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# **Evaluation of certain food additives and contaminants**

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





World Health Organization Technical Report Series 696



World Health Organization, Geneva 1983

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. 18

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. 28

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#### ISBN 92 4 120696 9

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PRINTED IN SWITZERLAND

83/5812 - Schüler S.A. - 7000

# WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES

No. 696

# EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

#### **CORRIGENDA**

#### Page 15, lines 16-17:

Delete the Committee allocated an ADI of 0-0.5 mg/kg of body weight for BHT,

Insert the Committee allocated a temporary ADI of 0-0.5 mg/kg of body weight for BHT,

#### Page 23, line 15:

Delete from appropriate long-term studies and adequate

Insert from appropriate long-term studies or adequate studies in man,

#### Page 29, lines 2–3:

Delete maximum acceptable daily limit for arsenic was set at 0.05 mg/kg of body weight.

Insert maximum acceptable load for arsenic was tentatively set at 0.05 mg/kg of body weight per day.

#### Page 39, lines 35-36:

Delete FAO Nutrition Meetings Report Series, No. 46A; WHO/Food Add/70.36.

Insert FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.

#### Page 39, lines 38-39:

Delete FAO Nutrition Meetings Report Series, No. 46B; WHO/Food Add/70.37.

Insert FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.

#### Page 41, lines 4-5:

Delete WHO Food Additives Series, No. 10, 1978.

Insert WHO Food Additives Series, No. 10, 1976.

#### Page 41, line 22:

Delete Evaluation of certain food additives (Twenty-second report...

Insert Evaluation of certain food additives and contaminants (Twenty-second report...

#### Page 41, lines 32-33:

Delete WHO Food Additives Series, No. 14, 1979.

Insert WHO Food Additives Series, No. 14, 1980.

#### Page 43, under antioxidants:

Delete	Butylated	
Deieie	Dutylated	

hydroxyanisole (BHA) S  $0-0.5^3$  Butylated

hydroxytoluene (BHT) R 0-0.59

#### Insert Butylated

hydroxyanisole (BHA) S 0–0.5<sup>3,9</sup>

Butylated

hydroxytoluene (BHT) R 0-0.5<sup>3,9</sup>

Page 43, under flavouring agents: Delete Ethyl ST No ADI allocatd<sup>2</sup> methylphenylglycidate Ethyl Insert No ADI allocated<sup>2</sup> methylphenylglycidate ST Page 43, under preservatives:  $0-0.7^7$ Delete Calcium metabisulfite O Page 43, under thickening agents: Delete Ethylhydroxyethyl  $0 - 25^{8}$ NT cellulose Ethylhydroxyethyl Insert  $0-25^{3,8}$ NT cellulose Page 43, under miscellaneous food additives: Delete Insoluble ADI not specified4 RT polyvinylpyrrolidone Insoluble Insert polyvinylpyrrolidone ADI not specified4 RT(PVPP) Page 44, under metals:  $[0.8]^{14}$ Delete Iron  $[0.8]^{7,14}$ Insert Iron Page 44, under xenobiotic anabolic agents: Provisional Delete Trenbolone acetate acceptance (see section  $3.3)^2$ Provisional Zeranol acceptance (see section  $3.3)^2$ Provisional Trenbolone acetate Insert acceptance (see section 3.2.2)<sup>2</sup> Provisional Zeranol acceptance (see section  $3.2.2)^2$ 

#### Page 45, under notes to Annex 2:

Delete <sup>7</sup> Group ADI for sulfur dioxide and sulfites expressed as sulfur dioxide, covering sodium and potassium metabisulfite, sodium sulfite, potassium and sodium hydrogen sulfite and sodium thiosulfate.

Insert 7 This figure applies to iron from all sources except for iron oxides and hydrated iron oxides used as colouring agents and iron supplements taken during pregnancy and lactation or for specific clinical requirements.

#### Page 45, note 9:

Delete Note that the ADI for BHA is temporary.

Insert Note that the ADIs for BHA and BHT are temporary.

#### Page 46, under antioxidants:

#### Delete Butylated hydroxyanisole (BHA)<sup>3</sup>

(1) Studies to show whether or not hyperplasia is induced in the stomach of species that do not have a forestomach—such as the dog, pig, and monkey.

(2) Studies to determine the mechanism involved in the effect of BHA on the forestomach.

#### Insert Butylated hydroxyanisole (BHA)<sup>3</sup>

(1) Studies to show whether or not hyperplasia is induced in the stomach of species that do not have a forestomach—such as the dog and monkey.

(2) Studies to determine the mechanism involved in the effect of BHA on the forestomach.

(3) Submission of the results of a multigeneration reproduction study in the rat.

Butylated hydroxytoluene (BHT)<sup>3</sup>

(1) Submission of the results of the lifetime feeding study currently in progress, including the single generation reproduction study.

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Geneva, 11-20 April 1983

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# EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 11 to 20 April 1983. 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 the World Health Organization. Dr Hamon briefly reviewed the history and activities of the Expert Committee and pointed out that consumers in both developing and developed countries were demanding firm assurance that food additives were safe. This called for their appropriate and thorough testing, followed by sound and balanced evaluation. In addition, technological, nutritional, and other public health considerations made it necessary to ensure the identity and purity of food additives.

An examination of the previous reports of the Committee led Dr Hamon to note that the number of food additives placed on the agenda of the Committee for evaluation was increasing, thereby increasing the workload of the Committee. However, the toxicological data and specifications made available to the Committee had allowed the establishment of acceptable daily intakes for less than half of the food additives evaluated in 1981 and 1982.

#### 1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955, there have been 26 previous meetings of the Committee (see Annex 1). The present meeting was convened on the recommendation made at the twenty-sixth meeting (see Annex 1, reference 60). The tasks before the Committee were: (a) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological

<sup>&</sup>lt;sup>1</sup> FAO Nutrition Meetings Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

evaluations of them; (b) to review specifications for selected food additives; (c) to undertake toxicological evaluations and reevaluations of certain food additives and contaminants; and (d) to undertake the toxicological evaluation of xenobiotic anabolic compounds used in the rearing of livestock intended for human consumption.

#### 2. GENERAL CONSIDERATIONS

#### 2.1 Modification of the agenda

Caramel colours (ammonium sulfite process) (previous reference, WHO Technical Report Series, No. 653, 1980) was removed from the agenda, since no new data were available for toxicological evaluation; the Committee was informed that studies were in progress and the findings would be available for evaluation by 1985.

Talc (previous reference, WHO Technical Report Series, No. 653, 1980) was also removed from the agenda since no new data were available. However, a revised specification was prepared.

Collagen and glutaraldehyde were added to the agenda for elaboration of specifications only.

# 2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (see Annex 1) and by a WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives and a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals. In addition, the Committee reaffirmed the need to take into consideration recent developments in toxicological techniques, as stated in its seventeenth report (Annex 1, reference 32). The Committee also had the benefit of the consolidated guidelines for evaluation of groups of food additives and contaminants which were appended as Annex 6 to the twenty-sixth report (Annex 1, reference 60).

<sup>&</sup>lt;sup>1</sup> WHO Technical Report Series, No. 348, 1967.

<sup>&</sup>lt;sup>2</sup> WHO Technical Report Series, No. 546, 1974.

## 2.3 Principles governing the establishment and revision of specifications

The Committee considered the role of specifications in the evaluation process and addressed the particular subjects of processing aids used in food and the levels of contaminants in food additives. Furthermore, the Committee reviewed a draft revision of the general methods contained in *Guide to specifications*.<sup>1</sup>

#### 2.3.1 The need for specifications

The Committee considered whether there was a need to elaborate specifications for all the substances evaluated by it. The fundamental criterion was not whether a substance was a food additive or a processing aid (mutually distinct definitions for which are difficult to develop), but whether the substance in question came into direct contact with the food in which it was used or with any of the ingredients of that food, since impurities in the substance may be transferred to the final product. In the case of food additives and processing aids that do come into contact with foods or their ingredients (e.g., extraction solvents and flour treatment agents) it is considered important to elaborate specifications.

Certain substances are used as chemical reagents in the preparation of food additives and processing aids and therefore only come into contact with food in association with the additive or processing aid (e.g., glutaraldehyde in the preparation of immobilized enzyme preparations, acetic anhydride, adipic anhydride, and vinyl acetate in the manufacture of modified starches). The Committee concluded that it is usually unnecessary to elaborate specifications for such reagents. Carry-over of these reagents together with impurities they contain into a food additive, and thus possibly into the final food, is best taken into account during the evaluation of that additive. Residues of the reagent and of any relevant impurities may be controlled in the specifications for the purity of the additive.

#### 2.3.2 Levels of contaminants in specifications

The Committee considered levels of contaminants in existing specifications and noted that the levels of contaminants present in

<sup>&</sup>lt;sup>1</sup> Report of the sixteenth session of the Codex Committee on Food Additives. Rome, FAO, 1983 (Unpublished FAO document, ALINORM 83/12A).

food additives depend on the manufacturing procedures and the levels of contaminants in raw materials used in making the additives. Improvements in manufacturing practices have resulted in reductions in the levels of contaminants in certain additives, such as arsenic and certain organic impurities. However, the Committee was informed that depletion of some sources of raw materials, in particular certain minerals used to manufacture additives, might result in increases in the levels of contaminants such as arsenic and fluoride in phosphates. The Committee decided against increasing the existing limits for such contaminants to encourage use of appropriate processing conditions and selection of high-quality raw materials.

### 2.3.3 Review of the general methods contained in Guide to specifications<sup>1</sup>

In its twenty-sixth report (Annex 1, reference 60), the Expert Committee had "considered it desirable to review, update, and expand the full publication on general methods contained in *Guide to specifications* in order to take into account advances in methodology". At its present meeting, the Committee, after considering the text, concluded that the following areas require further attention:

- (a) Colours. With regard to updating the methodology section, tests for specific impurities need to be developed, limits for trace metals need to be reviewed for consistency, and provision should be made for "lakes" of the colours. The Committee noted that similar observation on colours were made at the sixteenth session of the Codex Committee on Food Additives.<sup>1</sup>
- (b) Phosphates. Assays for phosphates need to be reviewed with particular reference to consistency.
- (c) Microbiological criteria. These need to be reviewed with particular reference to additives that may support microbiological growth.

#### 2.4 Intolerance to food additives

The Committee noted that two of the substances on the agenda, calcium benzoate and calcium metabisulfite, are members of groups of food additives for which there are reports of a relatively high incidence of adverse reactions in susceptible individuals. It is not

<sup>&</sup>lt;sup>1</sup> FAO Food and Nutrition Paper 5, Rome, 1978.

clear to what extent these reactions are manifestations of immunological hypersensitivity or of idiosyncratic hyper-reactivity. However, both types of reaction can be regarded as forms of intolerance.

In its seventeenth report, the Committee considered the problems raised by the allergenicity of food additives (see Annex 1, reference 32, pp. 12–13) and stressed that a substance that gave rise to serious or widespread hypersensitivity reactions would not be approved for food additive use; nevertheless, it was recognized that a number of food additives may cause allergic manifestations in susceptible individuals. It was suggested that foods containing additives with a potential for provoking allergic reactions should bear appropriate labelling so that sensitive individuals could recognize sources of possible reactions; however, it was acknowledged that the practicability and effectiveness of such a measure is uncertain.

The Committee was now of the opinion that appropriate labelling was the only feasible means of offering protection to susceptible individuals. It recommended that this matter be discussed again at a future meeting.

### 2.5 Adrenal medullary lesions produced by hydrogenated carbohydrates ("polyols")

The increase in the incidence of basophilic hyperplastic foci and of benign and malignant phaeochromocytomas in the adrenal medulla of the rat, originally reported from studies with xylitol, has been observed in feeding studies with other polyols. Of the substances on the agenda for the present meeting, lactitol (and lactose) and xylitol were reported to have increased the incidence of these lesions. But a common feature of the studies with these substances has been the occurrence of a high incidence of these lesions in control rats; enhancement over the level in controls is usually observed only at the highest dose level of polyols, which has been 10% or more of the diet in most of these tests. The occurrence of high incidences of these lesions in untreated rats and their variation in different strains are well recorded. Gilman et al. first drew attention to these lesions, reporting an incidence of phaeochromocytomas of 50% in female rats and of 82% in the males. Since then the IARC<sup>2</sup> has

<sup>&</sup>lt;sup>1</sup> GILMAN, J. ET AL. Cancer, 6, 494–511 (1953).

<sup>&</sup>lt;sup>2</sup> Pathology of tumors in laboratory animals, Vol. I. Tumours of the rat, Part 2, Lyons, International Agency for Research on Cancer, 1976.

provided a compilation of the different rates of incidence in several rat strains, and these range from 0 to 80%.

The nature of the adrenal hyperplasia and phaeochromocytomas is now under study. Investigations on the production of catecholamines in rats bearing these lesions were reported to the Committee. However, these studies are still preliminary.

In view of the high incidence of these lesions, their species specificity, and great variation within rat strains, the Committee found it difficult to extrapolate the significance of the findings to man without further information.

However, in view of the association of these lesions with a particular group of food additives – polyols – it is important that efforts be made to clarify this problem. In particular, the strain and species specificity of their effects require elucidation. In addition, the functional significance of these lesions must be determined.

#### 2.6 Laxative effect of hydrogenated carbohydrates "polyols"

The Committee had before it extensive data on polyols including xylitol, lactitol, and hydrogenated glucose syrup. On previous occasions the Committee had considered sorbitol and mannitol. The Committee was aware of human and animal studies clearly demonstrating that excessive consumption of these substances led to diarrhoea.

The Committee was of the opinion that polyols used as food additives could produce a laxative effect, and wished to inform the appropriate health authorities of this matter. It is recommended that controls be exercised to limit the consumption of polyols from all sources to levels below those at which they induce diarrhoea.

## 3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

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

#### 3.1 Specific food additives

#### 3.1.1 Antioxidants

The two antioxidants on the agenda, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), were previously considered by the Committee in 1961, 1965, 1973, 1976, 1980, and 1982 (Annex 1, references 6, 11, 32, 40, 54, 60, respectively). In its twenty-sixth report, where BHA was considered, the Committee continued the temporary group ADI of 0–0.5 mg/kg of body weight previously allocated to BHA, BHT, and tertiary butyl hydroquinone, singly or in combination. Since then, the Committee has been supplied with the results of new studies on the carcinogenicity of BHA in rats. Furthermore, the results of several studies with BHT have also become available since it was last considered by the Committee.

#### Butylated hydroxyanisole (BHA)

BHA has been extensively studied for chronic toxicity in several species of animals. A number of lifetime studies in rats with up to 0.5% in the feed failed to reveal any carcinogenic response. BHA has been shown to be both an inhibitor and an enhancer of certain carcinogens.

In a recent, well-conducted lifetime study in rats² carcinomas occurred in the forestomach of 34.6% of the animals and papillomas in the forestomach of 100% of the animals when 2% BHA was added to their feed. At the lower level tested (of 0.5% BHA in the feed), one papilloma was observed and hyperplasia of the forestomach was present in approximately 20% of the rats that received this feed. Reports on additional studies submitted to the Committee demonstrated that BHA administration to rats resulted in a rapid onset of forestomach hyperplasia accompanied by increased DNA synthesis. This effect was dose-related and has not yet been seen at dietary levels below 0.25%.³

<sup>&</sup>lt;sup>1</sup> Tertiary butyl hydroquinone was allocated a separate ADI of 0–0.5 mg/kg of body weight in the twenty-first report of the Committee (Annex 1, reference 43).

<sup>&</sup>lt;sup>2</sup> Ito, N. Et al. Journal of the National Cancer Institute 70: 343 (1983).

<sup>&</sup>lt;sup>3</sup> Lok, E. et al. Studies on effect of butylated hydroxyanisole (BHA) on cell proliferation in rat forestomach. 1983 (Unpublished report submitted to the World Health Organization by Health Protection Branch, Health and Welfare Canada, Canada).

The Committee was informed of preliminary findings in male Syrian hamsters. Groups of 10 hamsters were fed with 2% BHA in pelleted diet and 1% in powdered diet (plus 20% corn oil). They were sacrificed at the sixteenth week of the experiment and papillomas of the forestomach were found in 100% of the hamsters in both groups.<sup>1</sup>

In view of the nature of the reported lesions, the uniqueness of the specific site, the absence of any systemic carcinogenicity, and the presence of negative *in vitro* tests for genotoxicity, the Committee felt that further studies should be undertaken before the relevance of these findings to man can be assessed.

The Committee considered that, in future studies, advantage can be taken of the apparent association between the rapidly inducible hyperplasia and the eventually occurring neoplasia. It recommended that studies be undertaken as soon as possible to see whether or not hyperplasia can be induced in the stomach of species which do not have a forestomach—such as the dog and monkey. The Committee decided to retain the present temporary ADI of 0–0.5 mg/kg of body weight until the results of such studies become available. The Committee reiterated the requirement for the submission of the results of a multigeneration reproduction study in the rat. In addition, the Committee considered it desirable that work be undertaken to determine the mechanisms involved in the effects of BHA on the forestomach.

A new toxicological monograph was prepared, but the existing specifications were maintained.

#### Butylated hydroxytoluene (BHT)

The results of recent lifetime feeding studies in mice and rats did not reveal any indication of carcinogenicity of BHT. The effects of BHT in promoting certain chemical carcinogens was considered in the twenty-fourth report of the Committee (Annex 1, reference 54). The results of additional studies were available to the present Committee; these indicated that BHT is effective as a promoting agent in mice treated with polycyclic hydrocarbons or nitrosamine. BHT also inhibits the effects of certain carcinogens. This protective effect may be due to the induction by BHT of enzymes involved in the

<sup>&</sup>lt;sup>1</sup> ITO, N. ET AL. Personal communication to the Joint FAO/WHO Expert Committee on Food Additives, 1983.

metabolism of these carcinogens. More information is required on the conditions as well as the mechanisms of these inhibiting and promotional activities of BHT on chemical carcinogens before the results of such studies can be used in toxicological evaluations.

In a previously reported teratological study, an excess of deaths of offspring was observed at the levels of 5 g and 20 g per kg in feed. The Committee was presented with new data which showed that the reported effect was due to an abnormal number of deaths in a few litters. The available data indicate the no-effect level for BHTinduced reproductive effects in rats to be 1 g per kg of feed. The Committee was informed that a life time feeding study, which includes a single generation reproduction study, is in progress; the workers involved were requested to submit their results on completion of this study.

On the basis of the no-effect level in the rat, which was equivalent to a daily dose of 50 mg/kg of body weight, the Committee allocated an ADI of 0-0.5 mg/kg of body weight for BHT, or for the sum of BHA, BHT, and TBHQ (note that the acceptance for BHA is

temporary).

A new toxicological monograph was prepared, and the existing specifications were revised.

#### 3.1.2 Extraction solvents

Dichloromethane (methylene chloride)

This compound was previously evaluated in the twenty-third report of the Committee (Annex 1, reference 51) and at that time a temporary ADI of 0-0.5 mg/kg of body weight was established. The present Committee reviewed the available life time studies in rats and mice, but was unable to come to a conclusion about the potential carcinogenicity of dichloromethane because of a number of shortcomings in the studies. In the study in rats it was noted that there were numerous deaths due to gavage errors, and two batches of dichloromethane were used, each containing different impurities. The tumours identified in the rat liver were reported to be neoplastic nodules, which it is known, may progress to carcinoma. However, the occurrence of this lesion in the study was rare, and the distribution of the carcinoma in the various test groups was not dose-related. Furthermore, there was a reported increase in pancreatic acinar cell adenomas in male rats. Pancreatic acinar cell adenomas are being reported with increasing frequency both in control and treated male rats in other studies. The reasons for this are variously attributed to more detailed pathological examination or to the use of the corn-oil vehicle in gavage studies. This problem is under active review and no conclusions can be made at this time. In another study in rats in which dichloromethane was administered in drinking-water at slightly lower doses, no tumours other than those also noted in the controls were seen. In a study in mice, the major lesion reported was hepatocellular carcinoma. Evaluation of the significance of this lesion is difficult because of the known wide fluctuations in the background level of this tumour. The occurrence of mesenchymal tumours in or around the salivary glands of rats exposed to technical grade dichloromethane was noted. In another inhalation study in golden hamsters, at equivalent levels of exposure, no effects on salivary glands were observed.

The Committee noted that there are ongoing studies on lifetime exposure of mice to dichloromethane in drinking-water, and on exposure by inhalation in mice and rats. The data from these studies may resolve the problems raised in the previous studies. The Committee felt that the available studies were inadequate for a complete evaluation of the possible carcinogenicity of dichloromethane. Therefore, it withdrew the previously allocated ADI and recommended that the use of dichloromethane as an extraction solvent should be limited in order to ensure that its residues in food are as low as practicable.

A toxicological monograph was prepared, and the existing specifications were revised and designated as "tentative" (see section 4).

#### 1,1,2-Trichloroethylene (TCE)

This substance was previously considered in the twenty-fourth report of the Committee (Annex 1, reference 54) but no ADI was allocated, the present Committee reviewed the available lifetime studies in rats and mice treated with food grade 1,1,2-trichloroethylene (TCE), which was free of the stabilizer contained in the TCE used in previous studies. In the study in rats it was noted that the dose levels used produced extensive toxicity, as evidenced by early deaths. In addition, a number of animals were lost due to gavage errors. The significance of the three renal adenocarcinomas reported in this study was difficult to interpret because: (a) there was a high incidence of early deaths; (b) all the treated animals showed

toxic nephrosis and cytomegaly, indicating that the adenomas may have been secondary to these lesions; and (c) two batches of TCE were used in this study and each contained different impurities. The reported increase in hepatocellular carcinomas in treated mice as an indication of carcinogenicity is complicated by the facts that only one dose level was used in this study and that there is known to be variability in the background level of this tumour in the mouse strain used

Because of the inadequacies of the studies, the Committee was unable to reach any conclusions on the possible carcinogenicity of TCE. The Committee recommended that the use of TCE as an extraction solvent should be limited in order to ensure that its residues in food are as low as practicable.

A toxicological monograph was prepared. The existing specifications were revised and designated as "tentative" (see section 4).

#### 3.1.3 Flavouring agents

#### trans-Anethole

In its eleventh report the Committee allocated a conditional ADI for trans-anethole of 0–1.25 mg/kg of body weight (Annex 1, reference 14) and in its twenty-third report (Annex 1, reference 51) raised this to a temporary ADI of 0–2.5 mg/kg of body weight (Annex 1, reference 51). The results of an adequate long-term feeding study were required for re-evaluation of trans-anethole in 1983. The Committee was informed that the required long-term feeding studies had not yet been completed. Therefore, the Committee decided to continue the existing temporary ADI until the next meeting when the data required were expected to be available.

No new toxicological monograph was prepared, but the existing specifications were revised.

#### Benzyl acetate

Benzyl acetate was allocated an ADI of 0–5 mg/kg of body weight by the Committee in its eleventh report (Annex 1, reference 14). Since then, there had been a number of further studies of this compound which show that it is rapidly hydrolysed and metabolised, the benzyl moiety being oxidized, conjugated, and excreted as hippuric acid. Benzyl acetate is not mutagenic in the Ames test. The

present Committee considered benzyl acetate because of the concern raised by preliminary findings from screening tests for carcinogenicity. A number of technical problems that arose during their execution raised difficulties in the interpretation of the findings. A final report of the study was not available.

The Committee decided to retain the existing ADI for benzyl acetate at its present level of 0–5 mg/kg of body weight, but changed its status to a temporary ADI. The Committee required the submission of the final report of the recent study referred to above for a future evaluation.

No new toxicological monograph was prepared, but the existing specifications were revised.

#### (+)-Carvone and (-)-Carvone

A temporary ADI of 0–1.0 mg/kg of body weight was allocated to (+)- and (-)-carvone (as the sum of the isomers) at the twenty-third meeting of the Committee (Annex 1, reference 51), and this temporary ADI was continued at the twenty-fifth meeting (Annex 1, reference 57). The results of further relevant biochemical and metabolic studies were required for evaluation. The Committee was informed that lifetime feeding studies with (+)-carvone rats and mice were in progress. The Committee extended the temporary ADI 0–1.0 mg/kg of body weight for (+)-carvone and (-)-carvone, and required submission of the results of the above-mentioned studies for re-evaluation in 1986. In addition, the Committee considered it desirable that biochemical and metabolic studies be undertaken in several species, preferably including man.

No new toxicological monograph was prepared, but the existing specifications were revised.

#### Ethylmethylphenylglycidate

This flavouring agent was allocated a temporary ADI of 0-0.6 mg/kg of body weight in the eleventh report of the Committee (Annex 1, reference 14), but the ADI was withdrawn in the eighteenth report (Annex 1, reference 34) because the findings from feeding studies indicated that it produced adverse effects, including neurological damage. However, the identity and purity of the material used in those studies was not specified. The results of more

recent short- and long-term studies in rats using material from a different source were now available for evaluation by the Committee. The adverse effects observed previously did not occur, even at the highest level (5 g of test material per kg of feed). The Committee considered that the level producing no effects was 1 g per kg of feed, amounting to a daily intake of 50 mg/kg of body weight. However, chromatographic analysis of the test material revealed the presence of two major and five minor constituents, and these were not fully identified. Hence, the material could not be evaluated for use as a flavouring agent.

A toxicological monograph was prepared.

With regard to specifications, the Committee noted that the additional information requested had not yet been provided. It reiterated the requirement for such information before a revision of the specification could be undertaken. The existing tentative specifications were maintained.

#### 3.1.4 Food colours

#### Azorubine

This food colour was allocated a temporary ADI of 0–0.5 mg/kg of body weight in the eighteenth report (Annex 1, reference 34) of the Committee and this was raised to a temporary ADI of 0-1.25 mg/kg of body weight in the twenty-second report (Annex 1, reference 48). At the same meeting, the submission of results of various studies was requested for further evaluation of azorubine. The present Committee considered the findings from studies on the metabolism and elimination of azorubine, mutagenic studies, and several new feeding studies. The data indicate that azorubine is not mutagenic, carcinogenic, or teratogenic, and it produced no serious histopathological effects. The Committee considered that the previously stated requirement of a one-year feeding study in a nonrodent species was adequately met by a very thorough 90-day feeding experiment in pigs. On the basis of a level producing no effects in long-term feeding studies in rats and mice, the Committee allocated an ADI of 0-4 mg/kg of body weight to azorubine.

A new toxicological monograph was prepared, but the existing specifications were maintained.

#### Ponceau 4R

This colour has been considered at several previous meetings of the Committee. In the eighteenth report, it was allocated a temporary ADI of 0–0.125 mg/kg of body weight (Annex 1, reference 34), and a number of studies were required to permit a fuller evaluation. The temporary ADI was extended in the twenty-second (Annex 1, reference 48) and twenty-fifth (Annex 1, reference 57) reports of the Committee. The present Committee was supplied with adequate data from studies on metabolism, a long-term study in rats exposed in utero and through lactation, a multigeneration feeding study (indicating lack of carcinogenicity), and a teratogenicity study. On the basis of a no-effect level in a long-term study in mice, the Committee allocated an ADI of 0–4 mg/kg of body weight.

A new toxicological monograph was prepared, but the existing specifications were maintained.

#### 3.1.5 Preservatives

Two calcium salts, calcium benzoate and calcium metabisulfite, were placed on the agenda at the request of the Codex Committee on Food Additives (CCFA). There were no specific toxicological data on these substances, but the Committee decided to evaluate them in the context of the already established group ADIs for "benzoic acid and its potassium and sodium salts" and "sulfur dioxide and sulfites", respectively. The toxicological data on these groups of food additives were reviewed.

#### Calcium benzoate

In the seventeenth report of the Committee, benzoic acid and its potassium and sodium salts was allocated a group ADI of 0–5 mg/kg of body weight (Annex 1, reference 32). Since then, new data from several additional studies on benzoic acid and sodium benzoate were available, and the present Committee therefore took the opportunity to review this group of preservatives. The Committee considered the undertaking of further teratological studies to be desirable. The occurrence of intolerance to benzoic acid and benzoates is discussed in section 2.4 of this report.

The Committee confirmed the existing ADI and extended it to include calcium benzoate; thus the group ADI of 0-5 mg/kg of body

weight for benzoic acid now includes its calcium, potassium, and sodium salts, expressed as benzoic acid.

The Committee was informed that ammonium and magnesium benzoate may also be required for use as preservatives, but decided not to include these salts in the present evaluation because sufficient notice had not been given; these would be considered at a subsequent meeting.

A new toxicological monograph for benzoic acid and its calcium, potassium, and sodium salts and new specifications were prepared.

#### Calcium metabisulfite

Sulfur dioxide and sulfites have been considered on several previous occasions by the Committee (Annex 1, references 6, 8, 11 and 32). The ADI for this group, expressed as sulfur dioxide, is 0-0.7 mg/kg of body weight. Since the last evaluation, additional data had become available, and they were reviewed by the Committee (intolerance to these substances is considered in section 2.4 of this report). The previously allocated ADI was confirmed. However, it could not be extended to calcium metabisulfite because no specifications were available. Thus, for "sulfur dioxide and sulfites" the ADI is 0-0.7 mg/kg of body weight expressed as sulfur dioxide, and it covers the following salts: sodium and potassium metabisulfite, sodium sulfite, potassium and sodium hydrogen sulfite, and sodium thiosulfate. A synonym of sodium thiosulfate is sodium hyposulfate; the Committee felt that the nomenclature with regard to this compound should be clarified at a future meeting.

A new toxicological monograph on sulfur dioxide and sulfites was prepared. The Committee was not aware of the use of calcium metabisulfite as a food additive, and requested information in this regard. No specifications were prepared for calcium metabisulfite.

#### 3.1.6 Sweetening agents

#### Acesulfame potassium

This substance was last considered in 1981 (Annex 1, reference 57) but the data then available were inadequate for the allocation of an ADI. The results of the additional studies required were available for evaluation at the present meeting of the Committee. Data showed that accounts are potassium did not exhibit mutagenicity or

carcinogenicity. Information was available to the Committee about the stability of acesulfame potassium in foods, and it was considered that no toxicological problems were raised by the nature and amounts of its degradation products. On the basis of a no-effect level determined in a two-year feeding study in the dog, the Committee agreed to allocate an ADI for acesulfame potassium of 0–9 mg/kg of body weight.

A new toxicological monograph was prepared. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

#### Hydrogenated glucose syrup

Hydrogenated glucose syrup was considered by the Committee in its twenty-fourth report (Annex 1, reference 54) but the information then available was inadequate for its evaluation and no toxicological monograph was prepared.

Hydrogenated glucose syrup is a complex mixture prepared by hydrolysing starches from various sources with various enzymes to yield glucose and a range of oligosaccharides which are then hydrogenated to yield a mixture of sorbitol, maltitol, and other polyols. The main constituent of the hydrogenated glucose syrup evaluated by the Committee was maltitol, which constituted 50–90% of the preparations for which detailed specifications could be prepared (see section 4).

The Committee evaluated hydrogenated glucose syrup on the basis of toxicological studies of preparations that were chemically well defined. The data available from acute and subacute toxicity tests and from reproduction and metabolism studies were considered adequate for evaluation. However, the data were inadequate with respect to long-term feeding studies. Human studies available to the Committee demonstrated that hydrogenated glucose syrup produced a laxative effect at high concentrations (see section 2.6).

On the basis of the data available, the Committee decided to allocate a temporary ADI of 0–25 mg/kg body weight to hydrogenated glucose syrup. Further work required includes the submission of the results of a lifetime feeding study with a minimum of three dose levels.

No toxicological monograph was prepared. New specifications were prepared.

#### Thaumatin

Thaumatin is an aqueous extract from the fruit of Thaumatococcus danielli. The Committee was informed that crude extracts of this fruit have a long history of use in the Sudan for sweetening purposes. The main active agents in thaumatin are the proteins, thaumatin I and thaumatin II, both of which have a relative mass of about 20 000. They are rich in basic amino acids and therefore have a high isoelectric point of about pH 11, but they do not contain histidine. The Committee was provided with the information that thaumatin was digestible to about the same extent as ovalbumin. It was not allergenic, mutagenic, or teratogenic. In 90-day feeding studies in rats and dogs, high levels of thaumatin produced haematological abnormalities. The Committee considered that an ADI for thaumatin could be established only when data become available from appropriate long-term studies and adequate studies in man, possibly including epidemiological studies on the uses of crude thaumatin extracts.

No toxicological monograph was prepared. New specifications were prepared.

#### Lactitol and xylitol

While lactitol was being considered by the Committee for the first time, xylitol had been considered previously in 1977 (Annex 1, reference 43) and 1978 (Annex 1, reference 48). The Committee had before it extensive data relating to the toxicity and metabolism of both substances. Both were noted to produce somewhat similar effects in rats namely, changes in calcium uptake and excretion accompanied by nephrocalcinosis, adrenal medullary hyperplasia, and, in the case of xylitol, phaeochromocytoma. These changes, since they were not observed in other species tested, appear to be unique to the rat. In considering this matter, the Committee took note of the fact that in 1982 (Annex 1, reference 60) the Committee had concluded, on the basis of data submitted on sorbitol, that the adrenal medullary hyperplasia observed in rats was due to gross dietary imbalance which may result in metabolic and physiological disturbances. The present Committee reiterated this view with regard to the effects on the adrenal gland. The Committee also concluded that the changes in the kidneys induced by xylitol and lactitol were due to gross physiological disturbances. Studies on functional disturbances in aged rats with phaeochromocytoma showed that the clinical signs associated with phaeochromocytomas in man (increased catecholamines and their metabolites in the urine and elevated blood pressure) were not present. Furthermore, for reasons discussed elsewhere (see section 2.5) the toxicological significance to man could not be assessed.

New data were available to show that in humans, ingestion of xylitol is not associated with urinary oxalate excretion. The Committee reviewed the data on a two-year study in the dog and concluded that the minimal increase in serum enzymes was difficult to interpret because of the erratic fluctuations in enzyme levels occurring in individual dogs.

The Committee allocated an ADI "not specified" to xylitol and lactitol, as well as to sorbitol (Annex 1, reference 60). The Committee was aware, however, of human and animal studies clearly demonstrating that excessive consumption of polyols leads to diarrhoea (see section 2.6).

Toxicological monographs on xylitol and lactitol were prepared. For lactitol, new specifications were prepared. For xylitol, the existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

#### 3.1.7 Thickening agents

#### Ethylhydroxyethyl cellulose

This substance had not previously been considered by the Committee. A group ADI of 0–25 mg/kg of body weight was allocated to modified celluloses in the seventeenth report of the Committee (Annex 1, reference 32). After reviewing some general data available on modified celluloses and some specific studies on etylhydroxyethyl cellulose, the present Committee decided to include it, on a temporary basis, in the group ADI for modified celluloses. The results of a 90-day feeding study were required by 1985 for further evaluation.

No toxicological monograph was prepared, but new tentative specifications were prepared.

#### Karaya gum

When this substance was last considered, in the twenty-fourth report of the Committee (Annex 1, reference 54), the available data were inadequate for its evaluation and the Committee requested that

data from metabolic, short-term, long-term, and reproduction studies be made available.

The data available at the present meeting indicated that karaya gum is neither digested nor degraded by enteric bacteria and is not absorbed by man to any appreciable extent. Furthermore, the findings from a short-term feeding study in rats showed that karaya gum produces no effects in the gastrointestinal tract other than those to be expected of a bulking agent. The Committee decided that there were sufficient data for the allocation of a temporary ADI of 0–20 mg/kg of body weight to karaya gum. The Committee required the submission of results from a short-term feeding study in a nonrodent species by 1985 for its further evaluation.

A toxicological monograph was prepared. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification.

#### Tragacanth gum

When this gum was considered in the twenty-first (Annex 1, reference 43) and the twenty-fourth (Annex 1, reference 54) reports of the Committee, the toxicological data were inadequate for evaluation and no ADI was allocated. Unlike karaya gum, tragacanth gum is degraded by several strains of enteric microorganisms. It is likely, therefore, that there may be some absorption of its degradation products; in fact, tragacanth gum administered orally has systemic effects, including effects on hepatic metabolism in the rat. The Committee once again considered that it was not possible to allocate an ADI to tragacanth gum, and requested the submission of appropriate data for evaluation before this substance is again placed on the agenda.

No toxicological monograph was prepared, but the existing specifications were revised.

#### 3.1.8 Miscellaneous food additives

Ammonium phosphate, monobasic (monoammonium orthophosphate)

This phosphate salt has not been previously considered by the Committee for toxicological evaluation, and no specific data were available on it. However, since other ammonium salts and other phosphates have been previously accepted as food additives (Annex 1, reference 60), the Committee decided to add ammonium phosphate, monobasic, to the list of phosphates and polyphosphates previously accepted for food additive use (see WHO Technical Report Series, No. 683, Annex 4); it is thereby included within the maximum tolerable daily intake of 70 mg/kg of body weight (expressed as phosphorus), which applies to the sum of the phosphates and polyphosphates accepted as food additives and those naturally present in food.

No toxicological monograph was prepared. The existing specifications were maintained but the title was changed (see above) to make it consistent with other specifications.

Insoluble polyvinylpyrrolidone or polyvinyl polypyrrolidone (PVPP)

This substance has not been previously considered by the Committee for toxicological evaluation. It is an insoluble substance with a very high relative molecular mass. The Committee was provided with evidence that insoluble polyvinylpyrrolidone did not produce any adverse effects in short-term feeding studies in dogs and rats. Studies with <sup>14</sup>C-labelled insoluble polyvinylpyrrolidone showed almost complete lack of absorption, and the slight amount that did occur was probably a result of the presence of traces of soluble polyvinylpyrrolidone in the material. The Committee decided to allocate an "ADI not specified" to insoluble polyvinylpyrrolidone.

A toxicological monograph was prepared. Existing specifications were revised but maintained as "tentative". In addition, the title was changed from "polyvinyl polypyrrolidone" to "insoluble polyvinylpyrrolidone" to reflect the characteristics of the additive and to distinguish it clearly from "polyvinylpyrrolidone".

Polyvinylpyrrolidone (PVP) (Polyvidone)

An ADI of 0-1 mg/kg of body weight was allocated to this substance in the tenth report of the Committee (Annex 1, reference 12) but the ADI was withdrawn in the seventeenth report (Annex 1, reference 32) because of concern about the implications of accumulation of polyvinylpyrrolidine in cells of the reticuloendothelial system. The Committee considered the results of further studies in its twenty-fourth report (Annex 1, reference 54) but did not reallocate an ADI. However, in its twenty-fifth report the Commit-

tee re-evaluated the previous studies (Annex 1, reference 57) and restored the previous ADI of 0-1 mg/kg of body weight. This acceptance involved the application of a higher safety factor than that usually employed, and took into account the likely maximum intake of polyvinylpyrrolidone from food additives sources but excluded non-food sources. Reconsideration of polyvinylpyrrolidone was requested by the Codex Committee on Food Additives. Since new data were available at the present meeting, the Committee reevaluated the existing studies and decided to raise the ADI, but on a temporary basis, in accordance with the application of the usual safety factor to the observed feeding level producing no adverse effects in long-term studies. The present evaluation considered the effects of polyvinylpyrrolidone ingested from all sources. Thus, the Committee allocated to polyvinylpyrrolidone a temporary ADI of 0-25 mg/kg of body weight, and required the submission of 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.

No new toxicological monograph was prepared and the existing specifications were maintained.

#### Potassium bromate

Potassium bromate is used mainly as an agent for the treatment of flour and was considered in this respect in the seventh report of the Committee (Annex 1, reference 7). This substance was placed on the agenda of the present Committee because recent studies have demonstrated that it is carcinogenic when administered to rats in their drinking-water. The evidence available to the Committee indicated that bromate used as a flour-treatment agent is reduced to bromide during the baking of products prepared with the treated flour. Evidence was also adduced that potassium bromate used for another purpose—namely, for treating barley in beer-making—is reduced to bromide during the brewing process. However, the Committee was informed that the addition of potassium bromate to certain processed fish products results in appreciable residues of bromate in the food ingested by consumers. The Committee reiterated the evaluation contained in the seventh report and recognized that, as a general principle, bromate should not be present in food as consumed; therefore the use of potassium bromate could only be approved if it resulted in negligible residues. The main

toxicological consideration that arises is concerned with the maximum tolerable daily intake of bromide, which should be dealt with at a subsequent meeting in the light of more recent studies than those that were available to the Committee at the time of its seventh report.

The Committee decided to change the previous acceptance of potassium bromate for the treatment of flour used for baking products to a temporary acceptance with a maximum treatment level of 75 mg potassium bromate per kg of flour, provided that bakery products prepared from such treated flour contain negligible residues of potassium bromate. For other foods, no acceptable level of treatment was proposed. Further work was required to establish the residual levels of potassium bromate in foods treated with it.

A toxicological monograph was prepared, and the existing specifications were revised.

#### L-(+)-Tartaric acid, ammonium, calcium, and magnesium salts

L-(+)-Tartaric acid and its potassium, sodium, and mixed potassium-sodium salts were evaluated in the twenty-first report of the Committee (Annex 1, reference 43). Consideration of the additional salts was requested by the Codex Committee on Food Additives. However, since no specifications were prepared, no ADI was allocated.

No toxicological monograph was prepared.

DL- $(\pm)$ -Tartaric acid, ammonium, calcium, and magnesium salts

The Committee took this opportunity to revise the specifications for DL- $(\pm)$ -tartaric acid. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification. The Committee was not aware of the use of ammonium, calcium, or magnesium salts of DL- $(\pm)$ -Tartaric acid as food additives and requested additional information in this regard.

No toxicological monograph was prepared, and no ADI was allocated.

<sup>&</sup>lt;sup>1</sup> In 1966, the joint report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues established an ADI for man for inorganic bromide, from all sources, of 0–1.0 mg/kg of body weight (WHO Technical Report Series, No. 370, 1967; FAO, PL:CP/15; and WHO/Food Add./67.32).

#### 3.2 Contaminants

#### 3.2.1 Metals

Arsenic

In the tenth report of the Committee (Annex 1, reference 12) a maximum acceptable daily limit for arsenic was set at 0.05 mg/kg of body weight. The present Committee withdrew this limit since new data available to suggested that the limit is too high for inorganic arsenic.

The Committee recognized that inorganic and organic forms of arsenic present different problems. Epidemiological studies indicate that ingested inorganic arsenic may be carcinogenic in man at doses that produce signs of chronic arsenic toxicity, but accurate quantification of an acceptable exposure level is not possible owing to complicating factors in the populations that were exposed to drinkingwater containing high concentrations of arsenic or to arsenical therapy. Animal models so far employed have not been useful for studying the question of the carcinogenic effect of inorganic arsenic.

There is evidence that organic arsenical compounds occur in a wide variety of foods and that relatively high concentrations may be present in some foods, particularly in certain sea foods. However, little is known about the chemical nature of these arsenical compounds and their relative distribution in foods. Work is therefore needed on the identification, metabolism, and potential toxicity of these compounds. However, there is no evidence to suggest that people who regularly consume large amounts of fish suffer ill-effects from its content of organic arsenic; the limited amount of animal data that are available also support the conclusion that ingestion of such fish does not constitute a hazard.

On the basis of the data available, the Committee could arrive at only an estimate of 0.002 mg/kg of body weight as a provisional maximum tolerable daily intake for ingested inorganic arsenic; no figure could be arrived at for organic arsenicals in foods. A toxicological monograph was prepared.

Iron

Although iron is an essential nutrient and an unavoidable constituent of foods, it may also be present as a contaminant. It has not been previously considered by the Committee in this context, but

some iron-containing compounds have been accepted for food additive use. In the twenty-second (Annex 1, reference 48) and twenty-third (Annex 1, reference 51) reports of the Committee, "iron oxides and hydrated iron oxides" were evaluated for use as food colouring agents. The iron in these compounds is in the ferric form and has low bioavailability, and the results of feeding experiments with high levels did not result in any adverse effects. Hence, an ADI of 0–0.5 mg/kg of body weight for iron oxides and hydrated iron oxides (expressed as iron) was established (Annex 1, reference 51). In its nineteenth (Annex 1, reference 37) report, the Committee considered ferrous gluconate as a food colouring agent with a limited use, and established an ADI "not specified" provided that the ADI for gluconic acid was not exceeded.

A considerable body of information about iron is available from biochemical, physiological, and epidemiological studies, as well as from studies particularly oriented to toxicological aspects. The nutritional requirement for iron depends on age and sex. Recommended daily dietary requirements for iron range from 10 mg for adult men and post-menopausal women to 20 mg for women of child-bearing age. Adequate guidelines for nutritional requirements for iron have been published.<sup>1,2</sup>

There is still some uncertainty with regard to the maximum level of iron that can be tolerated. Normal individuals have taken daily supplements of 50 mg of iron per day (ferrous iron) for long periods without any adverse effects. The body has a considerable capacity to store iron, and chronic iron toxicity occurs only when the stores have been overloaded. This may occur in a number of disorders of absorption, distribution, and utilization of iron.

On the basis of the data available, the Committee allocated a provisional maximum tolerable daily intake to iron of 0.8 mg/kg of body weight. 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 and lactation or for specific clinical requirements.

The Committee reiterated the view, expressed in the twenty-sixth report, that the tolerable daily intake should not be used as a

<sup>&</sup>lt;sup>1</sup> Recommended dietary allowances, revised edition. Washington, DC, National Academy of Sciences, 1980.

<sup>&</sup>lt;sup>2</sup> Handbook of human nutritional requirements. Geneva, World Health Organization, 1974 (Monograph Series, No. 61).

guideline for fortifying processed food (Annex 1, reference 60, section 2.8).

A toxicological monograph was prepared.

#### 3.2.2 Xenobiotic anabolic agents

The use of hormones and substances with hormonal activity in animal husbandry was considered in the twenty-sixth report of the Committee (Annex 1, reference 60). In that report the Committee had recommended some general principles with respect to the evaluation of xenobiotic anabolic agents for use in the raising of animals for food. The data requirements included: "(a) adequate, relevant toxicological data; and (b) comprehensive data about the kinds and levels of residue when substances are used according to good animal husbandry practice." The Committee was aware of the extensive use of trenboline acetate and zeranol as anabolic agents in cattle.

Evaluating the toxicological data submitted to it, the Committee encountered several problems. Some of the data on residues were from studies in which the xenobiotic agents were used in combination with natural hormones (or their derivatives) and no toxicological studies of these combinations were available. The Committee also encountered problems with regard to the design of the necessary toxicological studies and to the potential tumorigenic activity of these compounds. The main problem was that the side-effects of the hormones used made the interpretation of results obtained difficult in the long-term studies with high doses. Furthermore, it was difficult to rule out completely some slight hormonal activity of even the lowest doses administered in the animal feeding studies. Therefore, the Committee had to determine whether or not the residues (or metabolites of the agents used) in animal tissue would be completely devoid of endocrinological or toxicological consequences for the consumer.

The Committee had for its consideration the results of detailed studies on the nature and levels of residues of trenbolone acetate and zeranol and their metabolites in muscle and edible organs of cattle and other animals treated with those agents. In cattle treated with trenbolone acetate according to good animal husbandry practice, the residue levels did not exceed 3  $\mu g$  of  $\alpha$ -trenbolone per kg of liver and 0.5  $\mu g$  of  $\beta$ -trenbolone per kg of other tissues. In cattle treated with zeranol according to good animal husbandry practice, the

residue level did not exceed 1  $\mu$ g/kg of any tissue. The limits of sensitivity for the radioimmunoassays used for measuring the residues were 0.1  $\mu$ g/kg of tissue for the trenbolone isomers and 0.5  $\mu$ g/kg of tissue for zeranol. The evidence before the Committee indicated that the concentrations of residues found in the tissues of experimental animals are far below the threshold for the concentrations producing endocrinological effects.

#### Trenbolone acetate

Trenbolone acetate was considered in the twenty-sixth report of the Committee (Annex 1, reference 60). At that time, the Committee had extensive data on the toxicity and metabolism of trenbolone, but no data were available on the levels of its residues and metabolites when trenbolone acetate is used in rearing animals for food. The present Committee reconsidered trenbolone acetate in the light of the available values for residue levels measured in rats and cattle using a highly sensitive and specific technique.

The Committee reviewed long-term studies in the mouse and rat, the latter involving *in utero* exposure to trenbolone acetate. In mice, significant increases in nodular hyperplasia and liver-cell tumours were noted only at the two highest dose levels tested in males and were restricted to the highest dose level tested in females. In rats, there was a slight increase in the incidence of islet-cell tumours of the pancreas with the highest dose level tested. The Committee considered that these lesions arose as a consequence of the hormonal action of trenbolone.

The apparent no-effect level for hormonal activity in mice was estimated to be 0.5 mg/kg in the diet (50  $\mu$ g/kg of body weight). In rats, a clear no-effect level for hormonal activity was not observed at the lowest test dose of 25  $\mu$ g/kg of body weight.

The Committee was informed that a study is being carried out to establish a no-hormonal-effect level in non-human primates.

The available data on residues in tissues indicate that the residue levels do not exceed 3  $\mu g$  of  $\alpha$ -trenbolone per kg of liver and 0.5  $\mu g$  of  $\beta$ -trenbolone per kg of other tissues; the Committee noted that the biological activity of  $\alpha$ -trenbolone is less than 10% of that of  $\beta$ -trenbolone.

The Committee was of the opinion that the low residue levels of trenbolone acetate and its metabolites in meat products would result in exposures far below the levels at which hormonal activity was observed in animal models. The Committee provisionally accepted the use of trenbolone acetate as an anabolic agent for the production of meat for human consumption in accordance with good animal husbandry practice, and requested the submission of the results of the study in non-human primates referred to above.

#### Zeranol

Zeranol was also considered in the twenty-sixth report of the Committee, in 1982 (Annex 1, reference 60). At that time, the Committee was supplied with extensive data on the toxicity and metabolism of zeranol, but it did not have the necessary documentation on residue levels and details of methods and analyses used in the studies. At the present meeting, the Committee reconsidered zeranol in the light of new data on residue levels of zeranol in rats, cattle, and sheep from studies that had employed highly sensitive and specific techniques.

Three factors were considered by the Committee for the evaluation of zeranol: (a) the available data on possible carcinogenic effects; (b) endocrine and non-endocrine effects; and (c) residues that were likely to occur in animal tissues.

Long-term feeding studies were available for the rat (1 and 2 years), the dog (2 and 7 years), and the monkey (10 years). Although there were shortcomings in the design of these studies, no carcinogenic effects were observed. Even at exaggerated levels of exposure, the only effects observed could be related to the estrogenic activity of the test compound. A dietary level of zeranol of 1 g/kg produced a clear estrogenic effect in a two-year study in dogs, but only slight effects were noted at dietary zeranol levels of 1 mg and 100 mg/kg, and these were not dose-related.

The estimated no-effect level for estrogenic activity in the two-year study in dogs was 1 mg/kg in the diet or  $25\,\mu\text{g/kg}$  of body weight. The Committee noted that a study is presently under way to establish a no-effect level for hormonal activity in non-human primates. In addition, because of the shortcomings of the available carcinogenicity data, the Committee required that an adequate carcinogenicity study in two rodent species be carried out.

The available data on residues in tissues indicated that the residue of zeranol or its metabolites would not exceed  $1 \mu g/kg$  in animal tissues. The Committee was of the opinion that the low residues of zeranol and its metabolites in meat products would result in ex-

posures far below the levels at which hormonal activity was noted in animal models.

The Committee provisionally accepted the use of zeranol as an anabolic agent for production of meat for human consumption in accordance with good animal husbandry practice, and requested the submission of the results of the studies (both ongoing and required) referred to above.

### 4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications of a large number of substances and also developed new specifications (some tentative) for five additional substances; these included emulsifiers, buffering agents, flavouring agents, sweetening agents, thickening agents, and miscellaneous food additives (see Annex 2).

A number of specifications were recommended by the sixteenth session of the Codex Committee on Food Additives for adoption by the Committee after editorial correction. The Committee reviewed these specifications with a view to making editorial changes and concurred with the revisions suggested. The compounds involved were (+)-carvone, (-)-carvone, light petroleum, and magnesium di-L-glutamate.

In considering certain hydrogenated carbohydrates (polyols), separate specifications could be readily elaborated for products such as lactitol and xylitol, which are prepared from individual carbohydrates such as lactose and xylose. Other products are manufactured from starting materials containing a mixture of carbohydrates known as "glucose syrups"—a term which can be applied to a wide range of products. When the glucose syrup contains predominantly glucose, the hydrogenated product is known as sorbitol syrup. However, a range of glucose syrups exists that contains predominantly maltose, which on hydrogenation yields maltitol. The latter range of products evaluated could be encompassed by one specification entitled "hydrogenated glucose syrup", whereas the former was a sufficiently different product to be characterized in a separate specification entitled "sorbitol syrup".

The Committee discussed which of the various tests for ash content was the most appropriate indication of quality for polysaccharide gums, and requested further information in this regard.

In evaluating the specifications for extraction solvents, the Committee noted the difficulty in establishing specifications for substances that might be subject to degradation. Stabilizers are usually added to extraction solvents, and residues of the breakdown products of the solvent are related to the nature of the added stabilizer. The revised specifications were designated as "tentative" and the Committee requested the submission of data on the nature, level(s), and methods of analysis for stabilizers and breakdown products in solvents.

The existing specifications for gaseous carbon dioxide were revised to include other forms used in food manufacture and were designated as "tentative".

In the evaluation of specifications for magnesium lactate, the Committee considered its two isomers: magnesium L-lactate and magnesium DL-lactate; both existing specifications were revised.

#### 5. FUTURE WORK

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

2. The specifications for food colours should be revised as a group to reflect current methodology; they should also be reviewed for consistency.

#### 6. RECOMMENDATIONS TO FAO AND WHO

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

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

3. The Directors-General of FAO and WHO should consider mechanisms by which extraordinary meetings of the Committee could be called at short notice if the potential for serious risk to public health were indicated by the findings of toxicological studies of a substance within the Committee's terms of reference.

- 4. In addition to the other criteria used in deciding on the list of substances to be evaluated by the Joint Expert Committee, it is recommended that evidence be obtained that the substance is actually used or is proposed for use as a food additive.
- 5. During sessions of the Codex Committee on Food Additives (CCFA), specific problems are sometimes identified for which the advice of the Joint FAO/WHO Expert Committee on Food Additives is sought. This would be facilitated if such problems were brought regularly to the attention of the Joint Expert Committee and if the joint CCFA secretariat were requested to prepare an appropriate working paper.
- 6. When a substance is proposed for evaluation by the Joint Expert Committee, any related substances that have been evaluated previously by it should be re-evaluated at the same time on the basis of the most recent data available.
- 7. The Committee had been requested to evaluate the two anabolic agents trenbolone acetate and zeranol. In so doing, it noted that a large number of substances are used in animal husbandry, and that careful attention should be paid in the future to the evaluation of these substances. The Committee concluded that any further evaluations of such substances should be carried out by a group including:

  (a) toxicologists to assess the safety of the anabolic agents to man;

  (b) veterinarians to establish husbandry practices regarding their use and to assess their safety to animals raised for food; and (c) chemists to assess the methods of analysis and residue levels in meat.
- 8. The Committee is aware that there are many national and international groups, including the Codex Committee on Special Dietary Foods, that are interested in the fortification of foods. There is a need to bring to the attention of these groups the fact that the maximum tolerable daily intakes recommended by the Expert Committee should *not* be construed as levels for fortification.
- 9. For all substances to be evaluated, the Committee recommended that the requirement that all data should be submitted well in advance of the meeting should be strictly adhered to.
- 10. The Committee reiterated the need to establish priorities for testing and evaluation of food additives and for reviewing the requirements for the data needed for evaluating various classes of food additives, in particular, flavouring agents, as recommended in the twenty-second and twenty-third reports of the Committee.

11. In considering arsenic as a contaminant and constituent of foods, the Committee emphasized the need for epidemiological studies on consumption of foods containing high levels of organic arsenicals, and further studies on population groups exposed to high levels of inorganic arsenic in drinking-water.

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

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

1. General principles governing the use of food additives (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).

 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).

 Evaluation of the carcinogenic hazards of food additives (Fifth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).

6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962.

7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 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.

\*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. 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 (out of print).
- \*13. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29, 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 (out of print).
- \*15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
- \*16. Specification and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
- 17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
- \*18. Specifications for the identity and purity of some antibiotics. FAO Nutrition Meetings Report Series, No. 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: WHO/Food Add/70.36.
- \*21. Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 46B; WHO/Food Add/70.37.
- 22. Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents (Fourteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No 48, 1971; WHO Technical Report Series, No. 462, 1971.
- \*23. Toxicological evaluation of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.
- \*24. Specifications for the identity and purity of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.

- \*25. A review of the technological efficacy of some antimicrobial agents. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.
- 26. Evaluation of food additives: some enzymes, modified starches, and certain other substances: toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants (Fifteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.
- 27. Toxicological evaluation of some enzymes, modified starches, and certain other substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.
- 28. Specifications for the identity and purity of some enzymes and certain other substances. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.
- 29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.
- 30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
- 31. Evaluation of mercury, lead, cadmium, and the food additives amaranth, diethylpyrocarbonate, and octyl gallate. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.
- 32. Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum.
- 33. Toxicological evaluation of certain food additives including anticaking agents antimicrobials, antioxidants, emulsifiers, and thickening agents. FAO Nutrition Meetings Report Series, No. 53A; WHO Food Additives Series, No. 5, 1974.
- 34. Evaluation of certain food additives (Eighteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.
- 35. Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.
- 36. Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents, and certain food additives. FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.
- 37. Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances (Nineteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.
- 38. Toxicological evaluation of some food colours, thickening agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 55A; WHO Food Additives Series, No. 8, 1975.
- 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.

- 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.
- Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 10, 1978.
- 42. 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.
- Evaluation of certain food additives (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.
- 44. Summary of toxicological data of certain food additives. WHO Food Additives Series, No. 12, 1977.
- 45. Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others. FAO Nutrition Meetings Report Series, No. 57, 1977.
- 46. Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers. FAO Food and Nutrition Paper, No. 4, 1978.
- 47. Guide to specifications General notices, general methods, identification tests, text solutions, and other reference materials. FAO Food and Nutrition Paper, No. 5, 1978
- 48. Evaluation of certain food additives (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
- 49. Summary of toxicological data of certain food additives and contaminants. WHO Food Additives Series, No. 13, 1978.
- 50. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 7, 1978.
- 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.
- Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 14, 1979.
- 53. Specifications for identity and purity of food colours, flavouring agents, and other food additives. FAO Food and Nutrition Paper, No. 12, 1979.
- 54. Evaluation of certain food additives (Twenty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 653, 1980.
- Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 15, 1981.
- Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives). FAO Food and Nutrition Paper, No. 17, 1980.
- 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.
- Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 16, 1982.

- 59. Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives). FAO Food and Nutrition Paper, No. 19, 1981.
- 60. 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.
- 61. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 17, 1983.
- 62. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 25, 1982.

#### Annex 2

## ACCEPTABLE DAILY INTAKES AND INFORMATION ON SPECIFICATIONS

	Specifications <sup>1</sup>	ADI for man (mg/kg of body weight [and other toxi- cological decisions])
A. Specific food additives		
Antioxidants Butylated hydroxyanisole (BHA) Butylated hydroxytoluene (BHT)	S R	0-0.5 <sup>3</sup> 0-0.5 <sup>9</sup>
Extraction solvents Dichloromethane (methylene chloride) 1,1,2-Trichloroethylene	RT RT	ADI withdrawn <sup>10</sup> No ADI allocated <sup>2</sup>
Flavouring agents trans-Anethole Benzyl acetate (+)-Carvone and (-)-carvone Ethyl methylphenylglycidate	R R R ST	0-2.5 <sup>3</sup> 0-5 <sup>3</sup> 0-1.0 <sup>3</sup> , <sup>5</sup> No ADI allocatd <sup>2</sup>
Food colours Azorubine Ponceau 4R	S S	0–4 0–4
Preservatives Calcium benzoate Calcium metabisulfite	N O	0-5 <sup>6</sup> 0-0.7 <sup>7</sup>
Sweetening agents Acesulfame potassium Hydrogenated glucose syrup Lactitol Thaumatin Xylitol	R N N N R	0–9 0–25 <sup>3</sup> ADI not specified <sup>4</sup> No ADI allocated <sup>2</sup> ADI not specified <sup>4</sup>
Thickening agents Ethylhydroxyethyl cellulose Karaya gum Tragacanth gum	NT R R	0–25 <sup>8</sup> 0–20 <sup>3</sup> No ADI allocated <sup>2</sup>
Miscellaneous food additives Ammonium phosphate, monobasic Insoluble polyvinylpyrrolidone Polyvinylpyrrolidone (PVP)	S RT S	[70] <sup>11</sup> ADI not specified <sup>4</sup> 0–25 <sup>3</sup>

Specifications <sup>1</sup>	ADI for man (mg/kg of body weight [and other toxi- cological decisions])
R	Temporary accep- tance <sup>15</sup>
0	No ADI allocated12
R	No ADI allocated <sup>13</sup>
	•
_	$[0.002]^{14}$
_	$[0.8]^{14}$
	Provisional acceptance (see section 3.3) <sup>2</sup>
<del>-</del> '	Provisional acceptance (see section 3.3) <sup>2</sup>
	0

	Specifications on	$ly^1$
Bacillus licheniformis α-amylase	R	
DL-Calcium malate	R	
Carbon dioxide	RT ·	
Carob bean gum	RT	•
Castor oil	R	•
Collagen	O	
Diethyl ether	RT	
Dioctyl sodium sulfosuccinate	R	
Disodium pyrophosphate	RŤ	•
Ethyl nonanoate	R	
Glutaraldehyde	O	
Isomalt	RT	
Magnesium chloride	R	
Magnesium di-L-glutamate	R	
Magnesium gluconate	R	
Magnesium hydroxide carbonate	R	
Magnesium lactate (DL and L isomers)	R	÷ ,
Modified starches	RT	÷
Nitrous oxide	S	<del>-</del> -
Pentapotassium triphosphate	S	
Polyethylene glycols	. <b>R</b>	
Polyglycerol esters of fatty acids	R	
Potassium dihydrogen citrate	R	

Potassium nitrate	R
Potassium polyphosphate	S
Propyl gallate	R
Sodium dihydrogen citrate	RT
Sodium fumarate	RT
Sorbitol syrups	R
Sucrose esters of fatty acids	R
Sucroglycerides	R
Talc	R
Tetrasodium pyrophosphate	RT
Triammonium citrate	R

#### Notes to Annex 2

- <sup>1</sup> N, new specifications prepared; O, specifications not prepared; R, existing specifications revised; S, specifications exist, revision not considered; T, the existing, new or revised specifications are tentative and comments are invited.
- <sup>2</sup> Insufficient toxicological data were available, or specifications were unsatisfactory.
- Temporary acceptance.
- The statement "ADI not specified" means that, on the basis of the available data (chemical, biochemical, toxicological, and other), the total daily intake of the substance, arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, and for the reasons stated in the individual evaluations, the establishment of an acceptable daily intake (ADI) is not deemed necessary.
- As the sum of the isomers.
- Group ADI for benzoic acid and its calcium, potassium and sodium salts expressed as benzoic acid.
- Group ADI for sulfur dioxide and sulfites expressed as sulfur dioxide, covering sodium and potassium metabisulfite, sodium sulfite, potassium and sodium hydrogen sulfite and sodium thiosulfate.
- Group ADI for modified celluloses.
- Group ADI. As BHA, BHT, and TBHQ, singly or in combination. Note that the ADI for BHA is temporary.

  10 The existing ADI was withdrawn since the available data were inadequate.
- 11 This figure represents the maximum tolerable daily intake (MTDI) of phosphates. It is not an ADI. The MTDI is expressed as phosphorus and it applies to the sum of phosphates naturally present in food. 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 proportionally higher, and the reverse relationship would also apply.
- <sup>12</sup> No ADI could be allocated in this case since no specifications were prepared.
- 13 No information was available on the use of this substance as a food additive.
- <sup>14</sup> Provisional maximum tolerable daily intake.
- 15 The previous acceptance of potassium bromate for the treatment of flour used for baking products was changed to a temporary acceptance with a maximum treatment level of 75 mg potassium bromate per kg of flour.

#### Annex 3

## FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

#### **Antioxidants**

Butylated hydroxyanisole (BHA)3

(1) Studies to show whether or not hyperplasia is induced in the stomach of species that do not have a forestomach—such as the dog, pig, and monkey.

(2) Studies to determine the mechanism involved in the effect of

BHA on the forestomach.

#### Flavouring agents

trans-Anethole1

(1) Adequate long-term feeding study.

Benzyl acetate<sup>2</sup>

- (1) Submission of the final report of the recent screening tests for carcinogenicity.
  - (+)-carvone and (-)-carvone<sup>3</sup>
- (1) Submission of the results of the long-term feeding studies in the rat and mouse known to be in progress.
- (2) Biochemical and metabolic studies in several animal species, preferably including man.

#### Sweetening agents

Hydrogenated glucose syrup<sup>2</sup>

(1) Submission of the results of a lifetime feeding study with a minimum of three dose levels.

#### Thickening agents

Ethylhydroxyethyl cellulose<sup>2</sup>

(1) 90-day feeding study in an animal species.

Karaya gum²

(1) Submission of the results from a short-term feeding study in a non-rodent species.

#### Miscellaneous food additives

Polyvinylpyrrolidone (PVP)<sup>2</sup>

(1) Submission of evidence from feeding studies in a non-rodent species showing that the accumulation of PVP in cells of the reticuloendothelial system does not entail adverse effects.

Potassium bromate<sup>2</sup>

(1) Studies to establish the residual levels of potassium bromate in foods treated with it.

<sup>&</sup>lt;sup>1</sup> Information required by 1984 <sup>2</sup> Information required by 1985

<sup>&</sup>lt;sup>3</sup> Information required by 1986

#### WORLD HEALTH ORGANIZATION TECHNICAL REPORT SERIES

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