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Evaluation of certain food additives and contaminants

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

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CONTENTS

	<i>Page</i>
1. Introduction	7
2. General considerations	8
2.1 Modification of agenda	8
2.2 General topics	8
2.3 Principles governing toxicological evaluation	11
3. Comments on specific food additives and contaminants	18
3.1 Evaluation and re-evaluation	18
3.2 Contaminants	25
4. Establishment and revision of certain specifications	28
5. Future work	28
6. Recommendations to FAO and WHO	29
Annex 1. Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives	31
Annex 2. Acceptable daily intakes and information on specifications	35
Annex 3. Further toxicological studies and information required	38

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Rome, 3-12 April 1978

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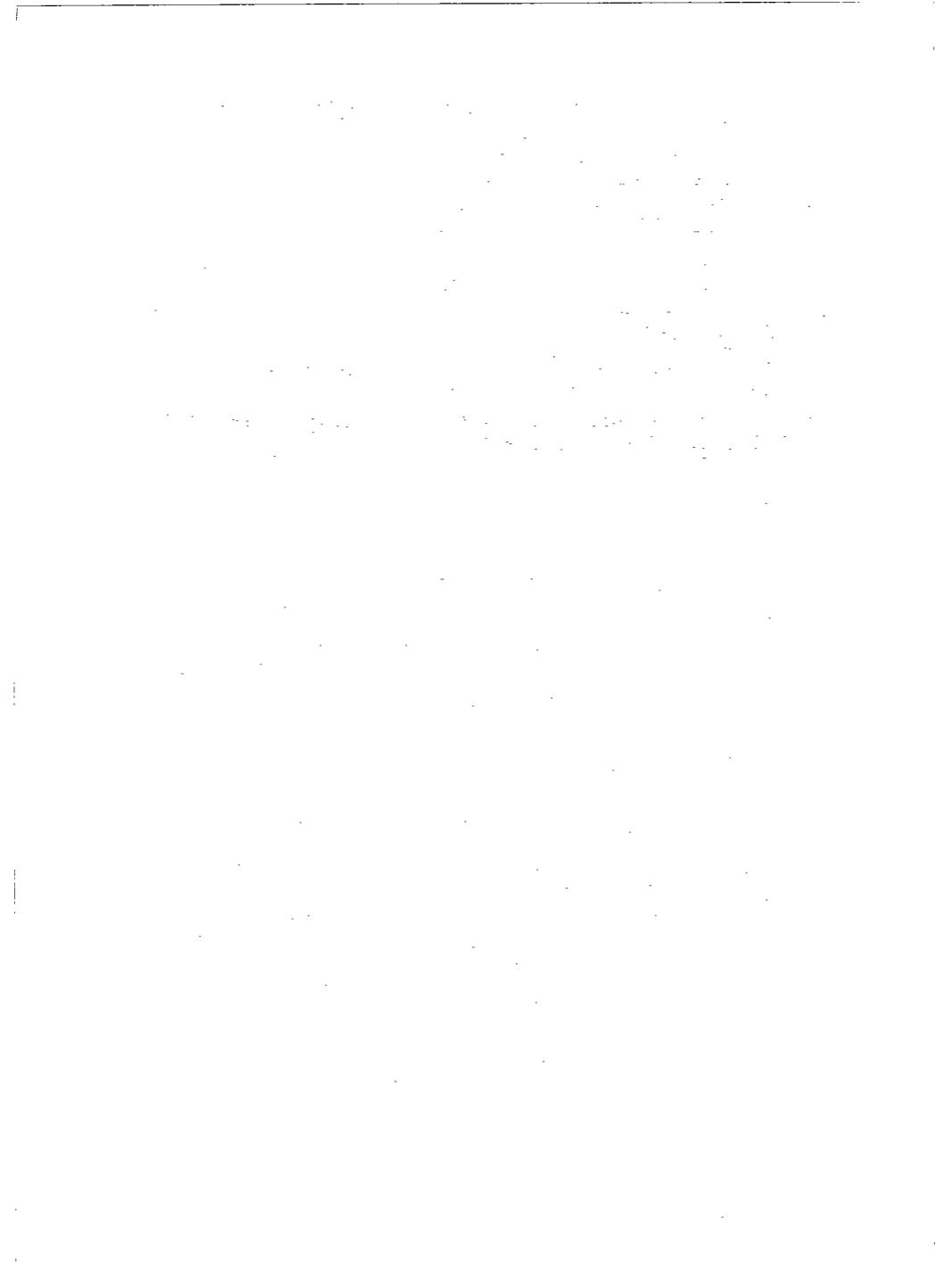
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EVALUATION OF CERTAIN FOOD ADDITIVES

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

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 3 to 12 April 1978. The meeting was opened by Mr G. O. Kermode, Officer-in-Charge, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Mr Kermode invited the Expert Committee to review the approach adopted so far in considering food additives. In spite of the great amount of work that had already been achieved, there were still formidable numbers of flavouring agents, enzymes, and additives belonging to other groups that the Committee had not yet been able to consider. Member States were concerned about many of these substances, and there was also a need to establish long-term strategies for the public health control of the chemicals used in industry, agriculture, and food production, and of the environmental pollution resulting from rapid industrialization and new technology.

1. INTRODUCTION

The tasks before the Expert Committee were: (1) to prepare specifications and carry out a toxicological evaluation of certain food additives; (2) to review the findings of toxicological studies of certain food additives; (3) to revise specifications for selected food additives including enzyme preparations; (4) to undertake a toxicological re-evaluation of certain food additives; (5) to review the problem of exposure of the general population to certain food contaminants; (6) to review the impact of new scientific methods on the safety evaluation of chemical substances; (7) to review long-term effects of food additives and contaminants following exposure *in utero* and during suckling; and (8) to consider suitable approaches for the systematic and expeditious testing and evaluation of food additives and contaminants.

2. GENERAL CONSIDERATIONS

2.1 Modification of agenda

The Committee agreed to consider the toxicological evaluation of maltol, xylitol, and sorbitol. It agreed to add pectin (amidated) and tertiary butyl hydroquinone (TBHQ) to the list of compounds for revision of specifications. In addition to glucose isomerase (*Bacillus coagulans*) the Committee agreed to prepare new specifications for the glucose isomerases from *Streptomyces olivaceus* and *S. violaceoniger* as well as for a carbohydrase from *Klebsiella aerogenes*.

2.2 General topics

Criteria for microbiological limits in specifications for food additives

The Committee had before it the two reports of the Joint FAO/WHO Expert Consultation of Microbiological Specifications for Foods, held in Geneva in 1975 and 1977.¹

The Committee was informed that the Consultation had not had sufficient time, at its meeting in 1977, to deal with the request made by the Joint FAO/WHO Expert Committee on Food Additives, at its twentieth meeting,² for advice on a number of food additives. The Consultation did, however, include some of the additives in the list of foods and ingredients for which the establishment of microbiological criteria should be explored further. These included enzyme preparations, gelatin, casein, and caseinates.

In addition, the Consultation drew attention to the possibility that, even though for a number of the food additives the manufacturing process included steps that could significantly reduce the number of viable microorganisms, this did not preclude recontamination upon subsequent handling. The Consultation therefore

¹ Microbiological specifications for foods. Report of a Joint FAO/WHO Expert Consultation. Rome, FAO, 1975 (EC/Microbiol/75/Report 1); Microbiological specifications for foods. Report of the Second Joint FAO/WHO Expert Consultation. Rome, FAO, 1977 (EC/Microbiol/77/Report 2).

² See Annex 1, reference 40.

recommended that the Codex Committee on Food Hygiene consider the preparation of a code of practice for foods and ingredients that might be subject to recontamination upon subsequent handling.

Furthermore, the Codex Committee on Food Hygiene had stressed that microbiological specifications should be applied with circumspection and that the primary concern of protecting the health of the consumer should be viewed in practical terms, taking into account the nature of foods and their processing.

Microbiological specifications cannot prevent occasional mishandling or misuse, which may lead to cases of foodborne disease. Therefore, taking into account the cost-benefit aspects of the application of criteria, the Consultation recommended that microbiological specifications should be set only for additives and ingredients that are known to be "sensitive" (e.g., caseins, enzymes) and that might be included in products receiving no further processing, to control the hazard before those products are consumed.

The Committee concluded that further information was needed, for instance from suppliers, on typical total bacterial counts of products of natural origin. Such information, once gathered, would enable experts to identify areas where work is warranted. It was therefore recommended that governments and experts in the private sector should be asked for their views on the major problems raised above, requesting their advice and available publications on the subject.

Enzymes: general considerations

Prior to revising existing specifications and developing new specifications for enzyme preparations for food processing, the Committee considered the following:

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

(6) A list of carriers and diluents, with limits where appropriate.

(7) A list of preservatives present from manufacture or deliberately added, with limits where appropriate.

The modifications deemed applicable by the Committee were then to be incorporated into the revision and preparation of new specifications.

Existing enzyme specifications were brought up to date and new ones were prepared in accordance with the general principles elaborated for these food additives in the fifteenth report of the Committee. In all instances attention was drawn to the fact that these specifications must be read in conjunction with the "General specifications for enzyme preparations for food processing".¹ In addition to the enzyme activity methods described in the above-mentioned publication, three new assay methods were included in the specifications: for glucose isomerase (2 methods) and for pullulanase.²

For the first time, IUB³ numbers were given to enzymes for which revised or new specifications had been prepared. However, such numbers were used solely for the major enzyme component of a given preparation.

Contaminating enzymes that might be expected to be present in particular products were listed as minor active principles.

The use of generic headings for enzymes derived from varieties of a given genus and species was retained in the case of "carbohydrase" and "protease". In this context "carbohydrase" refers to the group of enzymes hydrolysing O-glycosyl compounds such as starch.

Once again it is emphasized that carriers, diluents, and preservatives are permitted only if the Joint FAO/WHO Expert Committee on Food Additives considers them acceptable for use, and their presence should be declared on the label. This matter should be drawn to the attention of the Codex Committee on Food Additives. The presence of foreign non-functional substances should be reduced to a minimum by good manufacturing practice.

¹ See Annex 1, reference 28.

² See *Specifications for the identity and purity of certain food additives*. FAO Food and Nutrition Paper No. 7, Annexes 2, 3, and 4.

³ Recommendations (1972) of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry.

Specifications for an immobilized enzyme—e.g., glucose isomerase—were prepared for the first time. The only exogenous cross-binding agent presented for evaluation is glutaraldehyde, and the specifications are therefore limited to that reagent.

Attention is drawn to the isomerases requiring the presence of cobalt as an activator during use and the need for proper control of the syrup production process to ensure the minimum carry-over of cobalt. Good manufacturing practice should ensure residual levels of less than 5 µg/kg of this ion at a syrup solids content of 25%.

Attention is also drawn to the new specifications for pullulanase derived from *Klebsiella aerogenes*. At one time, this microorganism had been classified in the ATCC¹ as *K. pneumoniae*, but data have been presented² to show that the original classification was erroneous.

2.3 Principles governing toxicological evaluation

Setting priorities for testing and evaluation of intentional and unintentional food additives

During its 22 years of existence, the Committee has reviewed the most important of the intentional food additives used widely and in significant quantities for improving the storage and processing of food. In addition to evaluating specific substances, the Committee and two working groups^{3, 4} have played an important role in encouraging the development of toxicity testing and in outlining procedures for the evaluation of the results of toxicological studies in terms of the safety in use of food additives. When its terms of reference were expanded, the Committee also dealt with some of the most important of the food contaminants that were known to be hazardous to health, notably the heavy metals mercury, lead, and cadmium. At its successive meetings, the Committee has responded promptly and sensitively to new

¹ ATCC = American Type Culture Collection.

² See Annex 1, reference 28.

³ *Procedures for investigating intentional and unintentional food additives. Report of a WHO Scientific Group.* WHO Technical Report Series, No. 348, 1967.

⁴ *Assessment of the carcinogenicity and mutagenicity of chemicals. Report of a WHO Scientific Group.* WHO Technical Report Series, No. 546, 1974.

biological discoveries that appeared to have a bearing on the safety aspects of food additives and contaminants.

However, a large number of chemicals contained in food have never been studied by the Committee. Some of these are intentional additives, the most important and largest group being flavouring substances, of which only a few have been evaluated. Only a few of the adventitious additives, such as residues of processing aids, residues of animal feed additives, and substances migrating from packaging materials into food, have been evaluated. Furthermore, comparatively little attention has been paid to the many contaminants with known or suspected toxicity, or to potentially toxic natural constituents of foods.

The problem raised by the large numbers of food additives and contaminants that have not yet been evaluated was recognized in the twenty-first report of the Committee,¹ and the recommendation was made that WHO should consider ways and means of expediting the FAO/WHO programme on food additives. Subsequently, the World Health Assembly adopted a resolution concerning the evaluation of the health effects of chemicals generally and requesting the Director-General to undertake a study on the long-term strategies and possible options for international cooperation in this field.² As a first step in the study, a consultation on the implementation of the resolution was held in Geneva in September 1977, and the possible tasks to be undertaken were identified and a number of options for their implementation were proposed.

The present Committee noted this progress with satisfaction and recommended that, in any option adopted following the study recommended in the resolution, food additives and contaminants should be considered as one of the priority groups of substances for accelerated and systematic evaluation. Many of the compounds already considered and evaluated by the Committee could serve as models for assessing the validity of testing methods and the appropriateness of procedures for evaluation of the effects on health of chemicals generally. The proposals for the provisional assessment of potential hazards of food additives described below and for testing them in proportion to the perceived hazards (see page 14) may also be applicable to other types of chemical in the environment. A further aim in accelerating the evaluation of food

¹ See Annex 1, reference 43.

² WHO Official Records, No. 240, 1977, p. 27 (resolution WHA30.47).

additives is to provide Member States and the Codex Alimentarius Commission with prompt and adequate recommendations on the acceptability of food additives.

In considering the problem, the Committee recognized that it would be impossible to undertake full toxicological studies with all the known food additives and contaminants within a reasonable period. Furthermore, to carry out such studies assigning equal importance to substances posing unequal risks would be a waste of effort. It is necessary, therefore, to set priorities for testing and evaluating these substances. The Committee discussed extensively the mechanisms for setting such priorities. It stressed that the assignment of a priority is not a substitute for a proper evaluation, but merely a means of ensuring that the compounds with the greatest toxic potential are studied first in preference to those with a lower priority.

Assessment of priorities is based on various types of information:

- (1) structure-activity relationships in so far as they serve to predict potential toxicity;
- (2) human exposure, in terms of the range of foods containing the substance, its concentration, and its intake in the diet;
- (3) the available toxicological data;
- (4) prior experience of human use;
- (5) metabolic fate of the substance in animals and man;
- (6) use in special populations at risk, such as pregnant women, very young infants, and persons with special disabilities.

By means of these criteria, compounds may be classified into various categories. Substances with the lowest priority for testing and evaluation are those that, in their structural characteristics, are not related to substances of demonstrated toxicity and are consumed in very small quantities. Compounds with a high priority either have structural features known to be associated with toxicity or are of unknown toxic potential and are present in human food in appreciable quantities.

Most compounds are expected to fall somewhere between the two extremes, and their priority for testing and evaluation should be set accordingly. The Committee noted a recent proposal that provides a useful procedure for estimating the toxic potential of

chemicals from various structural features.¹ This method, as well as other procedures for estimating toxic potential from structure-activity relationships, should be explored.

The Committee recognized the urgent need to establish an inventory of intentional and unintentional food additives that have not yet been evaluated, and recommended that an interdisciplinary working group of experts be convened by FAO and WHO for that purpose. The compounds in the inventory should then be classified by these experts in terms of potential toxicity and extent of use, to establish priorities for testing and evaluation by the Committee. As a first attempt, the present Committee looked at an existing priority listing of flavouring substances and proposed to its FAO/WHO Secretariat that some of these be submitted for evaluation by the Joint FAO/WHO Expert Committee on Food Additives at its next meeting.

Requirements for toxicological testing

The Committee recommended that compounds with high priorities set according to the criteria mentioned above should be subjected to comprehensive toxicity testing in animals as outlined by previous committees (see Annex 1). Compounds with lower priorities—that is, those whose structural characteristics are not related to substances of demonstrated toxicity and that are consumed in very small quantities—will not necessarily require as comprehensive a testing as the high-priority substances. The Committee did not wish to recommend the precise tests to be used for the low-priority compounds at this time, and proposed that WHO should explore the means to assemble a working group of experts who would evaluate available testing procedures and issue guidelines for an abbreviated testing programme. A compound may be reclassified into a higher priority class in the light of results obtained from such toxicological screening. It would then have to be studied more extensively.

The problem of trace contaminants in food

Owing to the increasing sensitivity of the analytical methods developed in recent years, many hitherto unsuspected compounds

¹ CRAMER, G. M. Estimation of toxic hazard — a decision tree approach. *Food and cosmetics toxicology* (1978) (in press).

have been detected in minute amounts in foods. The Committee emphasized that the presence of a trace amount of a toxic substance is not in itself a hazard to man. A health hazard can be determined only by taking into account toxicological knowledge and information about potential exposure. However, in the case of potent carcinogens, for example certain mycotoxins, the Committee believed that efforts should be made to limit their presence in food to irreducible levels. It defined an irreducible level as that concentration of a substance which cannot be eliminated from a food without involving the discarding of that food altogether, severely compromising the ultimate availability of major food supplies.

Feeding studies employing the progeny of exposed parents

Several groups have considered the desirability of recommending long-term feeding studies in which animals are exposed to the agent under study *in utero* and during suckling.^{1, 2} This question was discussed again by the present Committee. It was agreed that such studies would assist in evaluating the potential hazards of food additives or contaminants consumed by child-bearing women, and would also broaden the scope of toxicological assessment generally.³ However, so far, there have been only limited applications of this approach, which presents significant technical and logistic difficulties. Because of the complexity of this important and rapidly developing field, and its significance to public health, the Committee recommended that WHO explore the means of convening a meeting of experts to draw up guidelines for such studies.

Specifically, these experts should be requested to assess: (a) the degree of any increase in the sensitivity of toxicological testing afforded by exposure *in utero* and through lactation, and (b) the need to include such exposure in toxicological tests as a means of increasing public health protection.

¹ WHO Technical Report Series, No. 348, 1967 (*Procedures for investigating intentional and unintentional food additives: report of a WHO Scientific Group*).

² See Annex 1, reference 43.

³ *Transplacental carcinogenesis*. Lyons, International Agency for Research on Cancer, 1973 (Scientific publication No. 4).

The experts should also propose the most appropriate guidelines for experimentation, taking into account: (a) the dosages used and the relative exposure of mother and fetus to the agent under study; (b) the possibility of combining this modified long-term test with reproduction studies; (c) the length of the studies required; and (d) the most appropriate species to use.

In the meantime, it was agreed that, in the case of certain substances, requirements for such studies should be based on the best judgement of the Committee, and that the studies should be carried out in the light of existing data and other information that indicated their desirability.

International liaison

The Committee was aware that several international groups are involved in the toxicological evaluation of food additives, and that their conclusions have sometimes differed from those of the Joint FAO/WHO Expert Committees on Food Additives. Such discrepancies may be due to differing interpretations of the data, but generally they arise because of a difference in the data available for evaluation. If an international group has substantial new data and consequently arrives at an evaluation of a compound different from that of the Committee, these data should be requested and the compound should be re-evaluated promptly by the Committee.

Mechanisms to effect better liaison between various expert groups should be sought in order to ensure a greater degree of uniformity of the various evaluations.

Impact of new scientific methods on the safety evaluation of chemical substances

A WHO Scientific Group¹ and the Committee at its twentieth meeting² made reference to the rapid progress being made in the biological and chemical sciences and stressed the need for toxicologists to use this knowledge for a better assessment of the safety of chemical substances. In recent years, many new toxicological approaches have been developed. Rapid developments are taking

¹ WHO Technical Report Series, No. 348, 1967 (*Procedures for investigating intentional and unintentional food additives. Report of a WHO Scientific Group*).

² See Annex 1, reference 40.

place, for example, in the areas of *in vitro* and *in vivo* assessment of mutagenic and carcinogenic effects. Pharmacology, histochemistry, cytochemistry, immunopathology, biochemistry, molecular biology, and the behavioural sciences are all involved in the evaluation of toxicological processes and electron microscopy is being used in many laboratories.

These scientific approaches are of great importance since they often provide more insight into mechanisms of toxicity and thus allow a more realistic extrapolation to man, particularly when they are used in conjunction with detailed information on the absorption, distribution, metabolism, and excretion of the compounds under study.

Many biological methods are very sensitive, permitting recognition of clearly discernible effects at levels considerably below those causing changes demonstrable in conventional toxicological studies. Consequently, the "no-effect levels" observed in such studies will often be much lower than those found in conventional studies.

In many toxicological tests, compounds are applied by routes that do not correspond to ingestion in the diet by man. Moreover, the results of some tests are qualitative rather than quantitative, and this makes it difficult to correlate them with other experimental data.

In evaluating data from such tests it is important to use flexibility and careful scientific judgement in applying safety factors and assigning acceptable daily intakes (ADIs).

Publication of monographs

The Committee noted with concern WHO's decision, prompted by financial stringencies, to cease publishing for general sale the toxicological monographs in the WHO Food Additives Series.¹ Since these monographs are the only source of much of the otherwise unpublished information upon which decisions are based, the Committee felt that, as a result of the change, much of its work would be lost.

¹ This series is still issued in document form; copies are available, upon request to WHO.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

The Committee evaluated a number of food additives for the first time and also re-evaluated some substances that had been considered at previous meetings. Comments and decisions arising from these evaluations are set out below. In the case of organic salts, specifications were prepared only for food additives that are items of commerce. The Committee established that not all the salts indicated in its agenda were in use. The acceptable daily intakes and information on specifications are summarized in Annex 2 and additional data required for certain substances are given in Annex 3. Further information about the substances is given in the summaries of toxicological data to be issued separately.

3.1 Evaluation and re-evaluation

Food colours

Amaranth. This compound was last reviewed by the Committee at its nineteenth meeting.¹ A recent collaborative teratogenicity study in three laboratories using two strains of rat revealed no adverse effects when amaranth was administered at 200 mg per kg of body weight daily by gavage or in the drinking water. Similarly, no teratogenic response was observed when cats received dietary levels of amaranth of up to 264 mg/kg daily. A long-term study in rats was available, but owing to technical inadequacies this study was not amenable to evaluation.

The Committee was of the opinion that the structure of this compound did not indicate that it would be a potential carcinogen when given orally. However, because of the potentially wide use of amaranth, the Committee requested additional long-term feeding studies.

The previously established temporary ADI of 0-0.75 mg per kg of body weight was extended until 1982. A summary of data and revised tentative specifications were prepared.

¹ See Annex 1, reference 37.

Azorubine. This compound was last reviewed by the Committee in its eighteenth report.¹ It was noted that little information is available on the metabolism of azorubine. An adequate long-term study has been carried out in the mouse. Long-term studies in the rat were considered inadequate because only tumour incidence and survival were recorded. Reproduction studies, including teratogenicity studies, did not reveal any compound-related adverse effects. A no-effect level of 250 mg per kg of body weight was determined in the 90-day feeding study in rats.

On the basis of these new data, the previously established temporary ADI of 0–0.5 mg per kg of body weight was changed to a new temporary ADI of 1.25 mg/kg. A summary of data was prepared. Tentative specifications were available.

Beet red. This compound was last evaluated by the Committee at its eighteenth meeting.¹ At that time, metabolic studies and a long-term study in one species were requested by the end of 1978.

The present Committee was made aware of the increasing interest in the use of this colour in foods. In view of the structure of the major colouring principle—betanine—it was concluded that a full toxicological evaluation was required. The Committee was informed that this major colouring principle had been isolated for commercial use, but that only limited information was available on it.

The previous temporary, “not specified” ADI for beet red was extended. The existing specifications were revised and considered as tentative. No summary of data was prepared.

Brilliant Black PN. The Committee had given a temporary ADI to this compound in its eighteenth report,¹ and had requested additional studies. These studies were not available; however, a long-term mouse feeding study and a 90-day feeding study in pigs were submitted. The former revealed no significant adverse effects. In the case of the latter, intestinal cysts were noted at the two highest feeding levels.

The Committee concluded on the basis of the additional data that the temporary ADI of 0–2.5 mg per kg of body weight could be extended until 1981, but felt that the etiology and pathology of the cysts should be determined. A summary of data was prepared. Tentative specifications were available.

¹ See Annex 1, reference 34.

Chlorophyllin Cu complex, Na and K salts. The existing specifications for chlorophyllin Cu complex, Na and K salts, were not revised owing to the absence of more precise information on the commercial products available, and in particular the level of copper in the complex.

Iron oxide and hydrated iron oxides. These colouring substances were evaluated by the Committee at its eighteenth meeting,¹ and a temporary, "not specified" ADI was established. The Committee reaffirmed the need for human absorption studies.

The Committee decided to develop three separate specifications for the three iron oxides: yellow (hydrated ferric oxide), black (ferroso-ferric oxide), and red (anhydrous ferric oxide). Further information was required for the determination of iron in the case of ferroso-ferric oxide and water-soluble impurities.

The Committee agreed to extend the temporary ADI until 1979. Tentative specifications were prepared, but no summary of data.

Ponceau 4R. Ponceau 4R was last reviewed at the eighteenth meeting,¹ when a temporary ADI of 0-0.125 mg per kg of body weight was established. The Committee was informed that the metabolic, long-term, and reproduction studies previously requested are under way.

The Committee agreed that the temporary ADI be extended until 1981. A summary of data was prepared. Tentative specifications were available.

Quinoline Yellow. Quinoline Yellow was last reviewed at the Committee's nineteenth meeting.² The temporary ADI of 0-0.5 mg per kg of body weight was extended until 1978 and further studies were requested.

In previous evaluations, short-term and long-term studies in the rat and dog were available and no compound-related effects were observed. The Committee evaluated newly submitted teratogenicity studies in the rat and rabbit. No adverse teratogenic effects were noted at dietary levels of up to 150 mg/kg. In a three-generation study in which Quinoline Yellow was fed to rats at levels of up to 50 mg/kg, no adverse effects were noted.

¹ See Annex 1, reference 34.

² See Annex 1, reference 37.

No data were available to the Committee to enable it to define more clearly the substances being used in commerce—in particular the percentage of mono- and disulfonated moieties and the degree of methylation. The Committee extended the temporary ADI of 0–0.5 mg per kg of body weight until 1982. A summary of data was prepared. The existing specifications remained tentative.

Turmeric and curcumin. These substances had been evaluated as food additives at the Committee's eighteenth meeting,¹ and temporary ADI values of 0–2.5 mg per kg of body weight for turmeric and 0–0.1 mg/kg for curcumin were assigned. Data from several *in vitro* studies showed that extracts of turmeric caused chromosomal damage. This information made it all the more necessary to perform the studies previously required. The Committee was informed that these long-term feeding studies and a multigeneration study were in progress, and on this basis agreed to extend the temporary ADI until 1980.

The existing tentative specifications were not revised, but the Committee decided to prepare new specifications for turmeric extracts. However, further information was required on the concentrations of three colouring principles in commercial products and methods for their assay. The Committee was aware that pure curcumin as a colour was not available. More precise information is required on this product.

A summary of data was prepared, but no new specifications for turmeric and curcumin.

Miscellaneous food additives

Aluminium salts (sodium and potassium sulfate). The use of aluminium metal as a silvery decoration for certain items of confectionery was not considered to present a health hazard. Exposure levels of aluminium from food, drink, cooking utensils, and drugs were not available. Furthermore, the data available on these salts did not permit an evaluation.

No summary of data was prepared. Tentative specifications were available for aluminium potassium sulfate and aluminium sulfate. New specifications were prepared for aluminium sodium phosphate.

¹ See Annex 1, reference 34.

Diocetyl sodium sulfosuccinate. This food additive was evaluated by the Committee at its eighteenth meeting,¹ and a temporary ADI of 0–2.5 mg per kg of body weight was established. The information required by 1978—i.e., (1) the effects on newborn animals, particularly those exposed to the substance through lactation; (2) an adequate long-term study in a rodent species; and (3) an investigation of pulmonary circulatory effects including pulmonary hypertension—was not provided.

The Committee was not aware of any new studies in progress, and considered that, since this compound is widely used as a food additive, such studies are essential for toxicological evaluation.

The Committee withdrew the temporary ADI. No summary of data was prepared. Tentative specifications were available.

Maltol. The Committee had reviewed this compound at its eighteenth meeting,¹ and had withdrawn the temporary ADI because the results of the long-term toxicity studies that had been requested were not available. New data were available to the Committee at its present meeting.

Levels of up to 400 mg per kg of body weight have been administered in the diet in long-term studies in rats and mice, as well as in a three-generation reproduction study in rats. In addition, there was an inadequate 90-day feeding study in dogs. In mice, the effects noted included growth reduction at the highest dose level. Changes in serum urea in male rats and mice given 200 and 400 mg/kg in the diet were also noted. At the 200 and 400 mg/kg levels there was an increased incidence of focal atrophy of the testes in mice. However, this effect also occurred in the control groups, although less severely. Maltol even at the highest level fed had no effect on the reproductive performance of the rats.

A major failing in both the rat and mouse studies is that the biochemical measurements were carried out when there may have been major aberrations due to geriatric impairment of organ function. The results in mice, rats, and dogs indicate that the main target organs for maltol-induced toxicity are the liver and kidneys. Because of this, the major emphasis in establishing a no-effect level was on the histopathological data.

The Committee established a temporary ADI of 0–0.5 mg per kg of body weight. A summary of data was prepared. Tentative specifications were available.

¹ See Annex 1, reference 34.

Nitrous oxide. Nitrous oxide is the oldest of the volatile anaesthetics. Its pharmacological and pharmacokinetic properties as an anaesthetic are well known, and are dealt with in the standard textbooks. The physical properties of nitrous oxide have led to its use as a propellant, to dispense certain food products, for more than 20 years.

The concentrations ingested with food are low and present no hazard to the consumer. No summary of data was prepared. New specifications were prepared.

Sodium thiosulfate. Sodium thiosulfate (synonym: sodium hyposulfite) decomposes in acid solution and liberates sulfur dioxide and elementary sulfur. This information was used for the toxicological evaluation.

Since sodium thiosulfate may be expected to produce the same decomposition products as do the previously evaluated sulfites when subjected to normal stomach acidity, the Committee agreed to include it in the same group as sulfur dioxide and sulfites, for which there is a group ADI of 0–0.7 mg per kg of body weight calculated as SO₂. New specifications were prepared, but no summary of data.

Sorbitol. This compound was last evaluated at the Committee's seventeenth meeting,¹ and an "ADI not specified" was allocated. The present Committee evaluated some new data on sorbitol. Long-term feeding studies in rats at the dose level of 20% in the diet gave rise to unilateral and bilateral hyperplasia of the adrenal medulla, as well as decreased thyroid weight. No lower doses were studied. Changes in body weight, relative organ weight, and total serum protein also were reported in a study with dogs exposed to 20% dietary sorbitol. No lower doses were studied. A reproduction study in rats given 20% sorbitol resulted in an increase in the duration of gestation and decreases in weight and litter size. No lower doses were studied. Teratogenicity studies in rabbits and rats did not show any compound-related effects. The available data are not sufficient to set a no-effect level.

The Committee therefore concluded that further toxicological work was required and the "ADI not specified" was changed to a "temporary ADI not specified". A summary of data was prepared. Tentative specifications were available.

¹ See Annex 1, reference 32.

Stannous chloride. Stannous chloride as a food additive was last evaluated by the Committee at its nineteenth meeting.¹ This compound is further reviewed on page 27.

The present Committee concluded that the very limited use of stannous chloride as an intentional food additive does not present a hazard. A summary of data and revised specifications were prepared.

Xylitol. Xylitol was evaluated at the Committee's twenty-first meeting.² At that time, no ADI was established, but the Committee was aware of work in progress. In long-term studies with mice fed with diets containing 2%, 10%, and 20% xylitol, there was an increased incidence, in males, of urinary bladder calculi and urinary bladder hyperplasia, metaplasia, and benign and malignant tumours at the 10% and 20% levels. These effects were not observed in females or in males fed on a diet containing 2% xylitol.

These changes in the epithelium of the urinary bladder in male mice were always associated with macroscopically observed calculi composed of calcium phosphate and oxalate. The relationship between the presence of calculi and the appearance of bladder tumours in rodents had been discussed previously.³ The effects on the urinary chemistry of human beings to whom high levels of xylitol are administered should be investigated.

In rats fed 2%, 5%, 10%, and 20% xylitol in the diet, adrenal medullary hyperplasia and, in some cases, phaeochromocytoma were noted. Though the occurrence of this tumour is unusual in rats, the control rats used in this study showed a relatively high incidence. In male rats fed 5% and in males and females fed 2% xylitol in the diet, the occurrence of medullary hyperplasia did not differ from that in the control group. The Committee stated that further long-term studies in two strains of rat exposed to xylitol *in utero* and through lactation, as well as studies on adrenal medullary function, should be undertaken. In addition, in studies with xylitol in man, adrenal function tests should be carried out.

Since xylitol is currently produced from a variety of raw materials, the possibility that the product used in these studies

¹ See Annex 1, reference 37.

² See Annex 1, reference 43.

³ *Assessment of the carcinogenicity and mutagenicity of chemicals. Report of a WHO Scientific Group.* WHO Technical Report Series, No. 546, 1974.

contained an impurity that induced phaeochromocytoma should be investigated.

Hepatomegaly and changes in liver function were present in the dogs given 10% and 20% xylitol in the diet. No effects were noted with 5% xylitol.

Teratogenicity and multigeneration reproduction studies in rats and rabbits carried out at levels up to 20% xylitol in the diet revealed no adverse effects. In addition, several *in vitro* mutagenic tests were carried out and no effects were seen.

Xylitol is an intermediary metabolite and a normal constituent of many foods. However, in the light of the available toxicological data commented upon above, the Committee was unable to arrive at an evaluation for its use as a food additive. The Committee did not consider the use of xylitol for dietetic purposes or for the control of dental caries.

A summary of data was prepared. Tentative specifications were available.

3.2 Contaminants

Asbestos

An expert group had considered this subject in 1976.¹ Experimental evidence indicated that ingested asbestos fibres may penetrate the wall of the gastrointestinal tract. However, results of adequate chronic feeding studies in animals with well-defined asbestos materials are not available. Therefore, there is insufficient experimental evidence that ingested asbestos fibres can produce cancer.

A recent epidemiological study in Quebec did not reveal an increase in cancer mortality that could be related to the demonstrated presence of asbestos fibres in the drinking water.

The Committee felt that monitoring for the presence of asbestos in food was not feasible at present because of the complexities of the methodology involved.

Since asbestos, by inhalation, is known to be carcinogenic in man and animals, the strictest precautions against environmental

¹ *Asbestos*. Lyons, International Agency for Research on Cancer, 1977 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, volume 14).

exposure must be observed. In the absence of unequivocal evidence relating the ingestion of asbestos fibres to cancer, the conclusions and recommendations in the eighteenth report of the Committee,¹ concerning possible hazards from oral ingestion of asbestos fibres, are still valid. A summary of data was prepared.

Lead

The Committee considered the WHO Environmental Health Criteria for lead.² Available experimental studies are not sufficient for the establishment of a definitive tolerance for the intake of lead by man.

It is generally recognized^{3,4} that young children and possibly pregnant women are the most vulnerable segment of the population with respect to the intake of lead from food and other sources.

The Committee agreed that the recommended provisional tolerable intake for adults of 3 mg per week, established by the Committee in 1972,³ should be retained as the maximum intake. The establishment of a provisional tolerable weekly intake for children is not yet possible, because of the lack of relevant scientific data. A summary of data was prepared.

Mercury

At its sixteenth meeting,³ the Committee had established a provisional tolerable weekly intake of 0.3 mg of total mercury per person, of which no more than 0.2 mg should be present as methylmercury. At its present meeting, the Committee considered also the WHO Environmental Health Criteria for mercury.⁵

Epidemiological data from accidental human poisonings and animal toxicity studies on methylmercury indicate, however, that the provisional tolerable weekly intake established by the Committee in 1972 could be maintained. A summary of data was prepared.

¹ See Annex 1, reference 34.

² *Lead*. Geneva, World Health Organization, 1977 (Environmental Health Criteria, 3).

³ See Annex 1, reference 30.

⁴ See Annex 1, reference 43.

⁵ *Mercury*. Geneva, World Health Organization, 1976 (Environmental Health Criteria, 1).

Inorganic tin and organotin compounds

Inorganic tin was last considered at the nineteenth meeting.¹ A draft of the WHO Environmental Health Criteria for tin and organotin compounds² was made available to the Committee.

Inorganic tin. Inorganic salts of tin are of varying toxicity. The low toxicological risk generally associated with the ingestion of inorganic tin is due largely to low absorption, low tissue accumulation, and rapid excretion of this element, primarily in the faeces. Short-term feeding studies of certain inorganic tin salts, including stannous chloride at dietary levels of 4000 mg per kg of body weight, have resulted in anaemia and pathological changes in the gastrointestinal tract, kidneys, and liver of the rat.

Inorganic tin was not fetotoxic in rats, and long-term studies with rodents have not produced an increased incidence of tumours. Toxicologically significant contamination of food from food containers (tin-plated cans) arises as a result of poor manufacturing practice or prolonged storage, or both. Although the available data did not permit the establishment of a tolerable weekly intake for inorganic tin salts as food contaminants, there is no reason to depart from the assessment, made at previous meetings of the Committee in 1966 and 1971, that extensive human experience does not indicate the existence of any general toxic hazard and, therefore, the presence of inorganic tin in foods may be limited by good manufacturing practice.

Organotin compounds. The organotins may be divided into alkyltin and aryltin compounds. Some organotin compounds, such as trimethyltin and triethyltin, are readily absorbed from the gastrointestinal tract. The most toxic compounds of this group produce oedema of the white matter of the nervous system in a number of species including man, and they have also been shown to be extremely active inhibitors of metabolic processes.

Most of the other higher alkyltin and aryltin compounds are poorly absorbed from the gastrointestinal tract and are less toxic when given orally than when given parenterally. Experimental studies have failed to reveal any evidence of carcinogenicity or

¹ See Annex 1, reference 37.

² *Tin and organotin compounds.* Geneva, World Health Organization (Environmental Health Criteria) (in preparation).

teratogenicity. Major use categories for organotins include miticides in agriculture, stabilizers in plastics, and catalysts. Their use as miticides was appraised at the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues.¹

Owing to the great variation in toxicity found between organotin compounds, a tolerable intake for this group as a whole cannot be estimated. Each organotin compound proposed for use should be evaluated by the Committee individually with respect to toxicity and, when the compound is used as a component of plastics, possible leaching into the packaged food should also be studied. No summary of data was prepared.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 18 substances, including enzymes, colours, and miscellaneous additives (see Annex 2).

Tentative specifications were prepared for 14 substances but, in the case of a number of organic salts, it was not possible to develop specifications because of the incompleteness of the information available and uncertainty whether these salts were used as food additives. The salts in question were: ammonium acetate, L(+) ammonium tartrate, calcium adipate, calcium fumarate, calcium hydrogen carbonate, L(+) calcium tartrate, magnesium acetate, magnesium citrate, L(+) magnesium tartrate, potassium fumarate, and DL-malate sodium hydrogen.

The Committee developed new specifications for six additional enzymes (see Annex 2).

5. FUTURE WORK

(1) A number of food additives have been allocated temporary ADIs, and should be re-evaluated when the required information becomes available.

¹ *Pesticides residues in food. Report of the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues.* WHO Technical Report Series, No. 502, 1972.

(2) A number of flavouring substances were evaluated by the Committee at its eleventh meeting,¹ and conditional ADIs were established for some of them. These should be re-evaluated, together with certain other flavouring substances for which toxicological data are available.

(3) Certain carrier and extraction solvents were tentatively placed in the list of compounds to be examined by the Committee in 1979. The Committee agreed to recommend these compounds for examination at that time.

(4) The Committee agreed to re-emphasize the future work recommended in its twenty-first report.²

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, until such time as a quicker procedure for data collection and evaluation has been developed.

(2) The Committee endorsed the recommendations made by the World Health Assembly (resolution WHA30.47) on the health effects of chemicals in the environment, and recommended that food additives and contaminants should be selected for accelerated systematic evaluation.

(3) In order to establish priorities for toxicological testing and evaluation of intentional and unintentional food additives, the Committee recommended that FAO and WHO should convene an interdisciplinary group of experts to establish an inventory of compounds that have not yet been fully evaluated, and to classify them in terms of their potential hazard to health on the basis of toxicological knowledge and extent of use. The Committee could then employ the priority list as a means of selecting the most relevant compounds for future evaluation.

(4) The expeditious testing of food additives and contaminants classified as having a low priority for evaluation requires the

¹ See Annex 1, reference 14.

² See Annex 1, reference 43.

development of *in vivo* short-term and *in vitro* tests to verify predictions of toxicity. The Committee recommended that these tests, the guidelines for their use, and the evaluation of the data they yield should be considered by a group of experts assembled by WHO.

(5) The need for testing the effects of exposure to food additives and contaminants *in utero* and on neonates during suckling was reaffirmed. However, in view of the complexity of the testing procedures, the Committee recommended that WHO should convene a meeting of experts to assess: (a) the degree of any increase in the sensitivity of toxicological testing afforded by exposure *in utero* and through lactation; and (b) the need to include such exposure in toxicological tests as a means of increasing public health protection. The experts should also propose the most appropriate guidelines for experimentation, taking into account: (a) the dosages used and the relative exposure of mother and fetus to the agent under study; (b) the possibility of combining this modified long-term test with reproduction studies; (c) the length of the studies required; and (d) the most appropriate species to use.

(6) The Committee recommended that WHO take the initiative in establishing liaison with international groups concerned with the evaluation of food additives.

(7) In order to use its time more efficiently, the Committee recommends that compounds not available as food additives, or whose use for that purpose has not been proposed, should not be placed on its agenda. FAO is requested to ensure that compounds selected for the agenda meet these criteria.

(8) The Committee recommended that FAO and WHO should in future provide it with the most recent information from governments and industry well in advance of its meeting.

**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: Food Safety, World Health Organization, 1211 Geneva 27, Switzerland, or from Food Standards and Food Science Service, Food and Agriculture Organization of the United Nations, 00100 Rome, Italy.

1. *General principles governing the use of food additives* (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of intentional food additives to establish their safety for use* (Second report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants)* (Third report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. I. *Antimicrobial preservatives and antioxidants*, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. *Specifications for identity and purity of food additives (food colours)* (Fourth report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. II. *Food colours*, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. *Evaluation of the carcinogenic hazards of food additives* (Fifth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. *Evaluation of the toxicity of a number of antimicrobials and antioxidants* (Sixth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962.
7. *Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents* (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 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.
- 12. *Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances* (Tenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.
- *13. *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids, and bases.* FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.
- 14. *Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents* (Eleventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.
- *15. *Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
- *16. *Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
- 17. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics* (Twelfth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
- *18. *Specifications for the identity and purity of some antibiotics.* FAO Nutrition Meetings Report Series, No. 43A, 1969; WHO/Food Add/69.34.
- 19. *Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances* (Thirteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.
- *20. *Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 46A; WHO/Food Add/70.36.
- *21. *Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 46B; WHO/Food Add/70.37.

22. *Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents* (Fourteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.
- *23. *Toxicological evaluation of some extraction solvents and certain other substances*. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.
- *24. *Specifications for the identity and purity of some extraction solvents and certain other substances*. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.
- *25. *A review of the technological efficacy of some antimicrobial agents*. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.
26. *Evaluation of food additives: some enzymes, modified starches, and certain other substances: toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants* (Fifteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.
27. *Toxicological evaluation of some enzymes, modified starches, and certain other substances*. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.
28. *Specifications for the identity and purity of some enzymes and certain other substances*. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.
29. *A review of the technological efficacy of some antioxidants and synergists*. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.
30. *Evaluation of certain food additives and the contaminants mercury, lead, and cadmium* (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
31. *Evaluation of mercury, lead, cadmium, and the food additives amaranth, diethylpyrocarbonate, and octyl gallate*. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.
32. *Toxicological evaluation of certain food additives with a review of general principles and of specifications* (Seventeenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum.
33. *Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents*. FAO Nutrition Meetings Report Series, No. 53A; WHO Food Additives Series, No. 5, 1974.
34. *Evaluation of certain food additives* (Eighteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.

35. *Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.
36. *Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents, and certain food additives.* FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.
37. *Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances* (Nineteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.
38. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 55A. WHO Food Additives Series, No. 8, 1975.
39. *Specifications for the identity and purity of certain food additives.* FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.
40. *Evaluation of certain food additives* (Twentieth report of the Expert Committee). FAO Food and Nutrition Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.
41. *Toxicological evaluation of certain food additives.* FAO Food and Nutrition Series, No. 1A, 1978; WHO Food Additives Series, No. 10, 1978.
42. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Series, No. 1B, 1977.
43. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.
44. *Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.

Annex 2

ACCEPTABLE DAILY INTAKES, TOLERABLE INTAKES, AND INFORMATION ON SPECIFICATIONS

Specifications and acceptable daily intakes

	<i>Specifications¹</i>	<i>ADI for man (mg/kg body weight)</i>
<i>Intentional food additives</i>		
aluminium potassium sulfate	ST	No ADI allocated
aluminium sodium sulfate	NT	No ADI allocated
aluminium sulfate	ST	No ADI allocated
amaranth	RT	0-0.75 ²
azorubine	ST	0-1.25 ²
Beet Red	RT	ADI not specified ^{2, 3}
Brilliant Black PN	ST	0-2.5 ²
chlorophyllin copper complex, sodium and potassium salts	ST	0-15
dioctyl sodium sulfosuccinate	ST	No ADI allocated ⁴
iron oxides and hydrated iron oxide ⁹	NT	ADI not specified ^{2, 3}
maltol	ST	0-0.5 ²
nitrous oxide	N	No ADI allocated ⁵
Ponceau 4R	ST	0-0.125 ²
Quinoline Yellow	ST	0-0.5 ²
sodium thiosulfate	N	0-0.7 ⁶
sorbitol	ST	ADI not specified ^{3, 7}
stannous chloride	R	ADI not specified ^{3, 8}
turmeric/curcumin	ST	0-2.5 ² (turmeric) 0-0.1 ² (curcumin)
xylitol	ST	No ADI allocated

Tolerable intakes

	<i>Evaluations</i>
<i>Food contaminants</i>	
asbestos	No tolerable intake established ¹⁰
lead	3 mg/kg/person (0.05 mg/kg body weight) ¹¹
mercury (total)	0.3 mg/kg/person (0.005 mg/kg body weight) ¹²

methylmercury (expressed as mercury)	0.2 mg/kg/person (0.0033 mg/kg body weight) ¹²
inorganic tin salts	No tolerable intake established ¹³
organotin compounds	No tolerable intake established

Specifications only

	<i>Specifications</i>
I. Organic salts	
ammonium chloride	NT
DL-calcium malate	NT
magnesium hydrogen carbonate	NT
magnesium chloride	NT
magnesium gluconate	NT
magnesium lactate	NT
potassium chloride	RT
potassium dihydrogen citrate	NT
potassium gluconate	NT
DL-potassium malate	NT
sodium dihydrogen citrate	NT
sodium fumarate	NT
sodium gluconate	NT
DL-sodium malate	NT
triammonium citrate	NT
II. Microbial enzyme preparations	
<i>Aspergillus awamori</i> varieties	
carbohydrase	NT
<i>A. niger</i> varieties	
catalase	ST
<i>A. oryzae</i> varieties	
carbohydrase	RT
protease	RT
<i>Bacillus coagulans</i> varieties	
glucose isomerase	NT
<i>B. licheniformis</i> varieties	
carbohydrase	NT
<i>Klebsiella aerogenes</i> varieties	
carbohydrase	NT
<i>Streptomyces olivaceus</i> varieties	
glucose isomerase	NT
<i>S. violaceoniger</i>	
glucose isomerase	NT

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

² Temporary acceptance.

³ 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.

⁴ The previous temporary ADI was revoked.

⁵ The concentrations ingested with food are low and present no hazard to the consumer.

⁶ Sodium thiosulfate was included in the same group as sulfur dioxide and sulfites for which a group ADI of 0-0.7 mg/kg body weight, calculated as SO₂, had previously been established.

⁷ The previous ADI not specified was converted to a temporary ADI not specified.

⁸ The very limited use of stannous chloride as an intentional food additive does not present a hazard.

⁹ Separate specifications are available for iron oxide, black, red, and yellow.

¹⁰ Unequivocal experimental evidence that ingested asbestos fibres can produce cancer is lacking. Monitoring for the presence of asbestos in food is not feasible at present.

¹¹ Provisional tolerable weekly intake for man. These intake levels do not apply to infants or children.

¹² Provisional tolerable weekly intake.

¹³ Although the available data do not permit the establishment of a tolerable intake for inorganic tin salts as food contaminants, extensive human experience does not indicate the existence of any general toxic hazard and, therefore, the presence of inorganic tin in foods may be limited by good manufacturing practice.

**FURTHER TOXICOLOGICAL STUDIES
AND INFORMATION REQUIRED**

Food colours

*Amaranth*¹

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

*Azorubine*¹

- (1) A long-term feeding study in rats.
- (2) A one-year feeding study in a non-rodent mammalian species.
- (3) Metabolic studies in several species, preferably including man.

*Beet Red*¹

- (1) A long-term feeding study in two species.
- (2) A short-term feeding study in a non-rodent mammalian species.
- (3) Multigeneration feeding studies, including a study on teratogenicity.
- (4) Metabolic studies in several species, preferably including man.

*Brilliant Black PN*²

- (1) Metabolic studies in several species, preferably including man.
- (2) Adequate reproduction studies, including a teratogenicity study.
- (3) Elucidation of the significance of intestinal cysts in the pig study.

*Iron oxides and hydrated iron oxides*³

Adequate information on the absorption and storage of iron following the use of these pigments as food additives.

*Ponceau 4R*²

Metabolic studies in several species, preferably including man; an adequate long-term study in another species; and a reproduction study.

*Quinoline Yellow*¹

- (1) Metabolic studies in several species, preferably including man.
- (2) An adequate long-term feeding study in another species.

*Turmeric/curcumin*⁴

An adequate short-term study in a non-rodent species; a long-term study at higher levels in a rodent species to establish a no-effect level, using turmeric with a well-defined curcumin content.

Miscellaneous food additives

*Maltol*¹

- (1) Six-month studies in the mouse and in the rat, to clarify the biochemical changes noted in the long-term study. These should include a full histopathological examination with particular emphasis on the testes.
- (2) An adequate short-term feeding study in the dog.

*Sorbitol*⁴

- (1) A long-term feeding study in rats with special attention to the effects on the thyroid and adrenal glands.
- (2) A multigeneration reproduction study.
- (3) A six-month feeding study in the dog, with emphasis on liver function and histopathology.

¹ Information required by 1982.

² Information required by 1981.

³ Information required by 1979.

⁴ Information required by 1980.

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