Evaluation of certain food additives and contaminants

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

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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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CORRIGENDUM

Page 4:

Mr A. M. Humphrey, Bush Boake Allen, London, England (FAO Consultant), should be listed under Secretariat and not under Members invited by FAO.
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3
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Geneva, 16–25 February 1987

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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 16 to 25 February 1987. The meeting was opened by Dr J.-P. Jardel, Assistant Director-General, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Jardel pointed out that this Committee provided a unique international mechanism for the toxicological evaluation and safety assessment of food chemicals, and that it had established a model of safety assessment that was widely accepted.

He announced that the document Principles for the safety assessment of food additives and contaminants in food, which was approved at the thirtieth meeting of the Committee, would soon be published (Annex 1, reference 76). This document, which was the culmination of a project undertaken by the International Programme on Chemical Safety in response to recommendations from earlier committees, would then be available for use by the Committee, governments, and international agencies and organizations.

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 19551, there have been 30 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the thirtieth meeting (Annex 1, reference 73).

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

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

Glycerol esters of wood rosin were added to the agenda for consideration of specifications. Ferrous gluconate was added to the agenda for reconsideration of its inclusion in the group ADI for gluconic acid.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76). This publication, developed in response to repeated recommendations by the Committee, embraces the major observations, comments, and recommendations on the safety assessment of food additives and contaminants contained in the previous reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate, and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.2.1 Coloration of food using animal feed additives

The present Committee considered several substances that could enter into the human food supply as a result of their presence in animal feeds. The diets of animals feeding in the wild or in free-range conditions contain carotenoids of various types that impart the characteristic colour to food products obtained from these animals, such as the yolk of eggs and the flesh of salmonid species. When these foods are produced under intensive conditions using prepared animal feeds, carotenoids (see section 3.1.3) are deliberately added to impart colour to the food derived from these animals. These substances may be regarded as indirect food/colour additives that will be present in the human food.

A number of factors must be taken into account when evaluating the suitability of particular carotenoids or sources of carotenoids (e.g., plant extracts) as additives to animal feed. Some of the factors
are the same as those considered when evaluating carotenoids for direct use as food additives. These include information from toxicological studies as well as the levels occurring in the foods presented to the consumer and the implications for nutrition. However, there are other considerations to be taken into account when there is indirect colouring of food using animal feed additives, such as the presence of metabolites of the additive in the food and the toxicological and nutritional significance of any such metabolites. Another consideration arises in connection with the source of the carotenoids; are they natural products or extracts of natural products? When a natural product source is regarded as a normal food, the Committee has taken this into account in evaluating the material as a direct food additive (Annex 1, reference 76, section 3.1.3). In the case of a colour additive to animal feed, the status of the natural product as a normal constituent of the animals' food supply in free-range conditions might be a more appropriate consideration.

2.2.2 Mycotoxin-contaminated animal feed

Animals may be fed mycotoxin-contaminated fodder as a result of mould growth on materials intended for use as feed. In addition, food materials originally intended for human use may be diverted for use as animal feed if they are affected by spoilage organisms. This practice can mitigate to some extent the losses to the food supply and the economic losses that would result from complete rejection of the contaminated materials. Whatever the source of the mycotoxin-contaminated animal feed, its use raises concern about the effects of mycotoxin residues and their metabolites in human food derived from the animals that have ingested the contaminated fodder. The presence of aflatoxin M$_1$ in milk from cows that have been fed on aflatoxin B$_1$-contaminated fodder is an example of this.

Because of the implications for human health (see section 3.2), the Committee agreed that every effort should be made to control the mycotoxin contamination of animal feed. To achieve this objective, the Committee therefore recommended the development of appropriate strategies, such as the education of farm workers and others involved in grain handling operations, the adoption of measures that could be taken to minimize the potential for toxin production, and the establishment of suitable surveillance programmes to monitor mycotoxin levels in animal feeds.
Information should also be collected on the mycotoxin levels in foodstuffs derived from animals that have ingested mycotoxin-contaminated fodder.

Methods to reduce the content of mycotoxin by the treatment of contaminated animal fodder should also be developed. Although ammoniation of animal feeds has been used commercially to eliminate aflatoxin contamination of such feeds, more information will be needed about this and other mycotoxin detoxification procedures for consideration by future committees. Some of the factors that would be helpful in evaluating the human health consequences of detoxifying animal feed material include specific information about the nature of the products formed as a result of the treatment, their toxicity, the possibility of metabolic reactivation, and the residues that appear in human food as a result of the treatment. In addition to potential adverse nutritional effects, the possibility should be considered that the treatment process itself may result in the \textit{de novo} production of toxic substances.

The present Committee had been requested to consider specifically aflatoxins. However, the Committee was aware that other mycotoxins also pose potential threats to public health. When the mycotoxin-producing organisms themselves are present in human food there is obvious cause for concern. The Committee stressed that the less obvious potential risk of using mycotoxin-contaminated fodder for food-producing animals should not be overlooked. The Committee recommended, therefore, that information be collected about the use of mycotoxin-contaminated animal fodder on a broad basis, including not only aflatoxin contamination but also other mycotoxins, including the effects of these toxins on food for human consumption.

2.2.3 \textit{Food additives in infant foods}

The issue of whether food additives should be used in infant foods arose at the present meeting with regard to monosodium glutamate (MSG) as a consequence of concern expressed at the seventeenth meeting of the Committee (Annex 1, reference 32) and with regard to beet red, since this colouring agent may contain high levels of nitrate. The Committee referred to the report of an FAO/WHO meeting on "Additives in Baby Foods" (Annex 1, reference 26) and reiterated the view that the use of additives in foods designed specifically for infants should be approached with caution where
specific data dealing with the intake and effect of additives on infants were not available. This Committee was reassured by information about the intake and effects of monosodium glutamate in infants since it shows that there is no cause for concern about health risks (see section 3.1). Nevertheless, the Committee concluded that additives should not be used in infant foods solely to accommodate the taste preferences of the adult as opposed to that of the infant. With regard to beet red, the Committee concluded that levels of nitrate arising from its use in infant foods could well be of concern.

2.2.4 The need for adequate information on natural products

A number of the substances evaluated by the Committee were natural products that are produced from normal edible materials or from materials not usually used as food. A full understanding of the source and chemical nature of such products was considered to be essential for an evaluation of their safety-in-use.

2.2.5 Evaluation of food processing aids

Some substances that have been considered at this and previous meetings of the Committee are used as food processing aids for specific technological purposes. Chemical and technological information on such substances, including effects on the food, fate of the substance during processing, and the nature and level of residues in the final product, were considered to be an essential part of the safety evaluation process.

2.2.6 Evaluation of complex mixtures

In evaluating complex mixtures, such as caramels, smoke flavours, and extracts of natural materials, the provision of sound analytical data, including variability of commercial products, is of major significance.

2.2.7 Multiple sources of the same chemical substance

Occasionally, the Committee is requested to evaluate different materials that are mixtures containing a common component for which an ADI has been allocated. Examples of such materials are β-carotene and α-tocopherol in natural extracts. When using such materials, the ADI for that component should not be exceeded.
2.3 Principles governing the establishment and revision of specifications

2.3.1 Justification for changes in specifications

The Committee considered several requests for the amendment of specifications to decrease the purity required. The Committee noted that there are specific instances where a decrease in the assay limits may result in a product containing lesser amounts of a hazardous impurity. In this regard, the Committee recalled its discussion at the twenty-eighth meeting relative to the food colour Brown HT, where a threefold reduction in the naphthionic acid content was accompanied by an increase in the combined salt and moisture content from 20% to 30% and a concomitant decrease in the assay of the main colouring component (Annex 1, reference 66).

The Committee’s specifications are intended to reflect and encourage good manufacturing practice (Annex 1, reference 76, section 4.3). Therefore, the Committee cannot lower the degree of purity represented by the specifications without a technological justification explaining the effects on the assurance of purity for the food additive, keeping in mind that the safety implications of any change in specifications must be taken into account.

2.3.2 Review of specifications for enzyme preparations

The Committee had on its agenda for this meeting several enzyme preparations derived from fungal sources. The Committee observed that enzyme preparations from different strains of the same species may have different characteristics, and this difference should be taken into consideration when formulating specifications for these products. The Committee noted that microbial sources may be changed and new strains selected; such a selection of new strains has been an accepted practice of enzyme manufacturers. For the evaluation of enzyme preparations derived from microorganisms, the Committee had previously laid down principles that include a consideration of the natural occurrence and ingestion of those microorganisms (Annex 1, reference 76, Annex 3).

The Committee reiterated the conclusion, reached at the twenty-ninth meeting, that an acceptable daily intake should be established for enzyme preparations derived from microorganisms not normally used as food or for enzyme preparations not removed from the food products to which they are added. In accordance with the
Committee's general principles (Annex 1, reference 76, section 4.3), specifications for such materials are required to identify the substance that has been biologically tested. However, for the fungal enzymes reviewed by the present Committee, it was found that insufficient information was available to define or characterize adequately some preparations.

The present consideration of enzyme preparations included a review of the specifications with respect to the identification of the microbial source of enzyme preparations. The existing specifications for enzyme preparations place the responsibility for assuring the maintenance of pure cultures of microbial species on the manufacturer of those preparations. While the Committee recognizes that manufacturers are motivated to control precisely the purity of microbial species and strains, specifications are meant to define the materials subjected to toxicological testing and to reflect and encourage good manufacturing practice. In general, the Committee requests data on any chemical, physical or microbiological criterion that can be used to test enzyme preparations and identify the source material.

The Committee noted that source organisms may produce toxins under certain conditions of growth. The current specifications for enzyme preparations require manufacturers to test for chemical contaminants that are known to occur in a particular microbial species or that may occur during culture as a result of inadvertent microbial contamination with another organism or as impurities contained in the culture medium. The Committee's specifications should be updated regularly as new microbial sources are reviewed by the Committee and as new toxins are discovered.

The Committee discussed the need to define the non-enzymic components of enzyme preparations and how information on such components might relate to the definition and safety of the product, because in many cases the enzymic portion of these products is a minor component (by weight). Different fermentation conditions or the use of different strains of microorganism might change the non-enzymic components.

In view of such considerations and the important role of the Specifications for enzyme preparations used in food processing (Annex 1, reference 69), the Committee concluded that the general specifications should be reviewed. The Committee agreed that the following information should be provided in order to define more clearly individual preparations:
—non-enzymic components, including hazardous contaminants;
—major and minor enzymic activities;
—international units of activity, where they have been defined;
—specific stabilizers and preservatives used in enzyme preparations;
—how fermentation processes are monitored to ensure a reproducible product;
—how the purity of microbial strains is controlled and how individual commercial strains might differ from naturally-occurring strains; and
— the utility of linking specific activity with some non-enzymic components (such as total organic solids, see section 3.1.1) to provide an index of purity.

2.3.3 Review of specifications for substances derived from natural products

The Committee had on the agenda of its present meeting several substances that are derived from natural products and are used to colour or flavour food.

The Committee recognized difficulties in establishing specifications for these substances that are as precise as those for synthetically manufactured chemicals because of the variability in the natural substance. For example, there will be substances that contain only a very small proportion of colouring or flavouring principles. Specifications prepared by the Joint FAO/WHO Expert Committee on Food Additives are minimum requirements for the composition and quality of food-grade additives, allowing for acceptable variation in their production (Annex 1, reference 38). Specifications of some additives derived from natural sources, such as natural colours, specify the content of main active components, such as colouring principles, as “not less than declared” which takes into account the quality of these substances actually traded.

Some natural active principles are unstable, and the vendor adjusts the content or assay value at the time of trade. The Committee noted that some of these substances may be degraded during subsequent storage and then they do not meet the specifications. In such cases, it is necessary to give appropriate advice if the degradation can result in the production of potentially hazardous substances.

The Committee considered whether limits for certain impurities in substances derived from natural products should be established on
the basis of colour or flavour intensity. The Committee agreed that it would be appropriate to specify certain impurity limits based on colour or flavour intensity when as a result the amounts of such impurities in the finished food products would be more tightly controlled. For those impurities that are not directly proportional to colour or flavour intensity, or in those instances where data were unavailable to correlate colour or flavour intensity with impurity levels, the Committee agreed to specify limits based on the weight of material.

Several of the substances derived from natural products may contain other naturally-occurring, potentially hazardous components as well as environmental contaminants such as pesticide residues. The Committee strongly re-emphasized the importance of technical data related to manufacture and contaminant levels for substances brought before it for review of the specifications.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

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

3.1 Specific food additives

3.1.1 Enzyme preparations

Problems in evaluating the safety of enzymes in food processing were discussed at the fifteenth, eighteenth, and twenty-ninth meetings of the Expert Committee, when principles relating to their evaluation were elaborated (Annex 1, references 26, 35, and 70). At the present meeting, the Committee reaffirmed those principles, which have been consolidated in Annex III of Principles for the safety assessment of food additives and contaminants in food (Annex 1, reference 76).

For the purpose of toxicological evaluation, the enzyme preparations considered by this Expert Committee can be grouped into the following classes:
Class III – Enzymes derived from *Aspergillus oryzae;*

Class IV – Enzymes derived from *Aspergillus niger;*

Class V – Enzymes derived from *Trichoderma reesei* and *Trichoderma harzianum,* and *Penicillium funiculosum* and *Aspergillus aliaceus*

The guidelines established by the Joint FAO/WHO Expert Committee on Food Additives for these classes of enzyme provide a basis for the toxicological studies required for their evaluation.

At the twenty-ninth meeting, the Committee concluded that when enzyme preparations from classes IV and V were added directly to food but not subsequently removed, an acceptable daily intake should be established to ensure that levels of enzyme preparation in the food are safe. In order to evaluate the information received on the estimate of the amount of enzyme preparation used in the toxicological studies and levels of consumption resulting from its use in food, the Committee adopted the concept of enzyme total organic solids (T.O.S.)$^{1,2}$, defined as follows:

$$\text{%T.O.S.} = 100 - (A + W + D)$$

where $A = \%$ ash, $W = \%$ water, and $D = \%$ diluent and carrier.

This concept overcomes the problem that enzyme preparations of different activities and forms were used in the toxicological studies. It also takes into account the fact that most of the organic solids in this fraction are not the enzyme *per se.*

In establishing acceptable daily intakes for the enzymes in classes IV and V, the present Committee noting that the animal feeding studies were primarily short-term, concluded that it would be appropriate to use a safety factor greater than the usual 100.

*Enzymes derived from *Aspergillus oryzae*

Enzymes from this source were considered at the fifteenth meeting of the Committee (Annex 1, reference 26). A decision on the acceptable daily intake was postponed because of the concern that one of the known metabolites of *A. oryzae* is β-nitropropionic acid, which was suspected to be a potential carcinogen. Later, at the

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eighteenth meeting of the Committee, a lipase derived from *A. oryzae* was considered (Annex 1, reference 35). It was determined at that time that there was no information to substantiate the suspicion of potential carcinogenicity of β-nitropropionic acid, and that analyses of foods have shown that the metabolite is present in very few foods and then only in minute amounts. The present Committee was also informed that different varieties of *A. oryzae* are used in certain parts of the world in the preparation of foods. The Committee restated its opinion that such enzymes should be considered as normal constituents of food (Annex 1, reference 26).

*a*-Amylase (E.C. 3.2.1.1). The Committee examined the short-term studies in rats showing that there was no adverse effect from a dietary level equivalent to 7 g of the enzyme preparation per kg of body weight per day. Based on the lack of evidence of toxicity in this study and the general considerations, this enzyme was considered acceptable for use in food. The existing specifications for *a*-amylase and glucoamylase mixtures were revised and designated as tentative. New, tentative specifications were drawn up for *a*-amylase preparations.

Proteases (E.C. 3.4.21.14; 3.4.23.6). A short-term study in rats showed that a dietary level equivalent to 7 g of the enzyme preparation per kg of body weight per day was without effect. Based on this lack of toxicity and on the consideration in the general remarks, this enzyme was considered acceptable for use in food. The existing specifications were revised and designated as tentative.

A combined toxicological monograph was prepared.

*Enzymes derived from Aspergillus niger*

*A. niger* is a contaminant of food and was not considered in the same way as those organisms that are regarded as normal constituents of food. Data are required to ensure that the strains used in the preparation of enzymes do not produce mycotoxins (Annex 1, reference 26).

Carbohydrases. Microbial carbohydrases prepared from some varieties of *A. niger* were evaluated at the fifteenth meeting and a temporary ADI ("not limited") was established (Annex 1, reference 26). An adequate 90-day study in rats was requested. The present
Committee reviewed carbohydases derived from *A. niger*. This group of enzymes was considered to include those carbohydases evaluated at the fifteenth meeting, and studies on this group of enzymes would meet those requirements.

*Amyloglucosidases* (E.C. 3.2.1.3). The Committee examined the results available from short-term feeding studies in rats. One study in which the preparation comprised up to 10% of the diet (7 g of the enzyme per kg of body weight per day) was considered acceptable by current standards. No compound-related effects were observed. Duckling tests had been carried out on two preparations that showed an absence of aflatoxin-related effects.

β*-Glucanase* (E.C. 3.2.1.6). The Committee noted that the preparation was not genotoxic in microbial or mammalian test systems. Short-term studies in rats and dogs have been carried out. In both species, no compound-related effects resulted from treatment with dose levels of 5 ml of the enzyme preparation per kg of body weight (2.5 g per kg of body weight per day).

*Hemi-cellulase*. This enzyme was not genotoxic in microbial or mammalian test systems. In one limited 90-day study in rats, no effects were observed at the highest dose fed (1 g per kg of body weight per day). The enzyme preparation contained high levels of pectinase, and the safety data derived from this preparation provided additional information on the safety of that enzyme.

*Pectinases* (E.C. 3.1.1.11; 4.2.2.10; 3.2.1.15). In a short-term study in rats, no adverse effects were observed at dietary levels of the enzyme preparation equivalent to 7 g per kg of body weight per day. This enzyme preparation may be identical to the hemi-cellulase preparation discussed above, and data from that preparation provided additional information on the safety of this enzyme preparation.

*Protease*. No toxicity data were available.

*Evaluation*. Although the Committee was aware of possible strain differences in *A. niger* and the possibility that different culture conditions might be used to prepare the various enzymes, the available toxicity data indicated that all the enzyme preparations
considered had very low levels of toxicity. Based on this information, the Committee established a single ADI for each of the separate enzyme preparations of 0–1 mg T.O.S. per kg of body weight. This ADI should apply to each of the carbohydrases as well as to the proteases. A combined toxicological monograph was prepared. New tentative specifications were prepared for amyloglucosidase, \( \beta \)-glucanase, hemi-cellulase, and pectinase preparations. No specifications were prepared for the protease preparation.

**Beta-glucanase derived from Trichoderma harzianum**

Beta-glucanase (E.C. 3.2.1.6) from *Trichoderma harzianum* has not been previously evaluated by the Committee. The preparation was not mutagenic in bacterial or mammalian systems. The preparation caused no adverse effects in a reproduction study in rats at levels up to 5\% of the diet, and was not teratogenic in a rat study at doses up to 1 g per kg of body weight per day. Short-term studies in rats and dogs showed no adverse effects at 3 g per kg of body weight per day in dogs, and 2 g per kg of body weight per day in rats. Based on the available information, the Committee established a temporary ADI of 0–0.5 mg T.O.S. per kg of body weight.

Because this enzyme is derived from a microorganism that is neither a normal constituent of food nor a common contaminant in food, in accordance with Annex III of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76), it is required that by 1992 this preparation will undergo a long-term study in a rodent species and that specifications will be established to show that the organism does not produce antibiotics and is non-pathogenic to man.

A toxicological monograph and new tentative specifications were prepared.

**Cellulase derived from Trichoderma reesei**

Cellulase from *Trichoderma reesei* has not been previously evaluated by the Committee. The enzyme preparation is characterized by two activities, exo-cellulobiohydrolase (E.C. 3.2.1.1) and 1,4-endo-glucanase (E.C. 3.2.1.4).

The preparation was not mutagenic in bacterial or mammalian systems. It caused no adverse effects in a reproduction study in rats at levels up to 5\% of the diet, and it was not teratogenic in a rat study.
at doses up to 7 g of preparation per kg of body weight. Short-term studies are available in dogs and rats, the no-adverse-effect levels being 3 g per kg of body weight per day in dogs, and 2 g per kg of body weight per day in rats. The Committee was also informed that tests have been performed to show that the strain of *T. reesei* used for the production of this enzyme does not produce any antibiotics and is not known to be a human pathogen. Based on the available information, the Committee established a temporary ADI of 0–0.3 mg T.O.S. per kg body weight.

Because this enzyme was derived from a microorganism that is neither a normal constituent of food nor a common contaminant in food, in accordance with Annex III of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76), it is required that by 1992 this preparation will undergo a long-term study in a rodent species.

A toxicological monograph and new tentative specifications were prepared.

*Cellulase derived from Penicillium funiculosum* (E.C. 3.2.1.4; 3.2.1.21; 3.2.1.91)

No safety data were available to the Committee, so no ADI could be established for cellulase from *Penicillium funiculosum*. New tentative specifications were prepared.

*Pectinase derived from Aspergillus alliaceus*

No safety data were available to the Committee, so no ADI could be established for pectinase from *Aspergillus alliaceus*. No specifications were prepared.

3.1.2 Flavouring agents.

*Trans-anethole.* *Trans-anethole* was evaluated for acceptable daily intake at the eleventh and twenty-third meetings of the Committee (Annex 1, references 14 and 50). At the twenty-third meeting, a temporary ADI of 2.5 mg per kg of body weight was established, with the requirement that an adequate long-term feeding study be performed. In 1983 the Committee extended the temporary ADI to 1987 pending completion of the long-term feeding study in rats that was then in progress.
The present Committee was aware of additional metabolic studies in rodents and man, and that the required long-term feeding study had been completed. However, there was not sufficient opportunity to evaluate fully the toxicological implications of a significant incidence of hepatoma observed in treated female rats. The Committee was of the opinion that the temporary ADI could be extended for an additional year to provide an opportunity for a full, in-depth review of this study. The existing temporary ADI for trans-anethole of 0–2.5 mg per kg of body weight was therefore retained until 1988 pending review of the new data.

A toxicological monograph was not prepared. The existing specifications were maintained.

**Benzyl acetate**

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

At the twenty-ninth meeting, the Committee extended the temporary ADI of 0–5 mg per kg of body weight until 1987 when lifetime gavage studies with benzyl alcohol, a normal metabolite of benzyl acetate, were expected to be available. In addition, a new study was planned that incorporated benzyl acetate into the diet of rats and mice. The present Committee decided to extend the temporary ADI because it was informed that the in-life phases of the benzyl alcohol studies have been completed, but that the histology studies are still in progress. The Committee requested that these data be submitted for review by the Committee in 1989.

A toxicological monograph was not prepared. The existing specifications were maintained.

**Smoke flavourings**

The Committee considered smoke condensates and liquid smoke at the nineteenth meeting (Annex 1, reference 38). Inadequate information was available at that time for an evaluation to be made.

The present Committee reviewed both the specifications and safety data for this group of products. It noted that smoke flavourings are complex mixtures of varying composition, primarily prepared by the condensation of smoke generated by the pyrolysis of
certain hardwoods in the absence or presence of a limited amount of air. The initial smoke condensate separates into an aqueous phase and a tarry phase. The smoke condensate may be separated into fractions by physical separation techniques or solvent extraction. These fractions may be further purified, if necessary, to remove hazardous constituents known to be present in smoke. Smoke flavourings include smoke condensates, fractions thereof, and mixtures of such fractions.

Products contain different amounts of a whole spectrum of compounds such as alkyl carboxylic acids with carbon numbers 2 to 5, ketones with carbon numbers 2 to 5, furfural derivatives, lactones, and phenol derivatives. Smoke flavourings were studied for the presence of two groups of hazardous constituents: nitrosamines and polycyclic aromatic hydrocarbons. Nitrosamines were not detected in those smoke flavourings tested, while certain non-carcinogenic polycyclic aromatic hydrocarbons were detected in smoke flavourings. To ensure the absence of hazardous polycyclic aromatic hydrocarbons the Committee adopted a specification which required that the concentration of benzo(a)pyrene should not exceed 10 μg per kg, which is the lowest practicable level for measurement.

Short-term studies were available for several types of liquid smoke flavouring (aqueous extract), but extensive studies were available only for a single product derived from the tarry extract. The Committee viewed the use of smoke flavourings generically, keeping in mind that the use of smoke flavourings replaces traditional smoking practices, and this represents a definite improvement since a large number of potentially toxic compounds are eliminated during the production of the flavourings. A similar view has been expressed by the Council of Europe (Resolution AP185/2).

The Committee considered that it may not be possible to allocate an ADI to such a complex group of products, and concluded that smoke flavourings of suitable specifications could be used provisionally to flavour foods traditionally treated by smoking. However, since the available safety data for these products were limited, new or novel uses of smoke flavourings should be approached with caution. The Committee concluded that detailed information on the production and composition of smoke flavourings is required, as described in section 2.2.6, and that it would be desirable to have further safety studies carried out on a well-defined spectrum of smoke flavourings.
A toxicological monograph and new tentative specifications were prepared.

3.1.3 Food colours

*Beet red and betanine.* The Committee noted that previous committees had considered together beet red and betanine, its major colour component. This Committee decided that it would be appropriate to evaluate these food colours separately and pointed out that, for the compound betanine, there were insufficient data available to establish an ADI, since that information available to the Committee did not meet currently accepted standards.

In evaluating beet red, the Committee took into account the principles laid down at the twenty-first meeting (Annex 1, reference 44) and endorsed in Annex III of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76). Thus, when the concentrate is used to enhance the colour of beet products it could be considered as food. If, on the other hand, the concentrate is used more generally as a colourant, careful specifications need to be established. Since nitrate is a component of beet red, it is necessary to ensure that levels of nitrate do not exceed the specifications. Under these conditions beet red could be used according to good manufacturing practice with an ADI “not specified”, keeping in mind the need to limit the nitrate content of foods produced for infants and young children (see section 2.2.3).

A toxicological monograph was prepared. The existing specifications for beet red were revised, and the Committee agreed to delete the “tentative” qualification. No specifications for betanine were prepared.

*Canthaxanthin*

The Committee was aware that canthaxanthin has been used as a direct food additive, as a feed additive, and as an orally-administered pigmenting agent for human skin in both pharmaceutical and cosmetic applications. It was evaluated for acceptable daily intake at the tenth and eighteenth meetings of the Committee (Annex 1, references 13 and 35).

The present Committee was asked to review the safety of canthaxanthin as a food additive because of reports of crystalline deposition in the retina during its use as an orally-administered skin-
pigmenting agent. The dose that resulted in this deposition was within the ADI established by the Committee at the eighteenth meeting (Annex 1, reference 35).

The Committee viewed the observation of crystal deposition in the retina as new data that warranted a complete review of this compound. Most of the new data from animal studies were available only as summaries, and therefore could not be used as a basis for evaluation. The Committee noted that, although pigment accumulation in the eye had been demonstrated analytically following oral administration of canthaxanthin to rats and dogs, no ophthalmoscopy had been carried out and no animal model for the human condition had been developed. In man, however, an estimate was made of the minimal level of exposure resulting in fundal pigment deposition in the retina.

In the light of all these considerations, the previous ADI was made temporary and reduced to 0–0.05 mg per kg of body weight on the basis of the minimal effect level for pigment deposition in the retina of human subjects, adjusted using a ten-fold safety factor.

When setting an ADI, the Committee does not consider therapeutic use, which is a matter for clinical judgement. The cosmetic use of canthaxanthin as an orally-administered skin-pigmenting agent was not anticipated when the ADI was established at the eighteenth meeting. Therefore, it is not included in the temporary ADI established at the present meeting; the temporary ADI applies only to the food and feed additive uses of canthaxanthin.

In allocating a temporary ADI to canthaxanthin, the Committee required that the following additional work be undertaken and the data submitted by 1989:

(a) Details of the long-term studies in mice and rats for which summary data had been submitted, including ophthalmological data where available;

(b) Clarification of the factors that influence deposition in the eye, including the establishment of the threshold dose, the influence of dose and duration of exposure, the reversibility of pigment accumulation, and the investigation of potential animal models; and

(c) Clarification of whether pigment deposition is causally related to impaired ocular function.

A toxicological monograph was prepared. The existing specifications were revised.
Carbon black

Activated vegetable carbon (food grade), that is carbon black derived from vegetable material or lignites, was evaluated for an ADI for man at the fourteenth meeting of the Committee (Annex 1, reference 22). An ADI “not limited”, except that good manufacturing practice be followed, was established. This refers to its use as a clarifying agent, not as a food colour.

Carbon black colours

There are two main groups of carbon blacks used for colouring purposes, the first group are derived from hydrocarbons and the second group are derived primarily from peat and plant materials and are commercially described as vegetable black.

The food colouring uses of carbon blacks derived from both sources were evaluated by the Committee at the twenty-first meeting (Annex 1, reference 44). No ADI was established for food colouring uses from either source. A major concern of that Committee related to the question of how strongly and irreversibly polynuclear aromatic hydrocarbons are adsorbed onto carbon black.

(a) Carbon black (hydrocarbon sources). The present Committee considered data from studies involving carbon blacks derived from hydrocarbon sources. Benzene extracts of certain carbon blacks were found to be carcinogenic to mice. These carcinogenic extracts contain polynuclear aromatic hydrocarbons (PAHs) that were adsorbed onto the carbon black. Data were available to show that only small amounts of polynuclear aromatic hydrocarbons (less than 0.005% of the benzene-extractable PAHs) were eluted from carbon black by biological fluids. Carbon black was not mutagenic in bacterial or mammalian systems. Dietary carbon black was not carcinogenic in limited lifetime studies in rats and mice at levels up to 10% of the diet. Information was also presented to show that carbon black was able to adsorb some chemical carcinogens and, under certain experimental conditions, was shown to reduce their carcinogenic potential.

Based on the available information, the Committee provisionally accepted the use of carbon blacks from hydrocarbon sources in food.

1 This substance is now known as activated carbon (synonyms activated charcoal, decolorizing carbon).
contact materials, including wax coating for cheese. However, it emphasized that future specifications of these carbon blacks should include figures relating to residual polynuclear aromatic hydrocarbons. However, given the fact that carbon blacks from hydrocarbon sources are shown to contain different amounts of known carcinogens and the lack of knowledge on the ability of man to extract such carcinogens from carbon blacks upon ingestion, and considering the limited lifetime feeding studies in experimental animals with defined carbon blacks, the Committee concluded that it was unable to determine the suitability of carbon blacks from hydrocarbon sources as food additives at this time. Therefore, an ADI was not established for direct use as a food colourant. The Committee did not receive information on identity and purity of carbon blacks from hydrocarbon sources and therefore no specifications were prepared.

A toxicological monograph was prepared.

(b) Carbon black (vegetable black): No toxicological data were available on carbon blacks derived from vegetable sources and therefore an ADI could not be established.

No toxicological monograph was prepared.

The existing specifications for carbon black (vegetable black) were revised but maintained as "tentative".

Carotenes (natural)

These substances were reviewed at the eighteenth meeting of the Committee (Annex 1, reference 35) when it was concluded that further information was required before a specification could be developed. Therefore, no toxicological evaluation was possible for these materials at that time.

While there is a substantial toxicological data base relating to carotenes and an acceptable daily intake has been established for synthetic β-carotene (Annex 1, reference 35), this could not be applied to carotenes (natural) since these substances did not comply with the specifications for β-carotene and differed significantly in composition with regard to materials other than carotenes.

The Committee considered three sources of carotenes, namely a hexane extract of carrots, a byproduct of the manufacture of chlorophyll from alfalfa/grass meal by a process of solvent extraction and fractionation, and algal extracts obtained by
supercritical carbon dioxide or vegetable oil extraction. These materials differed significantly from each other and from synthetic β-carotene such that separate evaluations were required. For the natural materials, carotenones comprised at maximum about 5% of the extract, further diluted with vegetable oil for standardization in some cases.

No toxicological data were available on these substances. Because of the origin and method of extraction, the Committee concluded that such data were necessary under the guidelines laid down in the twenty-first report of the Committee (Annex 1, reference 44) and endorsed in Annex III of Principles for the safety assessment of food additives and contaminants in food (Annex 1, reference 76). Accordingly, the Committee was unable to evaluate these materials for an ADI. However, with regard to extracts of carrots or alfalfa, the Committee felt that the need for toxicity tests may be obviated if detailed analytical data were supplied to confirm that natural toxicants occurring at low levels in food/feedstuffs are not concentrated in the extract and that levels of use would not materially exceed the levels of exposure that would result from their normal use.

A toxicological monograph was not prepared. New tentative specifications were prepared, one covering the two substances derived from vegetable sources, and the other covering products extracted from the alga Dunaliella salina. The Committee requested further information on these products, especially on possible levels of urethane in products obtained by extraction with supercritical carbon dioxide.

The existing tentative specifications for carotenones (natural) were withdrawn.

Citramaxanthin

The Committee was informed that the major present day use of this synthetic carotenoid is as an animal feed additive to impart a yellow colour to chicken fat and egg yolks. It may also be used as a colouring agent by adding it directly to foods.

If the substance were to be used as a direct food colouring agent, the data were not sufficiently comprehensive for evaluation (e.g., only one lifetime feeding study was available). The Committee concluded that further data of the type outlined in Annex III of Principles for the safety assessment of food additives and contaminants
in food for synthetic food colours are required before the substance can be fully evaluated for direct food use (Annex 1, reference 76).

In the case of use as an animal feed additive, an evaluation could not be performed because the data base did not include sufficient information on the nature of residues to be found in animal-derived foodstuffs and because there was no information concerning the use levels that would constitute good animal husbandry practice.

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

*Xanthophylls*

Xanthophylls were considered at the twenty-first meeting of the Committee, when it was noted that two dry types were available, citranaxanthin produced synthetically or from dried *Tagetes* petals (*Tagetes erecta* L.) or algae (genus *Spongiococcus*) (Annex 1, reference 44, page 23). At that time no toxicity data were available and no evaluation could be made.

The present Committee considered the uses of xanthophylls both as food additives and in poultry feed. The Committee was informed that commercial xanthophyll preparations were obtained by hexane extraction of *Tagetes* petals and contained primarily lutein, with variable amounts of antheraxanthin and other xanthophylls. In addition another product, designated mixed carotenoids, derived by solvent extraction of nettles, alfalfa, or grass meal consists of carotenoids with xanthophyll lutein accounting for the major part.

No toxicological data were available on the *Tagetes* extract or on lutein. The Committee was unable, on the basis of the information before it, to determine whether *Tagetes* petals were used as food. Such products would not require toxicological evaluation according to the guidelines contained in the twenty-first report of the Committee (Annex 1, reference 44) and endorsed in Annex III of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76). Therefore the Committee was unable to evaluate the safety of xanthophylls.

In noting that xanthophyll preparations were used as feed additives, the Committee concluded that it would be necessary to have qualitative and quantitative information on xanthophylls and metabolites in animal-derived foods before an evaluation could be made.
No toxicological monograph was prepared. New tentative specifications were prepared for *Tagetes* extract and for mixed carotenoids. The existing specifications for xanthophylls were withdrawn.

### 3.1.4 Miscellaneous food additives

*Ferrous gluconate*. At the nineteenth meeting, the Committee evaluated ferrous gluconate as a colouring adjunct (Annex 1, reference 38). An ADI "not specified" was established, with the proviso that the contribution of ferrous gluconate to the total dietary gluconic acid intake from all sources should be included in the ADI for gluconic acid.

Because this is a soluble bioavailable ferrous salt, the iron moiety poses a greater potential threat of toxicity than does the gluconate moiety. Therefore, the present Committee concluded that it would be more appropriate to link the ADI for ferrous gluconate to the provisional maximum tolerable daily intake (PMTDI) for iron established at the twenty-seventh meeting (Annex 1, reference 62) than to the ADI for gluconate. On this basis, the contribution of iron from the use of ferrous gluconate should be included with all other sources of iron, the total of which should not exceed the PMTDI for iron of 0.8 mg per kg of body weight.

A toxicological monograph was not prepared. Revision of the existing specifications was not considered.

*L-Glutamic acid and its ammonium, calcium, magnesium, monosodium, and potassium salts*

The above glutamates were evaluated at the fourteenth and seventeenth meetings of the Committee (Annex 1, references 22 and 32). A toxicological monograph was prepared after the seventeenth meeting, when an ADI of 0–120 mg per kg of body weight (calculated as glutamic acid) was allocated.

The Committee was informed of dietary studies carried out in some Asian countries from which there is evidence that the consumption of monosodium glutamate has increased in recent years, and the effort of the Codex Committee on Food Additives to determine whether the intake of this compound exceeded the previously established ADI.
Monosodium glutamate is used in small quantities as a flavour enhancer in manufactured foods. A more significant dietary source of glutamate may be from the direct use of monosodium glutamate by the consumer and by restaurants as part of preparations used to season food. It would be desirable to obtain data on this use of monosodium glutamate and the probable intake of free glutamate from food preparations, such as soups and sauces, including appropriate intake studies, bearing in mind possible individual intolerance to single high intakes of this compound and other free glutamates. The intake studies should include data on the temporal distribution of intakes as well as on daily intakes.

The Committee considered information obtained since the seventeenth meeting including extensive metabolic studies relating dose regime to plasma levels of glutamic acid, endocrinological and neurotoxic effects, and studies of intolerance to monosodium glutamate.

The Committee concluded, based on the analysis of blood levels of glutamic acid in human subjects associated with various dietary regimens, that peak plasma levels are dependent on the food vehicle in which the compound is incorporated and that infants metabolize monosodium glutamate in a similar way to adults. In the light of all the data, the Committee allocated an ADI “not specified” to monosodium glutamate when incorporated into food or used as a condiment; this ADI applies to all glutamates, alone and in combination.

Caution should be used when ingesting monosodium glutamate as a large single dose rather than divided between several meals because high plasma levels may be reached under the former conditions.

In its previous evaluation, the Committee concluded that it would be prudent not to apply the ADI for glutamate to infants under 12 weeks of age (Annex 1, reference 32). In view of the finding that infants metabolize monosodium glutamate in a similar way to adults, no additional hazard to infants was indicated. However, the present Committee expressed the general opinion in section 2.2.2 that the use of any food additives in infant foods should be approached with caution.

Substances given an ADI “not specified”, such as glutamate salts in this instance, are of low toxicity. On the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of glutamates arising from their use at the levels necessary to
achieve the desired technological effect and from their acceptable background in food do not, in the opinion of the Committee, represent a hazard to health. For that reason, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. The Committee reiterated the general principle expressed in its first report (Annex 1, reference 1) that the amount of an authorized additive used in food should be the minimum necessary to produce the desired effect.

A toxicological monograph was prepared. The existing specifications for L-(+)-glutamic acid, monosodium L-glutamate, monopotassium L-glutamate, monoammonium L-glutamate, calcium di-L-glutamate, and magnesium di-L-glutamate were revised.

4-Hydroxymethyl-2,6-diisert-butylphenol

The Committee had before it for evaluation 4-hydroxymethyl-2,6-diisert-butylphenol. The compound was considered by the twenty-third meeting of the Committee (Annex 1, reference 50), at which time additional data were requested. Since the requested data were not forthcoming, this Committee was unable to evaluate the compound. The Committee was unaware of commercial production of this antioxidant or of its use in food and the existing tentative specifications were therefore withdrawn (Annex 1, reference 56).

Polydextroses

Polydextrose A and polydextrose N were evaluated by the twenty-fourth meeting of the Expert Committee, at which time an ADI of 0-70 mg per kg of body weight was allocated (Annex 1, reference 53). The twenty-fifth Committee revised the specifications to include a limit of 0.05% for 5-hydroxymethyl-furfural in polydextroses (Annex 1, reference 56).

Polydextroses showed no toxic effects in acute, subacute, or chronic studies in three species of animal at levels equivalent to 10% of the diet. Studies have shown that metabolism of these compounds is comparable in animals and man. Polydextroses are poorly absorbed and are metabolized by the gut flora to their normal metabolites, primarily carbon dioxide and volatile fatty acids.

Studies in man have demonstrated that polydextroses, when administered at very high doses, exert a laxative effect, with a mean
laxative threshold of 90 g per day or 50 g as a single dose. This factor should be taken into account when considering appropriate levels for the use of polydextroses alone or in combination with other substances causing laxative effects by osmotic action.

The Committee re-examined polydextroses on the basis of the above considerations and those expressed in *Principles for the safety assessment of food additives and contaminants in food*, sections 5.5.1 and 6.2 (Annex 1, reference 76), and allocated an ADI “not specified”.

A toxicological monograph was not prepared. The existing specifications were maintained.

Tannic acid

The substances previously evaluated at the tenth and fourteenth meetings of the Committee (Annex 1, references 13 and 22) were hydrolysable gallotannins. The Committee changed the name used on the agenda “tannins (food-grade)” to “tannic acid” to separate the commercial products used as food additives and processing aids from chemically unrelated substances also called tannins.

Temporary ADIs for tannins of 0.6 mg per kg of body weight from Peruvian tara and of 0.3 mg per kg of body weight from Turkish aleppo, Chinese tara, and Sicilian sumac were allocated at the fourteenth meeting on the basis of the results of a multigeneration reproduction study and a long-term feeding study in rats performed with Peruvian tara. Studies in a second species and further information on the specifications for these tannins were requested at the fourteenth meeting (Annex 1, reference 23).

New toxicological information available to the Committee demonstrated that a tannic acid product was not mutagenic in bacterial and yeast systems, even with metabolic activation. In addition, it was not teratogenic in rats and mice.

On the basis of the existing toxicological data on tannic acid (hydrolysable gallotannins) and considering that the use of tannic acid in food processing as a flocculant, under conditions of good manufacturing practice, results in very low levels in food and beverages, the Committee changed the previous temporary ADI to a temporary ADI “not specified” for tannic acid used as a filtering aid.

The data were not comprehensive enough to be used to evaluate the use of tannic acid as a flavouring agent added directly to food.
The Committee concluded that additional data on the composition of tannic acid from different sources and evidence that its use does not result in a significant increase in total intake of tannic acid (as hydrolysable gallotannins) are required to decide whether the substance should be subjected to further toxicity tests before it can be evaluated for direct food use.

The Committee revised the previous specifications for “tannins (food-grade)” and changed the title to “tannic acid” as described above. The Committee maintained the tentative designation.

3.2 Contaminants

3.2.1 Aflatoxins

The Committee noted that FAO and WHO had requested the evaluation of aflatoxins from the viewpoint of their impact on health when present as food contaminants. A specific request by the FAO Intergovernmental Group on Oilseeds, Oils and Fats\(^1\) for the possible establishment of acceptable international maximum levels of aflatoxins had led to the need for the evaluation of aflatoxins from a toxicological point of view. The Committee was informed of the activities of the Joint UNEP/FAO/WHO Food Contamination Programme, where data are collected on levels of aflatoxin in groundnuts, tree nuts, maize, and other grains of major dietary importance, in milk and animal feed, and to some extent in total diets.\(^2\)\(^3\) The Committee was informed that a conference was being planned in the near future to consider the various questions relating to food contamination by mycotoxins. Documents being prepared for this meeting included analyses of the current relevant regulations and a synopsis of national control measures, taken in relation to aflatoxin contamination. These documents are available from


FAO. Information on the available toxicity data is contained in a number of recent reviews.2–5

The present evaluation was concerned with the health effects of aflatoxin present in the human diet, although the Committee recognized the importance of aflatoxin in animal feed as a source of human exposure to aflatoxin and its metabolites (see section 2.2.2).

Four major aflatoxins (B₁, B₂, G₁, and G₂) occur in fungally contaminated plant products. The major aflatoxin-producing fungi are Aspergillus flavus and Aspergillus parasiticus. In addition, aflatoxins M₁ and M₂, the hydroxylated metabolites of aflatoxins B₁ and B₂, occur predominantly in the milk of cows fed rations containing aflatoxins B₁ and B₂. However, aflatoxin B₁ is usually found in the greatest concentration in the food supply, and most of the available toxicological data relate to this compound.

The Committee considered information from studies on the biochemistry and toxicology of aflatoxins, as well as the effects on human health and information on the possible relationship between aflatoxin ingestion and the occurrence of primary liver cancer in man. The acute toxic effect of aflatoxins B₁, B₂, and M₁ in all animal species studied is characterized by haemorrhagic necrosis of the liver. Many data exist on the carcinogenic effects of orally-administered aflatoxin B₁; it is a well known potent hepatocarcinogen in all mammalian species studied. Animal species exhibit a range of susceptibilities to the carcinogenic effects of aflatoxin B₁, ranging from the duck which is extremely sensitive, to adults of certain strains of mice and sheep which are relatively insensitive. Dose–response studies in rats show that dietary levels of aflatoxin as low as 0.005 mg/kg of purified aflatoxin B₁ result in an 80% incidence of liver tumours in 65–80 weeks. A number of factors, such

as dietary content of protein, lipid, and vitamins and hormones, have been shown to modify the carcinogenic response of rats to aflatoxin B$_1$. Limited data are available on the carcinogenicity of some of the aflatoxin congeners or metabolites. The available information indicates a decreasing order of potency of B$_1$ > G$_1$ > B$_2$ > G$_2$. Aflatoxicol, a major metabolite of aflatoxin, may be as potent as aflatoxin B$_1$; aflatoxin M$_1$ appears to be at least an order of magnitude less potent than aflatoxin B$_1$. Information was also available on the effects of aflatoxin on man from cases of acute intoxication and death and on epidemiological studies relating intakes of aflatoxin and incidence rates of primary liver cancer.

The Committee considered a number of alternative ways of evaluating the risk associated with human exposure to aflatoxin B$_1$. It was noted that death had occurred following short-term exposure to aflatoxins at an estimated level of 6 mg/day.$^1$ The Committee considered that it was possible that the acute toxic effects might be eliminated by ensuring that the levels of aflatoxin in the diet were at least an order of magnitude lower than those causing the toxic effects.

The more difficult goal was the attempt to establish the possible carcinogenic risk resulting from chronic exposure to aflatoxin. Good animal data are available on the relationship between aflatoxin levels, duration of exposure, and carcinogenicity. The available human data on the association between aflatoxin exposure and primary liver cancer are difficult to evaluate because of the large number of uncertainties in the studies, which include inadequate data on the dietary intake of aflatoxins, contribution of hepatitis B virus to the etiology of cancer, and cultural and dietary status and habits. The Committee agreed that at present the available scientific information does not permit a determination of the extent to which exposure to aflatoxins contributed to the increased incidence of primary liver cancer in the populations that were studied.

The Committee considered aflatoxin to be a potential human carcinogen. There is not sufficient information available to establish a figure for a tolerable level of exposure. The Committee urged that the intake of dietary aflatoxin be reduced to the lowest practicable levels, so as to reduce, as far as possible the potential risk. It reiterated the view expressed at the twenty-second meeting of the

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Committee that dealt with the problem of trace contaminants in food (Annex 1, reference 47), namely: "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".

Data on the occurrence of aflatoxins in various foods and estimated aflatoxin dietary intakes for various countries clearly demonstrate the wide ranging levels of aflatoxins in susceptible food commodities (e.g., peanuts, cereal grains) and confirmed that consumers throughout the world are being exposed to these substances albeit at different levels. In this latter regard, the limits enforced by different countries for aflatoxins in food undoubtedly contribute positively to minimizing consumer exposure. In the main, these limits have been based on the recognition that aflatoxins are undesirable from a human health standpoint, but at present there is no practical means of eliminating them completely without restricting the availability of otherwise nutritious commodities. In addition, these limits reflect technological developments that have resulted in the reduction of aflatoxin contamination of foods as well as analytical improvements permitting analysis and regulatory control at lower levels.

The Committee acknowledged the complexities of the problem of the reduction of aflatoxin exposure, but was aware that this could be achieved in a number of ways. In the first instance, it was noted that aflatoxin contamination can be controlled by minimizing mould growth. To do this, several pre-harvest control measures have been identified, e.g., selection of a resistant seed variety, prevention of physical damage to crops by insects, and appropriate crop rotation. Similarly, harvest precautions, e.g., proper handling to avoid physical damage and crop cleaning to remove field soil have been shown to minimize susceptibility to contamination. The effect of storage conditions has also been investigated by a number of researchers and moisture content together with temperature have been identified as the most important factors to be taken into account for the protection of stored grains against aflatoxin
contamination. Accordingly, continuous, adequate aeration and monitoring of moisture content and temperature are to be encouraged. In addition to harvesting and storage precautions, screening of crops prior to processing and sale has been shown to be an important way of minimizing exposure to aflatoxins. For example, manual, mechanical, and electronic methods have been used successfully to exclude damaged or discoloured peanuts. The Committee urged the application of these means to minimize aflatoxin contamination of food.

The Committee was also informed of research activities related to the detoxification of aflatoxin-contaminated produce. At the present time, the only treatment that the Committee was aware is used commercially is the ammoniation of animal feeds. It was stressed that detoxification procedures should not be regarded as an alternative to good agricultural practice and that such procedures should only be considered when preventive measures have failed. Furthermore, any detoxification treatment must not adversely affect the nutritional quality of the treated crop or result in the presence of other toxic substances that could compromise the overall safety of the crop.

A toxicological monograph was not prepared.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

Twenty-four substances were considered for specifications only. Specifications for seventeen substances were revised and seven were maintained. In addition, the Committee was asked to consider the specifications for glycerol esters of wood rosin. However, the Committee noted that information on this substance had not been solicited from all sources and therefore it agreed to review these specifications at a future meeting.

4.1 Food colours

The Committee was asked to reconsider certain of the specifications for food colours drawn up at the twenty-eighth meeting.
Caramel colours

The Committee last evaluated caramel colours in 1985 when the specifications were made tentative pending receipt of further information on starting materials, methods of manufacture, and composition (Annex 1, reference 70 p. 28). At that time, limits for the various parameters in the specifications were set on the basis of the solids content. The Committee has since received limited information on starting materials, methods of manufacture, and composition. The Committee was asked to reconsider the basis for the limits on the grounds that limits set on an equivalent colour basis provide a better control for levels of 4-methylimidazole and 2-acetyl-4-tetrahydroxybutylimidazole in the final food product. The Committee agreed that for caramels with a low colour intensity limits set on an equivalent colour basis represented a tighter restriction on the levels of these components in the final food. However, such a method of expressing limits could be less restrictive for caramel colours with a high colour intensity. Furthermore, the ADI allocated in 1985 was set on an “as is” or equivalent solids basis in terms of total caramel colour. Therefore, the Committee agreed that limits for 4-methylimidazole and 2-acetyl-4-tetrahydroxybutylimidazole on an equivalent colour basis provided a valuable supplementary control, and the specifications were revised accordingly. Nevertheless, the Committee also maintained, for 4-methylimidazole and 2-acetyl-4-tetrahydroxybutylimidazole, an upper limit on the solids content and maintained all other limits on a solids basis. Limits for solids content and colour intensity were added. The existing tentative specifications were revised and the “tentative” qualification deleted.

Patent blue V

The Committee was informed that the manufacture of the calcium salt of this colour (which is provided for in the specifications) resulted in the unavoidable presence of calcium sulfate producing more water-insoluble matter. The Committee revised the specifications accordingly.

Brilliant black BN and Ponceau 4R

The Committee had been requested to reduce the assay levels of the specifications for Brilliant black BN and Ponceau 4R, although
it was informed that these levels could be met. The Committee reiterated the opinion expressed in section 2.3.1 that such amendments to the specifications should be fully justified in terms of a net improvement in quality. The existing specifications for Brilliant black BN and Ponceau 4R were maintained.

Paprika oleoresin

The Committee’s tentative specifications for paprika oleoresin were revised to include an assay test based on colour value and to place a maximum limit on capsaicin content. The Committee had also received a request to include provisions for an additional processing solvent, 1,2-dichloroethane. However, the Committee could not include this solvent in its specifications without a toxicological review of the solvent.

4.2 Sweetening agents

Malitol and xylitol. The Committee considered specifications for maltitol powders and xylitol.

The Committee was not aware that chemically-pure maltitol is used in food. Dry, food-grade maltitol is covered by the existing specifications for hydrogenated glucose syrups. The specifications for hydrogenated glucose syrups were revised to make it clear that they include the dried product.

Both hydrogenated glucose syrups and xylitol are added to foods as replacements for sugar. Since such foods may be consumed by children, the Committee felt that the lead content of these substances should be subject to more stringent control than that usually applied to food additives and agreed that a maximum limit of 1 mg per kg was called for. The specifications for xylitol were also revised and both specifications were made tentative pending confirmation that the lower limit for lead can be met. The Committee further recommended that at some future date the specifications for mannitol, sorbitol, sorbitol syrup, and isomalt should be reviewed with the aim of reducing the lead limit of these substances as well.

4.3 Miscellaneous food additives

Polyglycerol esters of fatty acids. The Committee received a request to amend the specifications to increase the range of average
polyglycerol chain lengths permitted from 3 to 10 glycerol units. The Committee concluded that the specifications could not be amended without a review of the toxicological data on these substances to ensure that the material tested included the range of polyglycerol units requested. The existing specifications were maintained.

Sucrose esters of fatty acids

The Committee received requests to permit three additional solvents to be used for the manufacture of this additive together with proposals for residual solvent limits. The Committee agreed not to add these solvents to those already permitted for the manufacture of this additive without a review of the toxicological data on these substances to determine the nature of the substances tested or an evaluation of the solvents themselves. The existing specifications were maintained.

Talc

The Committee was requested to review methods available for the determination of asbestos in talc. It was concluded that, because of the complexity and expense of instrumentation required for the quantification of asbestos in talc, the present test should not be revised. The existing specifications were maintained and the Committee agreed to delete the “tentative” qualification.

4.4 Establishment and revision of methods of analysis

4.4.1 General methods

New general methods were prepared for:

(a) method of assay for oil-soluble food colours;
(b) limit test for pyrrolidone-carboxylic acid in glutamic acid and its salts by thin-layer chromatography.

4.4.2 Tentative methods of analysis

In the course of revising a number of specifications, the Committee identified the need to update several of its analytical methods. The following tentative, alternative general methods were prepared as proposals for use in future revisions of specifications:
(a) general method for the determination of polyols by high pressure liquid chromatography;
(b) alternative method for the determination of the nominal molecular mass of polyethylene glycols by size exclusion chromatography;
(c) determination of the content of ethylene oxide and 1,4-dioxane in polyethylene glycols by gas–liquid chromatography.

5. FUTURE WORK

1. The Committee was informed of recent changes in the methods of manufacture of iron oxides used as food colours, which could result in increased levels of contaminants. Iron oxides should be reviewed as a group, taking into account the origin of raw materials and all methods of manufacture. Information on the current use of iron oxides in foods and intake data are desirable.
2. Glycerol esters of wood rosin should be reviewed taking into account data provided in reply to the request of the twentieth meeting.
3. Paprika oleoresin, polyglycerol esters of fatty acids, and sucrose esters of fatty acids should be toxicologically evaluated in light of proposed changes in specifications.
4. Lead limits in the specifications for all polyol sweetening agents should be reviewed (see section 4.2).
5. The General Specifications for enzymes used in food processing (Annex 1, reference 69, Annex 1) should be reviewed.
6. Methods of analysis should be established to identify and assay the principal components of food colours prepared by the extraction of plant materials.

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 once a year.
2. Every effort should be made to reduce aflatoxin levels in food to the lowest levels practicable.

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3. FAO and WHO should encourage governments to investigate and implement preventive and control measures for limiting the levels of aflatoxin in the diet.

4. FAO and WHO should encourage international collaboration between governments so as to harmonize aflatoxin regulatory controls as far as is feasible.

5. FAO and WHO, in cooperation with other international organizations, should encourage the development of improved analytical methods for aflatoxins in order to enhance their usefulness as well as their application for regulatory control.

6. FAO and WHO should continue efforts aimed at establishing appropriate sampling procedures that take into account the non-homogeneous distribution of aflatoxin contamination.

7. The agencies concerned should consider strengthening the Joint UNEP/FAO/WHO Food Contamination Monitoring Programme to increase the value of the data collected as well as its usefulness as a basis upon which advice can be provided to Member States concerning food and feed surveillance programmes.

8. Since the available data on the intake of dietary aflatoxins are limited, intake studies should be carried out, especially in countries where climatic conditions are conducive to aflatoxin contamination of foods.

9. FAO and WHO together with other international organizations should encourage the conduct of adequate epidemiological studies concerning the health effects thought to be related to aflatoxin exposure, ensuring that confounding variables are accounted for.

10. Further information is required about aflatoxin and other mycotoxin detoxification procedures, including the nature of the products resulting from the treatment, their toxicity, the possibility of metabolic reactivation, residues in human food as a result of treatment, adverse nutritional effects, and the potential de novo formation of toxic substances by the treatment process.

11. Information submitted to the Committee to be used to set specifications should, whenever possible, be in accordance with internationally accepted rules for nomenclature. In particular:

—physical constants and chemical parameters should be expressed in SI units (Système international d'Unités);
— the chemical names of organic compounds should be in accordance with the IUPAC rules for nomenclature, and if official names are known these should be used.
ACKNOWLEDGEMENTS

The Expert Committee wish to thank the following WHO Staff members for their valuable contributions to the meeting: Dr H. Galal Gorchev, Food Safety Programme, Division of Environmental Health, WHO, Geneva, Switzerland; Dr M. Ten Ham, Senior Scientist, Pharmaceuticals, WHO, Geneva, Switzerland.
Annex 1

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


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).


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


63. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.
64. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 28, 1983.
# Annex 2

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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Specifications</th>
<th>ADI for men (and other toxicological recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Food additives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzyme preparations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Amylase from Aspergillus oryzae</td>
<td>N, T</td>
<td>Acceptable¹</td>
</tr>
<tr>
<td>Proteinase from Aspergillus oryzae</td>
<td>R, T</td>
<td>Acceptable²</td>
</tr>
<tr>
<td>Amyloglucosidases from Aspergillus niger</td>
<td>N, T</td>
<td>0-1 mg/kg body weight³</td>
</tr>
<tr>
<td>β-Glucanase from Aspergillus niger</td>
<td>N, T</td>
<td>0-1 mg/kg body weight³</td>
</tr>
<tr>
<td>β-Mannanase from Aspergillus niger</td>
<td>N, T</td>
<td>0-1 mg/kg body weight³</td>
</tr>
<tr>
<td>Protease from Aspergillus niger</td>
<td>O</td>
<td>0-1 mg/kg body weight³</td>
</tr>
<tr>
<td>β-Glucanase from Trichoderma harzianum</td>
<td>N, T</td>
<td>0-0.5 mg/kg body weight⁴ *</td>
</tr>
<tr>
<td>Cellulase from Trichoderma reesei</td>
<td>N, T</td>
<td>0-0.3 mg/kg body weight⁴ *</td>
</tr>
<tr>
<td>Cellulase from Pseudomonas fluorescens</td>
<td>N, T</td>
<td>No ADI allocated⁵</td>
</tr>
<tr>
<td>Pectinase from Aspergillus niger</td>
<td>O</td>
<td>No ADI allocated⁵</td>
</tr>
<tr>
<td><strong>Flavouring agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-Anethole</td>
<td>S</td>
<td>0-2.5 mg/kg body weight⁷</td>
</tr>
<tr>
<td>Benzoylecetate</td>
<td>S</td>
<td>0-5 mg/kg body weight⁷</td>
</tr>
<tr>
<td>Smoke flavourings</td>
<td>N, T</td>
<td>Provisional acceptance⁸</td>
</tr>
<tr>
<td><strong>Food colours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beet red</td>
<td>R</td>
<td>ADI &quot;not specified&quot;¹¹</td>
</tr>
<tr>
<td>Carthamus</td>
<td>R</td>
<td>0-0.05 mg/kg body weight⁹</td>
</tr>
<tr>
<td>Carbon black</td>
<td>R, T</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Carotenes (algae)</td>
<td>N, T⁸</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Carotenes (vegetable)</td>
<td>N, T⁸</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Citranaxanthin</td>
<td>R</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Xanthophylls (mixed carotenoids)</td>
<td>N, T¹²</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Xanthophylls (Tagetes extract)</td>
<td>N, T¹²</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td><strong>Miscellaneous food additives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>S</td>
<td>0.8 mg/kg body weight¹¹</td>
</tr>
<tr>
<td>Glutamic acid and its salts</td>
<td>R</td>
<td>ADI &quot;not specified&quot;¹², ¹³</td>
</tr>
<tr>
<td>4-Hydroxymethyl-2,6-dihydroxyphenol</td>
<td>W</td>
<td>No ADI allocated¹⁰</td>
</tr>
<tr>
<td>Polydextrose</td>
<td>S</td>
<td>ADI &quot;not specified&quot;¹⁷</td>
</tr>
<tr>
<td>Tannic acid</td>
<td>R, T</td>
<td>ADI &quot;not specified&quot;¹⁴, ¹⁷, ¹³</td>
</tr>
<tr>
<td><strong>B. Contaminants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflatoxins</td>
<td>–</td>
<td>Lowest practicable level¹⁴ *</td>
</tr>
</tbody>
</table>

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*Specifications only¹*
<table>
<thead>
<tr>
<th>Specified compound</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorophylls</td>
<td>R</td>
</tr>
<tr>
<td>Chlorophylls, copper complexes</td>
<td>R</td>
</tr>
<tr>
<td>Chlorophyllins, copper complexes, sodium and potassium salts</td>
<td>R</td>
</tr>
<tr>
<td>Hydrogenated glucose syrups</td>
<td>R, T</td>
</tr>
<tr>
<td>Insoluble polyvinylpyrrolidone</td>
<td>S</td>
</tr>
<tr>
<td>Paprika oleoresin</td>
<td>R</td>
</tr>
<tr>
<td>Patent blue V</td>
<td>R</td>
</tr>
<tr>
<td>Polyethylene glycols</td>
<td>R</td>
</tr>
<tr>
<td>Polyglycerol esters of fatty acids</td>
<td>S</td>
</tr>
<tr>
<td>Ponceau 4R</td>
<td>S</td>
</tr>
<tr>
<td>Potassium bromate</td>
<td>R</td>
</tr>
<tr>
<td>Potassium dichromate</td>
<td>R</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>R</td>
</tr>
<tr>
<td>Riboflavin 5'-phosphate, sodium</td>
<td>R</td>
</tr>
<tr>
<td>Sucrose esters of fatty acids</td>
<td>S</td>
</tr>
<tr>
<td>Talc</td>
<td>S</td>
</tr>
<tr>
<td>Triammonium citrate</td>
<td>S</td>
</tr>
<tr>
<td>Xylitol</td>
<td>R, T</td>
</tr>
</tbody>
</table>

**Notes to Annex 2**

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

2. Acceptable for use in food processing. These enzymes are derived from microorganisms that are traditionally accepted as constituents of foods or are normally used in the preparation of foods. These products are regarded as foods and, consequently, considered acceptable, provided that satisfactory chemical and microbiological specifications can be established.

3. Based on the percentage of T.O.S. (total organic solids); % T.O.S. = 100 − (A+W+D), where A = % ash, W = % water, and D = % diluent and carrier.

4. Temporary acceptance (see Annex 3).

5. Insufficient information available on its toxicology and/or chemical composition to establish an ADI.

6. Analytical and compositional data, including data on variability, are required; further safety studies on a well-defined spectrum of smoke flavourings are desired.

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

8. The use of carbon black from hydrocarbon sources in food contact materials is provisionally accepted.

9. The previous specifications for carotenes (natural) were withdrawn.

10. The previous specifications for xanthophylls were withdrawn.

11. Provisional maximum tolerable daily intake (PMTDI) for iron.

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12. Group ADI for L-glutamic acid and its ammonium, calcium, magnesium, monosodium, and potassium salts.
13. For use as a processing aid.
14. Presence in food should be reduced to irreducible levels. An irreducible level is defined as that concentration of a substance that cannot be eliminated from a food without involving the discarding of that food altogether, severely compromising the ultimate availability of major food supplies.
15. This specification also covers dry, food-grade maltitol, which is the substance listed on the agenda of this meeting.
Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

Enzyme preparations

$\beta$-Glucanase from *Trichoderma harzianum*\(^1\)

1. Submission of the results of a long-term study in a rodent species.
   2. Specifications showing that this organism does not produce antibiotics and is not pathogenic to man.

*Cellulase* from *Trichoderma reesei*\(^1\)

Submission of the results of a long-term study in a rodent species.

Flavouring agents

*trans*-Anethole\(^2\)

Submission of the results of the long-term feeding study in rats that has been completed recently.

*Benzyl acetate*\(^3\)

Submission of the results of lifetime gavage studies with benzyl alcohol, the lifetime phases of which have been completed recently.

Food colours

*Canthaxanthin*\(^3\)

1. Submission of details of the long-term studies in mice and rats for which summary data have been submitted, including ophthalmological data where available.
   2. Clarification of the factors that influence pigment deposition in the eye, including the establishment of the threshold dose and the influence of dose and duration of exposure, the reversibility of pigment accumulation, and the investigation of potential animal models.

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\(^1\) Information required by 1992.
\(^2\) Information required by 1988.
\(^3\) Information required by 1989.

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3. Clarification of whether pigment deposition is causally related to impaired ocular function.

**Miscellaneous food additives**

*Tannic acid*

Further data are required on the composition of tannic acid from different sources. Before it can be evaluated for direct food use, evidence must also be provided that its use does not result in a significant increase in total intake of tannic acid (as hydrolysable gallotannins); these data will be used to decide whether tannic acid should be subjected to further toxicity testing.
Recent reports:

705 (1984) The role of food safety in health and development
   Report of a Joint FAO/WHO Expert Committee on Food Safety
   (79 pages) .............................................................. 7.—

   Report of a WHO Scientific Group on the Epidemiology of Aging
   (84 pages) .................................................................. 8.—

707 (1984) Recommended health-based occupational exposure limits for
   respiratory irritants
   Report of a WHO Study Group (154 pages) ......................... 14.—

708 (1984) Education and training of nurse teachers and managers with
   special regard to primary health care
   Report of a WHO Expert Committee (54 pages) .................... 6.—

709 (1984) WHO Expert Committee on Rabies
   Seventh report (104 pages) .............................................. 9.—

710 (1984) Evaluation of certain food additives and contaminants
   Twenty-eighth report of the Joint FAO/WHO Expert Committee on
   Food Additives (44 pages) .............................................. 5.—

711 (1984) Advances in malaria chemotherapy
   Report of a WHO Scientific Group (218 pages) ................... 20.—

712 (1984) Malaria control as part of primary health care
   Report of a WHO Study Group (73 pages) .......................... 8.—

713 (1984) Prevention methods and programmes for oral diseases
   Report of a WHO Expert Committee (46 pages) .................. 5.—

714 (1985) Identification and control of work-related diseases
   Report of a WHO Expert Committee (71 pages) .................. 7.—

715 (1985) Blood pressure studies in children
   Report of a WHO Study Group (36 pages) .......................... 5.—

716 (1985) Epidemiology of leprosy in relation to control
   Report of a WHO Study Group (60 pages) .......................... 6.—

717 (1985) Health manpower requirements for the achievement of health for
   all by the year 2000 through primary health care
   Report of a WHO Expert Committee (92 pages) .................... 8.—

718 (1985) Environmental pollution control in relation to development
   Report of a WHO Expert Committee (63 pages) .................... 6.—

719 (1985) Arthropod-borne and rodent-borne viral diseases
   Report of a WHO Scientific Group (116 pages) ................... 10.—

720 (1985) Safe use of pesticides
   Ninth report of the WHO Expert Committee on Vector Biology and
   Control (60 pages) ...................................................... 6.—

721 (1985) Viral haemorrhagic fevers
   Report of a WHO Expert Committee (126 pages) .................. 10.—
722 (1985) The use of essential drugs
Second report of the WHO Expert Committee on the Use of Essential Drugs (50 pages) .......................................................... 6.—

723 (1985) Future use of new imaging technologies in developing countries
Report of a WHO Scientific Group (67 pages) ......................... 7.—

724 (1985) Energy and protein requirements
Report of a Joint FAO/WHO/UNO Expert Consultation (206 pages) 17.—

725 (1985) WHO Expert Committee on Biological Standardization
Thirty-fifth report (140 pages) .................................................... 11.—

726 (1985) Sudden cardiac death
Report of a WHO Scientific Group (25 pages) .......................... 4.—

727 (1985) Diabetes mellitus
Report of a WHO Study Group (113 pages) .............................. 9.—

728 (1985) The control of schistosomiasis
Report of a WHO Expert Committee (113 pages) .................... 10.—

729 (1985) WHO Expert Committee on Drug Dependence
Twenty-second report (31 pages) ................................................ 4.—

730 (1986) Dementia in later life: research and action
Report of a WHO Scientific Group (74 pages) .............................. 10.—

731 (1986) Young people’s health—a challenge for society
Report of a WHO Study Group on Young People’s Health and “Health for All by the Year 2000” (117 pages) ....................... 16.—

732 (1986) Community prevention and control of cardiovascular diseases
Report of a WHO Expert Committee (62 pages) ....................... 9.—

733 (1986) Evaluation of certain food additives and contaminants
Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives (59 pages) ........................................ 9.—

734 (1986) Recommended health-based limits in occupational exposure to selected mineral dusts (silica, coal)
Report of a WHO Study Group (82 pages) .................................. 12.—

735 (1986) WHO Expert Committee on Malaria
Eighteenth report (104 pages) .................................................... 14.—

736 (1986) WHO Expert Committee on Venereal Diseases and Treponematoses
Sixth report (141 pages) ......................................................... 18.—

737 (1986) Resistance of vectors and reservoirs of disease to pesticides
Tenth report of the WHO Expert Committee on Vector Biology and Control (87 pages) ..................................................... 12.—

738 (1986) Regulatory mechanisms for nursing training and practice: meeting primary health care needs
Report of a WHO Study Group (71 pages) .................................. 10.—

739 (1986) Epidemiology and control of African trypanosomiasis
Report of a WHO Expert Committee (127 pages) ..................... 16.—

740 (1986) Joint FAO/WHO Expert Committee on Brucellosis
Sixth report (132 pages) ......................................................... 18.—

741 (1987) WHO Expert Committee on Drug Dependence
Twenty-third report (64 pages) .................................................. 9.—

742 (1987) Technology for water supply and sanitation in developing countries
Report of a WHO Study Group (38 pages) ................................. 7.—
Report of a WHO Scientific Group (229 pages).......................... 32.—
744 (1987) Hospitals and health for all
Report of a WHO Expert Committee on the Role of Hospitals at the
First Referral Level (82 pages).................................................. 12.—
745 (1987) WHO Expert Committee on Biological Standardization
Thirty-sixth report (149 pages).................................................. 20.—
746 (1987) Community-based education for health personnel
Report of a WHO Study Group (89 pages).................................. 12.—
747 (1987) Acceptability of cell substrates for production of biologicals
Report of a WHO Study Group (29 pages).................................. 5.—
748 (1987) WHO Expert Committee on Specifications for Pharmaceutical
Preparations
Thirlieh report (50 pages)......................................................... 9.—
749 (1987) Prevention and control of intestinal parasitic infections
Report of a WHO Expert Committee (86 pages).......................... 12.—
Report of a WHO Expert Committee (58 pages).......................... 9.—
751 (1987) Evaluation of certain food additives and contaminants
Thirtieth report of the Joint FAO/WHO Expert Committee on Food
Additives (57 pages)............................................................... 9.—
752 (1987) WHO Expert Committee on Onchocerciasis
Third report (167 pages).......................................................... 24.—
753 (1987) Mechanism of action, safety and efficacy of intrauterine devices
Report of a WHO Scientific Group (91 pages)............................ 12.—
754 (1987) Progress in the development and use of antiviral drugs and interferon
Report of a WHO Scientific Group (25 pages)............................ 5.—
755 (1987) Vector control in primary health care
Report of a WHO Scientific Group (61 pages)............................ 9.—
756 (1987) Children at work; special health risks
Report of a WHO Study Group (49 pages).................................. 9.—
757 (1987) Rational use of diagnostic imaging in paediatrics
Report of a WHO Study Group (102 pages)............................... 14.—
758 (1987) The hypertensive disorders of pregnancy
Report of a WHO Study Group (114 pages)............................... 16.—