revised tentative specifications. The previous temporary ADI was withdrawn, and the existing specifications were revised, but maintained as tentative.

The limit for 4-methylimidazole (4-MeI) in the previous tentative specifications designated at the twenty-first meeting of the Expert Committee was 200 mg 4-MeI/kg of caramel colour IV with an absorbance (colour strength) of 0.085. A number of products on the market have an absorbance in the region of 0.25 and a solids content of around 50% which gives a concentration of 1000 mg of 4-MeI per kg of caramel colour IV, when calculated on a solids content basis. All the limits in the revised tentative specifications for caramel colour IV are calculated on a solids content basis and therefore a limit of 1000 mg/kg was established.

The data submitted to the Committee indicated that there is no obvious relation between the level of 4-MeI and the colour strength. Thus, many highly coloured products on the market contain no more 4-MeI than products with a much lower colour strength. The new tentative limit of 1000 mg of 4-MeI per kg of caramel colour IV should not be taken as an encouragement to work up to this limit. At the next review it is hoped that a substantial reduction could be made in this limit.

Toxicological monograph. A consolidated toxicological monograph was prepared on all 4 classes of caramel colours.

Specifications for caramel colours. The Committee last reviewed the specifications for caramel colours at its twenty-fourth meeting (Annex 1, reference *53*). At that time the Committee encouraged industry to provide better insight into precise chemical differences, not only between caramel colours of different classes, but also between different caramel colours within each class. The present Committee considered that significant progress had been made in differentiating between the various caramel classes.

However, much of the information submitted on caramel products within each class was insufficient to determine variability in the occurrence and level of individual chemical constituents. The Committee reiterated the need for these data. In addition, information regarding the following was requested:

— sources and identity of starting materials (classes I, II, and III);
— conditions of manufacture, including the stage of addition of all materials (classes I, II, and III);
— an indication of the nature and identity of nitrogen-containing and sulfur-containing constituents (all classes); and
— detailed information regarding the relation between manufacturing processes and the content of THI and 4-MeI in the final products (classes III and IV).

In considering specifications for caramel colours, the Committee concluded that the solids content is a more meaningful basis for determining specifications than consideration of starting materials and processing conditions or of colour intensity. The individual specifications for all four classes were grouped under the title "Caramel colours".

Carthamus yellow

This substance was previously evaluated at the twenty-first meeting of the Committee (Annex 1, reference *44*), when no ADI was allocated because of insufficient data. No new data have been made available to the Committee since then and, thus no ADI could be established. No toxicological monograph was prepared. The existing specifications were revised but maintained as tentative.

Fast green FCF

Fast green FCF was evaluated at the twenty-fifth meeting of the Committee (Annex 1, reference *56*), when a toxicological monograph was prepared. A temporary ADI of 0–12.5 mg/kg of body weight was allocated pending the results of adequate long-term feeding studies and multigeneration reproduction/teratogenicity studies. These results were considered by the present Committee. The Committee reiterated the view that the occurrence of local sarcomas in rats at the site of subcutaneous injection does not constitute evidence of carcinogenicity by the oral route and noted that the results of oral carcinogenicity tests in mice were negative.

However, in carcinogenicity studies in rats, urothelial hyperplasia and/or neoplasia of the bladder were observed; the significance of benign and malignant tumours at other sites was questionable. The three-generation reproduction/teratogenicity study was uneventful.

In view of the equivocal results of the carcinogenicity study in rats, the temporary ADI was extended until 1986 to permit completion of the histological examination of all groups of rats and biometric examination of the data. A new toxicological monograph was prepared. The existing tentative specifications were revised, and the Committee agreed to delete the "tentative" qualification.

Saffron

This substance was previously evaluated by the Committee at its twenty-first meeting (Annex 1, reference *44*). Crocin and crocetin, the main colouring principles of saffron, were on the agenda, but they are not produced as food colours. The Committee concluded that, because saffron is often regarded as a food rather than as a food additive, it is not appropriate to allocate an ADI. No toxicological monograph was prepared.

The Committee reviewed the specifications for saffron and concluded that the name saffron, without crocin and crocetin, accurately reflects the commercial product. Therefore, the Committee deleted the terms crocin and crocetin from the title. The existing specifications were revised but maintained as tentative.

3.6 Sweetening agents

Hydrogenated glucose syrups

Hydrogenated glucose syrups were evaluated for acceptable daily intake by the Committee at its twenty-fourth and twenty-seventh meetings (Annex 1, references *53* and *62*). At the twenty-seventh meeting, the Committee decided, on the basis of acute and subacute tests and reproduction and metabolism studies, to allocate a temporary ADI of 0–25 mg/kg of body weight to hydrogenated glucose syrups containing 500–900 g of maltitol/kg. However, at that time, the Committee requested that the results of a lifetime feeding study should be made available.

The present Committee reviewed data which showed that most hydrogenated glucose syrups are hydrolysed in the gastrointestinal tract to glucose and sorbitol by maltase. Only traces of maltitol are

absorbed unchanged into the bloodstream, and the amount of unchanged maltitol excreted in human urine is less than 0.05%. The metabolic observations demonstrate that the α-1,4-glucose-sorbitol linkage of maltitol is partially hydrolysed in the small intestine to liberate glucose and sorbitol, whether the maltitol is free or bound by glycosidic linkage into more than two units. Further metabolism by the microflora of the large intestine results in almost complete disappearance of maltitol from the faeces.

The Committee concluded that the previously requested lifetime feeding study is not necessary because hydrogenated glucose syrups are fully metabolized to natural body constituents. Therefore, the Committee established an ADI "not specified" for hydrogenated glucose syrups that meet the established specifications.

The Committee noted that hydrogenated glucose syrups exert a laxative effect in man and animals at high doses, a common feature of all polyols. This factor should be taken into account when considering appropriate levels of use of polyols, alone and in combination (Annex 1, reference *62*, section 2.6). A toxicological monograph was prepared. The existing specifications were revised.

Isomalt

Isomalt is an equimolar mixture of α-D-glucopyranosido-1,6-glucitol and α-D-glucopyranosido-1,1-mannitol. Isomalt was evaluated at the twenty-fifth meeting under the name isomaltitol (Annex 1, reference *56*), when the Committee allocated a temporary ADI of 0–25 mg/kg of body weight. Further results from lifetime feeding studies and multigeneration reproduction studies in rats were required by 1985.

The present Committee was supplied with adequate data from lifetime feeding studies, carcinogenicity studies, multigeneration reproduction and teratogenicity studies, and metabolic studies.

Isomalt is partially hydrolysed by intestinal disaccharidases to glucose, sorbitol, and mannitol; further metabolism by microbial flora of the large intestine results in complete disappearance of isomalt from the faeces.

On the basis of the above studies the Committee decided to establish an ADI "not specified". The Committee noted that high doses of isomalt exert a laxative effect in man and animals, a common feature of all polyols. This factor should be taken into account when considering appropriate levels of use of polyols, alone

and in combination (Annex 1, reference *62*, section 2.6). A toxicological monograph was prepared. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

Mannitol

Mannitol was evaluated in 1974 at the eighteenth meeting of the Committee (Annex 1, reference *35*), when a temporary ADI of 0–50 mg/kg of body weight was allocated pending the results of a long-term study in rats. At the twentieth meeting, the Committee decided to retain the temporary ADI (Annex 1, reference *41*). Although the present Committee was aware that a number of long-term studies have been completed, the results have not been submitted for evaluation. The Committee therefore extended the temporary ADI to 1986 pending submission of the results of these studies. Specifications will be considered at that time. No toxicological monograph was prepared.

Thaumatin

Thaumatin was first evaluated by the Committee at its twenty-seventh meeting (Annex 1, reference *62*). At that time, the Committee requested the results of an appropriate long-term animal study or adequate studies in man; no ADI was allocated. The present Committee received data showing that thaumatin has a normal complement of amino acids, with the exception of histidine. The amino acid sequence of the protein is known and there is no indication of the presence of unusual amino acid side-chains, or atypical peptide linkages or end-groups. Thaumatin, *in vitro*, can be broken down to the same extent as ovo-albumin, and the *in vivo* nitrogen digestibility of both compounds appears comparable. No antibodies to thaumatin were detected in either rats or man after prolonged oral administration. Thaumatin was not mutagenic or teratogenic, and 90-day toxicity studies in rats and dogs showed no-effect levels of 30 g/kg of body weight and 10 g/kg of body weight, respectively. No treatment-related changes were observed in an adequate 13-week study of human volunteers who ingested 280 mg of thaumatin daily.

Considering that the anticipated maximum daily intake of thaumatin is calculated to be in the order of 2 mg/person per day, and in view of the fact that thaumatin makes an insignificant

contribution to the normal protein diet and is metabolized into normal body constituents, the Committee decided to establish an ADI "not specified". A toxicological monograph was prepared. The existing specifications were maintained.

3.7 Thickening agents

Dammar gum

At is twenty-eighth meeting the Committee established tentative specifications for dammar gum (Annex 1, reference *66*), but no toxicological evaluation was made. The present Committee reviewed the only data available on this substance—the results of mutagenicity and acute toxicity studies. On the basis of these limited data, no ADI could be established. The problem of generating adequate toxicological data for vegetable gums was discussed (see section 2.2.4). No toxicological monograph was prepared. The existing tentative specifications were maintained.

Ethylhydroxyethyl cellulose

This substance was considered at the twenty-seventh meeting of the Committee (Annex 1, reference *62*). At that time, the Committee, after reviewing general data available on modified celluloses and some specific studies on ethylhydroxyethyl cellulose, decided to include it, on a temporary basis, in the group ADI of 0–25 mg/kg of body weight for modified celluloses; however, the results of a 90-day feeding study were required by 1985 for further evaluation. Although the data were not available at the present meeting the Committee was aware that the study is under way and decided to extend the temporary ADI for ethylhydroxyethyl cellulose to 1986. No toxicological monograph was prepared.

The Committee reviewed the specifications for ethylhydroxyethyl cellulose. It decided to adopt a new method of assay and, in addition, requested data regarding methods of analysis and limits, where applicable, for ethylene glycol; 1,4-dioxane; and ethylene chlorohydrin. The existing specifications were revised but maintained as tentative.

Gum ghatti

This material was last evaluated by the Committee at its twenty-sixth meeting (Annex I, reference *59*). No ADI was allocated because

of insufficient data. No new data have become available since then; thus, no ADI could be established. The problem of generating adequate toxicological data for vegetable gums was discussed (see section 2.2.4). No toxicological monograph was prepared. The existing specifications were revised.

Karaya gum

This substance has been reviewed many times by the Committee (Annex 1, references *19, 32, 44, 53* and *62*). A temporary ADI was established in 1983 at the Committee's twenty-seventh meeting (Annex 1, reference *62*). At that time, the Committee requested additional information on feeding studies in non-rodent species. A preliminary report of such a study was submitted to the present Committee for review. The draft report provided additional information on the apparent lack of toxicity of karaya gum when fed at high dietary levels. In addition, limited studies in man show that there is no metabolic degradation of the gum in the intestinal tract, and that a dose level of 10 g/day is tolerated without any adverse effects. The Committee extended the temporary ADI of 0–20 mg/kg of body weight and requested submission of detailed information on the results of a feeding study in a non-rodent species by 1986. No toxicological monograph was prepared. The existing specifications were revised.

Oat gum

This compound was previously evaluated by the Expert Committee at its twenty-first meeting (Annex 1, reference *44*). No toxicological data were available at that time, and no ADI was established. The Committee was informed that no information had become available on the use or production of food-grade oat gum. Thus, no ADI was established. No toxicological monograph was prepared. No specifications were prepared.

Tragacanth gum

The Expert Committee has reviewed this compound many times in the past (Annex 1, references *19, 32, 44, 53* and *62*), but had not been able to establish an ADI because of insufficient toxicological data.

The present Committee reviewed additional data submitted since the last review in 1983. One study of rats fed tragacanth gum had

shown changes in microsomal enzyme activity in the liver and abnormal oxidative phosphorylation in mitochondria isolated from the heart and liver. However, a more recent study in rats had shown no detectable ultrastructural abnormalities of the heart or liver and no changes in microsomal protein and cytochrome P450 content of the liver. Tragacanth gum was not mutagenic in bacterial and mammalian systems. No teratogenic effects were observed in studies in mice, rats, guinea-pigs, or rabbits. In short-term studies in rats, which involved a one-generation reproduction study at dietary levels of up to 60 g/kg of feed, no effects were observed. Relatively high levels of tragacanth gum (approximately 10 g/day) are well tolerated by man, although, as with other gums, allergic reactions may occur. Allergic reactions may be related to the degree of purity of the gum. There is a long history of use of tragacanth gum in food.

Considering all the available information, and in keeping with the principles stated in section 2.2.3, the Committee established an ADI "not specified". A toxicological monograph was prepared. The existing specifications were revised.

Xanthan gum

This compound was previously evaluated by the Committee at its eighteenth meeting (see Annex 1, reference *35*). An ADI of 0–10 mg/kg of body weight was established on the basis of the maximum level tested in animal experiments.

The Committee considered the request by the Codex Committee on Food Additives to review the ADI in terms of potential intake, rather than conventional factors, and to establish a new ADI of "not specified".

No new toxicological data were submitted. The Committee was, however, given information on the strong water-binding property of the gum; this property limits the amount of gum that can be added to the diet of experimental animals in long-term studies.

The Committee noted that xanthan gum is prepared from a microbial source not normally used in food, and has the potential for high exposure levels. It also noted that information on the composition of the gum, e.g., the nature of the 1.5% nitrogenous component, is insufficient. The Committee requested that the additional information, be submitted, in keeping with the principles stated in section 2.2.3, before an ADI "not specified" was allocated.

The Committee recommended that the previous ADI of 0–10 mg/kg of body weight be retained and that this gum be re-evaluated when the relevant information becomes available. No toxicological monograph was prepared. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

3.8 Miscellaneous food additives

Bone phosphate

This compound was previously reviewed by the Committee at its twenty-sixth meeting in 1982 (Annex 1, reference *59*). Bone phosphate is used as a free-flow additive (anti-caking agent). In respect of this use, the Committee considered the toxicological problems associated with the contaminants normally present in bone phosphate, particularly lead and fluoride, that could be controlled by the adoption of adequate specifications. Because of the high levels of lead and fluoride, the Committee concluded that bone phosphate is not suitable for use as a food additive in foods intended for infants and children. Bone phosphate as a food additive should be included in the group maximum tolerable daily intake for phosphates and polyphosphates of 70 mg/kg of body weight (Annex 1, reference *59*). No toxicological monograph was prepared. The existing tentative specifications for bone phosphate were revised, and the "tentative" qualification was deleted.

The Committee was aware of another extensive use of bone phosphate, namely, as a source of calcium in dietary supplements, particularly for infants, pregnant women, and the elderly. For this use, the contaminants fluoride and lead may cause special problems.

Carbon dioxide

Carbon dioxide was evaluated at the twenty-third meeting (Annex 1, reference *50*), when the Committee concluded that it was not necessary to allocate an ADI. The present Committee confirmed that the food additive uses of carbon dioxide are safe and established an ADI "not specified". No toxicological monograph was prepared.

The Committee considered the scope of its specifications for commercial forms of carbon dioxide. In commerce, carbon dioxide is shipped and handled as a compressed liquid or in a solid state which could contain extraneous matter if not handled according to

good manufacturing practice. The Committee emphasized that products containing such material are not suitable for use in food. The Committee noted that some solid forms of carbon dioxide ("dry ice") contain binding agents, such as food-grade mineral oil, and that the types of chemical used as binding agents differ from country to country. In view of the fact that the toxicological evaluation applies to carbon dioxide in its gaseous state and that the substances added to "dry ice" forms of carbon dioxide are subject to approval by national authorities, the Committee developed specifications only for gaseous carbon dioxide as it is evolved from its commercial forms. The existing specifications were revised but maintained as tentative.

Nitrous oxide

This compound was previously considered by the Committee at its twenty-second meeting (Annex 1, reference *47*). No ADI was established, but it was noted that the concentrations ingested in food are low and present no hazard to the consumer. The toxicological effects of nitrous oxide have been extensively studied. However, these effects are observed at doses that are far greater than those found in food dispersed through aerosol containers. The Committee concluded that the food use of nitrous oxide as a propellant is acceptable. No toxicological monograph was prepared. The existing specifications were revised.

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) was previously reviewed by the Committee at its twenty-seventh meeting (Annex 1, reference *62*), when a temporary ADI of 0–25 mg/kg of body weight was established. The present Committee reviewed the results of a study on the effects of polyvinylpyrrolidone on the canine immune response that were submitted to satisfy the Committee's previous request for "evidence from feeding studies in a non-rodent species that the accumulation of polyvinylpyrrolidone in cells of the reticuloendothelial system does not entail adverse effects" (Annex 1, reference *62*).

The Committee also reviewed a study of the antigen response of lymph node cells isolated from dogs that had been inoculated with polyvinylpyrrolidone; within the limitations of the study, polyvinylpyrrolidone did not inhibit the immune response.

These studies suggest that accumulation of polyvinylpyrrolidone in the reticuloendothelial system is unlikely to have any immunotoxic effects. The Committee noted that the data previously submitted had shown a lack of similar deposition in the reticuloendothelial system of other species, and that the absorption of polyvinylpyrrolidone in man is extremely low. The Committee expressed the view that this information, plus the new data submitted, resolves concern about the significance of the deposition of polyvinylpyrrolidone in the reticuloendothelial system of the dog.

The Committee was also informed that very low levels of hydrazine have been identified as a contaminant of polyvinylpyrrolidone (average relative molecular mass 40 000). However, the probability of carcinogenic effects arising from such low levels of hydrazine seems remote in view of the large amount of data that indicates that polyvinylpyrrolidone itself is not a carcinogen. Available data include the results of lifetime feeding studies in rats given 100 g of polyvinylpyrrolidone per kg of feed; no carcinogenic effects were reported. However, because of the concern about the possible carcinogenic effects of hydrazine, the Committee maintained the temporary ADI of 0–25 mg/kg of body weight, pending the submission of data to establish the lowest technically attainable level of hydrazine in the final product. No toxicological monograph was prepared. The existing specifications were revised and designated as tentative.

Quillaia extract

The Committee had previously considered quillaia extract at its twenty-sixth meeting (Annex 1, reference *59*). The available toxicological data were reviewed, including the results of adequate lifetime studies in mice and rats from which a no-effect level was derived. No specifications were prepared; hence, no ADI could be established. A toxicological monograph was published (Annex 1, reference *60*). The present Committee prepared new tentative specifications, and an ADI of 0–5.0 mg/kg of body weight was established.

Sodium thiocyanate

The Committee was asked to evaluate the practice of adding small quantities of sodium thiocyanate and hydrogen peroxide (the lactoperoxidase/thiocyanate/hydrogen peroxide system) to raw milk

to maintain its quality. This method of milk preservation is used in the absence of cooling facilities.

The Committee held the view that, before it could express an opinion, the process should be studied by the Joint FAO/WHO Committee of Government Experts on the Code of Principles Concerning Milk and Milk Products, which should establish appropriate guidelines. No evaluation was made and no toxicological monograph was prepared. The existing specifications for sodium thiocyanate were maintained.

4. ESTABLISHMENT, REVISION, AND WITHDRAWAL OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 45 substances and prepared new specifications for 11 substances.

4.1 Antioxidants

Butylated hydroxyanisole

The Committee reviewed the specifications for butylated hydroxyanisole in response to a request to revise (*a*) the test for phenolic impurities and (*b*) the method of assay. The assay was revised but it was felt that revision of the test for phenolic impurities could not be justified.

4.2 Emulsifying agents

Sorbitan monolaurate and sorbitan mono-oleate

The Committee was requested to review the limits and assay methods for sorbitan monolaurate and sorbitan mono-oleate. Insufficient data were available and the Committee, therefore, requested further information on the composition of commercially-produced emulsifiers and on improved methods of assay. The existing specifications were revised but maintained as tentative.

4.3 Extraction solvents

Ethyl alcohol (formerly ethanol)

The title of the specifications for ethanol was changed to ethyl alcohol, which the Committee preferred for describing the food-grade product. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

4.4 Sweetening agents

Acesulfame potassium

The Committee reviewed the specifications for acesulfame potassium in response to a request from the Codex Committee on Food Additives that a thin-layer chromatographic method be considered as a test for organic contaminants. No traces of organic contaminants can be found even when using methods that are more sensitive than thin-layed chromatography. Therefore, the committee considered it inappropriate to require routine use of this technique.

4.5 Thickening agents

Carrageenan

The status of semi-refined carrageenan was reviewed and the Committee reiterated the opinion reported in its twenty-eighth report (Annex 1, reference *66*), namely that specifications for carrageenan do not include degraded carrageenan or semi-refined carrageenan. The specifications were revised to take into account new information and to include a new test for residual solvents.

Substituted celluloses (ethylhydroxymethyl, hydroxypropyl, hydroxypropylmethyl, and methylethyl celluloses)

Although the Committee was aware that a new test method had been developed to determine alkoxy groups on substituted celluloses, it concluded that further information regarding the precision and reliability of the test would be required to justify recommending its routine use. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

4.6 Miscellaneous

Sucrose acetate isobutyrate

The existing specifications for sucrose acetate isobutyrate were revised by the Committee but maintained as tentative. The Committee requested the following:

— the development of a suitable test to distinguish sucrose acetate isobutyrate from other sucrose esters by identifying and quantifying the products of hydrolysis;
— the clarification of the apparent inconsistency between saponification value and the extent of substitution by acetyl and isobutyl groups; and
— the assessment of the usefulness of optical rotation as a criterion for determining purity.

4.7 General methods

Fluoride

The Committee revised the general test for fluoride.

5. PRINCIPLES FOR THE SAFETY ASSESSMENT OF CHEMICALS IN FOOD

The Committee reviewed a draft of a monograph on the principles for assessing the safety of chemicals in food, prepared by a group of experts under the auspices of the International Programme on Chemical Safety in response to the Committee's repeated recommendations (Annex 1, references *56, 59,* and *62*). The Committee had discussed the preparation of this monograph at its twenty-eighth meeting (Annex 1, reference *66*); consideration of the issues raised at that time have been included in the draft.

The recommendations and views of the present Committee will be taken into account when the final document is prepared. The monograph is to be considered at the next meeting of the Committee.

6. FUTURE WORK

1. Vegetable gums should be reviewed as a group.

2. The lactoperoxidase/thiocyanate/hydrogen peroxide system for milk preservation should be reviewed for safety and efficacy (see sodium thiocyanate in section 3.8).

3. The provisional tolerable weekly intake (PTWI) established for lead applies only to adults. In view of the high potential intake of lead from food and other sources, tolerable intakes of lead for infants and children should be developed.

4. The intake of sulfur dioxide, which includes its occurrence in different forms, should be examined.

5. Intolerance to food additives should be considered as and when relevant data become available.

6. Contaminants and residues of immobilized enzyme preparations such as ethylenimine and glutaraldehyde that may occur in food should be reviewed.

7. The level of aluminium in food and its toxicity, especially its neurotoxicity, should be reviewed in detail.

8. Microbiological specifications for food additives and establishment of appropriate methods of safety testing should be developed. The safety of residues of antimicrobial agents should be considered at the same time as the specifications are developed.

9. New techniques of genetic manipulation are available for the preparation of food additives, including food enzyme preparations. The potential health consequences of such techniques should be reviewed.

7. 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 once a year.

2. The lactoperoxidase/thiocyanate/hydrogen peroxide system, which has been developed for maintaining the quality of raw milk, especially when technical and/or economic reasons do not allow the adoption of cooling facilities, should be studied and guidelines developed by the Joint FAO/WHO Committee of Government Experts on the Code of Principles Concerning Milk and Milk Products.

3. FAO and WHO should consider ways and means of providing assistance to developing countries in which revenues from the

vegetable gum industry are an important part of the economy in order to generate the information required for the toxicological examination of the gums for use as food additives. The type of assistance could be in the form of strengthening the research capabilities of the country or providing funds to evaluate the substances elsewhere.

4. The Committee reiterated the need to establish priorities for testing and evaluating food additives, and for reviewing the requirements for the data needed to evaluate various classes of food additives, in particular, flavouring agents, as recommended in its twenty-second, twenty-third, and twenty-seventh reports.

5. The Committee was not provided with information on the manufacture or use in foods of several substances on its agenda. In the future, specifications should be withdrawn for substances for which essential information is not submitted within a reasonable amount of time (in the Committee's judgement), whether or not an ADI has been allocated (or not specified). FAO and WHO should consider the consequences of maintaining specifications for substances that have no use in food or for which the Committee has decided that their use in food is unacceptable.

6. In relation to changes to the Committee's specifications proposed by the Codex Committee on Food Additives, the Committee felt that it would continue to be appropriate to exchange essential information regarding the reasons for the proposed changes and, where appropriate, the reasons for which such proposals were not accepted.

Annex 1

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

1. *General principles governing the use of food additives* (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of 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 Commiteee). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. *Evaluation of the toxicity of a number of antimicrobials and antioxidants* (Sixth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. *Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents* (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. *Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants* (Eighth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants.* FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).
10. *Specifications for identity and purity and toxicological evaluation of food colours.* FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.
11. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases* (Ninth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).
12. *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases.* FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29, 1967.

13. *Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances* (Tenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.
14. *Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents* (Eleventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.
15. *Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
16. *Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
17. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics* (Twelfth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
18. *Specifications for the identity and purity of some antibiotics.* FAO Nutrition Meetings Report Series, No. 45A, 1969; WHO/Food Add/69.34.
19. *Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances* (Thirteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.
20. *Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.
21. *Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.
22. *Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents* (Fourteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.
23. *Toxicological evaluation of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.
24. *Specifications for the identity and purity of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.
25. *A review of the technological efficacy of some antimicrobial agents.* FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.
26. *Evaluation of food additives: some enzymes, modified starches, and certain other substances: toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants* (Fifteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.
27. *Toxicological evaluation of some enzymes, modified starches, and certain other*

substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.
28. *Specifications for the identity and purity of some enzymes and certain other substances*. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.
29. *A review of the technological efficacy of some antioxidants and synergists*. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.
30. *Evaluation of certain food additives and the contaminants mercury, lead, and cadmium* (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
31. *Evaluation of mercury, lead, cadmium, and the food additives amaranth, diethylpyrocarbonate, and octyl gallate*. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.
32. *Toxicological evaluation of certain food additives with a review of general principles and of specifications* (Seventeenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).
33. *Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents*. FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.
34. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers*. FAO Food and Nutrition Paper, No. 4, 1978.
35. *Evaluation of certain food additives* (Eighteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.
36. *Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives*. FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.
37. *Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents, and certain food additives*. FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.
38. *Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances* (Nineteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.
39. *Toxicological evaluation of some food colours, thickening agents, and certain other substances*. FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.
40. *Specifications for the identity and purity of certain food additives*. FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.
41. *Evaluation of certain food additives* (Twentieth report of the Expert Committee). FAO Food and Nutrition Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.
42. *Toxicological evaluation of certain food additives*. WHO Food Additives Series, No. 10, 1976.

43. *Specifications for the identity and purity of some food additives.* FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additive Series, No. 11, 1977.
44. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.
45. *Summary of toxicological data of certain food additives.* WHO Food Additives Series, No. 12, 1977.
46. *Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.
47. *Evaluation of certain food additives and contaminants* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
48. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series, No. 13, 1978.
49. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 7, 1978.
50. *Evaluation of certain food additives* (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980, and corrigenda.
51. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1980.
52. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.
53. *Evaluation of certain food additives* (Twenty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 653, 1980.
54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.
55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.
56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.
57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1981.
58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.
59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.
60. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 17, 1982.
61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.
62. *Evaluation of certain food additives and contaminants.* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.

63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.
64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.
65. *Guide to specifications—General notices, general methods, identification tests, test solutions, and other reference materials.* FAO Food and Nutrition Paper No. 5, Rev. 1, 1983.
66. *Evaluation of certain food additives and contaminants* (Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 710, 1984.
67. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 19, 1984.
68. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 31/1, 1984.
69. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 31/2, 1984.

Annex 2
ACCEPTABLE DAILY INTAKES, OTHER TOXICOLOGICAL RECOMMENDATIONS, AND INFORMATION ON SPECIFICATIONS

	Specifications[1]	ADI for man and other toxicological recommendations
A. Specific food additives		
Enzyme preparations and enzyme immobilizing agents		
Carbohydrase (α-amylase) from *Bacillus licheniformis*	R	ADI not specified[2]
Glucose isomerase (immobilized) from *Actinoplanes missouriensis*	S	Acceptable[3]
Glucose isomerase from *Bacillus coagulans*	S	No ADI allocated[4]
Glucose isomerase (immobilized) from *Bacillus coagulans*	S	Acceptable[3]
Glucose isomerase (immobilized) from *Streptomyces olivaceus*	S	Acceptable[3]
Glucose isomerase (immobilized) from *Streptomyces olivochromogenes*	S	Acceptable[3]
Glucose isomerase from *Streptomyces rubiginosus*	R	No ADI allocated[4]
Glucose isomerase (immobilized) from *Streptomyces rubiginosus*	R	Acceptable[3]
Polyethylenimine	–	Suitable[5]
Flavouring agent		
Benzyl acetate	S	0–5 mg/kg body wt[6]
Flour treatment agent		
Chlorine	S	2.5 g Cl_2/kg flour[7]
Food acids and their salts		
Aluminium ammonium sulfate	N	0–0.6 mg/kg body wt[6,8]
Aluminium, calcium, magnesium, potassium, and sodium salts of capric, caprylic, lauric and oleic acids	O	No ADI allocated[9]
Ammonium succinate	O	No ADI allocated[9]
Calcium adipate	O	No ADI allocated[9]
Calcium aluminium silicate (previously aluminium calcium silicate)	S	ADI "not specified"[2,10]
Calcium fumarate	O	No ADI allocated[9]
Calcium hydrogen carbonate	O	No ADI allocated[9]
Calcium succinate	O	No ADI allocated[9]

	Specifications[1]	ADI for man and other toxicological recommendations
Dipotassium guanylate	N	ADI "not specified"[2,12]
Dipotassium inosinate	N	ADI "not specified"[2,13]
Ferric ammonium citrate	S	0–0.8 mg/kg body wt[11]
Guanylic acid	N	ADI "not specified"[2,12]
Inosinic acid	N	ADI "not specified"[2,13]
Magnesium acetate	O	No ADI allocated[9]
Magnesium adipate	O	No ADI allocated[9]
Magnesium citrate	O	No ADI allocated[9]
Magnesium succinate	O	No ADI allocated[9]
Monomagnesium phosphate	O	No ADI allocated[9]
Potassium aluminosilicate	O	No ADI allocated[9]
Potassium fumarate	O	No ADI allocated[9]
Potassium succinate	O	No ADI allocated[9]
Potassium sulfate	N	ADI "not specified"[2]
Potassium sulfite	N	0–0.7 mg/kg body wt[14]
Sodium aluminium polyphosphate	O	No ADI allocated[9]
Sodium sorbate	O	0–25 mg/kg body wt[15]
Food colours		
Brown FK	N	0–0.075 mg/kg body wt[6]
Caramel colours		
Class I	R,T	ADI "not specified"[2]
Class II	N,T	No ADI allocated[16]
Class III	R,T	0–200 mg/kg body wt (0–150 mg/kg body wt on solids basis)
Class IV	R,T	0–200 mg/kg body wt (0–150 mg/kg body wt on solids basis)
Carthamus yellow	R,T	No ADI allocated[16]
Fast green FCF	R	0–12.5 mg/kg body wt[6]
Saffron	R,T	Food ingredient[17]
Sweetening agents		
Hydrogenated glucose syrups	R	ADI "not specified"[2]
Isomalt	R	ADI "not specified"[2]
Mannitol	T	0–50 mg/kg body wt[6]
Thaumatin	S	ADI "not specified"[2]
Thickening agents		
Dammar gum	S,T	No ADI allocated[16]
Ethylhydroxyethyl cellulose	R,T	0–25mg/kg body wt[6,18]
Gum ghatti	R	No ADI allocated[16]
Karaya gum	R	0–20 mg/kg body wt[6]
Oat gum	O	No ADI allocated[16]

	Specifications[1]	ADI for man and other toxicological recommendations
Tragacanth gum	R	ADI "not specified"[2]
Xanthan gum	R	0–10 mg/kg body wt
Miscellaneous food additives		
Bone phosphate	R	70 mg/kg body wt[19]
Carbon dioxide	R,T	ADI "not specified"[2]
Nitrous oxide	R	Acceptable[20]
Polyvinylpyrrolidone (PVP)	R,T	0–25 mg/kg body wt[6]
Quillaia extract	N,T	0–5 mg/kg body wt
Sodium thiocyanate	S	Decision postponed
B. Contaminants		
Ethylenimine	—	Provisional acceptance[21]

Specifications only[1]	
Acesulfame potassium	S
Ammonium hydrogen carbonate	R
Ammonium polyphosphate	S,T
Butylated hydroxyanisole	R
Calcium polyphosphates	S
Calcium, potassium, and sodium salts of myristic, palmitic, and stearic acids	R
Carrageenan	R
Diethyleneglycol monomethylether	S,T
Diethyl tartrate	R
Ethyl alcohol (previously ethanol)	R
Ethylhydroxymethyl cellulose	R
Eugenyl methyl ether	R
Gum arabic	R
Hydrogen peroxide	R
Hydroxypropyl cellulose	R
Hydroxypropylmethyl cellulose	R
Insoluble polyvinylpyrrolidone	R
Methylethyl cellulose	R
Modified starches:	
Acetylated distarch adipate	R
Acetylated distarch phosphate	R,T
Hydroxypropyl distarch phosphate	R
Pentapotassium triphosphate	R
Polydimethylsiloxane	R
Saccharin	R
Sodium aluminium phosphate, acidic	R
Sorbitan monolaurate	R,T

Specifications only[1]	
Sorbitan mono-oleate	R,T
Sorbitol	R
Sucrose acetate isobutyrate	R,T
Turmeric oleoresin	N

Notes to Annex 2

[1] N, new specifications prepared; 0, specifications not prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; and T, the existing, new or revised specifications are tentative and comments are invited.

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

[3] Acceptable for use in food processing.

[4] No information was available on the food use of this enzyme.

[5] Polyethylenimine is considered to be a suitable substance for use as an immobilizing agent in the production of immobilized enzymes. (See also note 21.)

[6] Temporary acceptance.

[7] Acceptable level for treatment of flours for cake manufacturing.

[8] Group ADI for aluminium salts expressed as aluminium.

[9] No information was available on the food use of these salts.

[10] Group ADI for silicon dioxide and certain silicates (aluminium, calcium and sodium aluminosilicate); the previous ADI "not limited" was changed to ADI "not specified".

[11] Included in the group maximum tolerable daily intake for iron.

[12] Group ADI for guanylic acid and its calcium, dipotassium, and disodium salts.

[13] Group ADI for inosinic acid and its calcium, dipotassium, and disodium salts.

[14] Group ADI for sulfur dioxide and sulfites (sodium and potassium metabisulfites, sodium sulfite, and sodium hydrogen sulfite expressed as sulfur dioxide).

[15] Group ADI for sorbic acid and its calcium, potassium, and sodium salts expressed as sorbic acid.

[16] Insufficient information available on its toxicology and chemical composition.

[17] This substance is regarded as a food rather than as a food additive.

[18] Group ADI for modified celluloses.

[19] This figure represents the maximum tolerable daily intake (MTDI) of phosphates expressed as phosphorus; it applies to the sum of phosphates naturally present in food and the additives listed in Annex 4 of the twenty-sixth report (WHO Technical Report Series, No. 683, 1982). 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; the reverse relationship would also apply.

[20] The food use of nitrous oxide as a propellant is acceptable.

[21] Acceptable on condition that the amount of ethylenimine migrating into food is reduced to the lowest technically attainable level.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

Flavouring agent

Benzyl acetate

The Committee extended the temporary ADI pending the submission of the results of lifetime feeding studies with benzyl alcohol known to be in progress. The information is required by 1987.

Food salt

Aluminium ammonium sulfate

The assessment of this substance is dependent on the results of studies to be carried out on sodium aluminium phosphate (acidic and basic). The results should be submitted by 1986.

Food colours

Brown FK

The Committee requested the results of a complete histological examination of the low and intermediate dose groups in a long-term study in rats to be made available by 1986.

Fast green FCF

The Committee requested the completion of carcinogenicity studies in rats, in particular the histological examination of all groups of test animals and biometric examination of the data. Results should be submitted by 1986.

Sweetening agent

Mannitol

In 1976, at the twentieth meeting of the Expert Committee, an interim report was reviewed on the long-term studies being

conducted on three strains of female rats. The results of these studies should be made available by 1986.

Thickening agents

Ethylhydroxyethyl cellulose

The Committee requested the results of a 90-day feeding study known to be in progress to be made available by 1986.

Karaya gum

The Committee requested the submission of detailed information on the results of a feeding study in a non-rodent species by 1986.

Miscellaneous food additive

Polyvinylpyrrolidone

Submission of data, by 1986, to establish the lowest technically attainable level of hydrazine in the final product was requested.

Annex 4

MATTERS ARISING FROM THE REPORTS OF SESSIONS OF THE CODEX COMMITTEE ON FOOD ADDITIVES

The Committee considered matters referred to it from previous sessions of the Codex Committee on Food Additives (CCFA).

1. Tolerable weekly intake of lead for infants and children

The Committee was informed of the concern of the CCFA regarding the intake of lead from food and other sources by infants and children. The Committee noted that the tolerable weekly intake in food of 0.05 mg/kg established for lead (Annex 1, references *30* and *47*) applies only to adults, and expressed the view that there is a need to establish tolerable intakes for infants and children.

The Committee noted that the principles for evaluating health risks from chemicals during infancy and childhood developed by the International Programme on Chemical Safety and the Commission of the European Communities will prove useful in this exercise.[1] Data on the total exposure of infants and children to lead in different countries are lacking at present and efforts should be made to collect such data from all possible sources, including the Codex Alimentarius Commission and its subsidiary bodies, and the Joint FAO/WHO Food Contamination Monitoring Programme.

2. Sulfur dioxide

The Committee was informed that the intake of sulfur dioxide through consumption of foods exceeds the acceptable daily intake in certain populations. The Committee agreed to re-evaluate sulfur dioxide at a future meeting, and to consider the occurrence and availability of different forms of sulfur dioxide.

3. Withdrawal of temporary ADI

Food additives for which the temporary ADI has been withdrawn (e.g., beet red) should be submitted for future evaluation only when

[1] WHO/CEC. *Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach.* Geneva, World Health Organization, 1986 (Environmental Health Criteria 59).

the appropriate information is made available to the Committee. The Committee suggested that the Codex Alimentarius Committee could collect such information.

4. Intolerance to food additives

The Committee noted that the problem of intolerance to food additives was raised by the CCFA and that there is a need to gather information on the extent and kinds of intolerance occurring in different populations. In view of new developments in the areas of allergy and hypersensitivity, the Committee agreed to consider the subject of intolerance to food additives as and when relevant material accumulates. The Committee reiterated the opinion expressed at its twenty-seventh meeting that appropriate labelling is the only feasible means of offering protection to susceptible individuals.

5. Limitation of ADI imposed by lack of observed toxicity

The CCFA raised a question regarding the use of the 100-fold safety factor when setting ADIs for certain thickening agents, e.g., xanthan gum. It considered this to be a general problem arising from the physiological limitations of some animal models. The present Committee considered this issue (see section 2.2.3 and "xanthan gum" in section 3.7).

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