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**WORLD HEALTH ORGANIZATION  
TECHNICAL REPORT SERIES**

No. 557

**FAO NUTRITION MEETINGS REPORT SERIES**

No. 54

# **EVALUATION OF CERTAIN FOOD ADDITIVES**

**Eighteenth Report  
of the Joint FAO/WHO Expert Committee  
on Food Additives**

Rome, 4-13 June 1974



Published by  
FAO and WHO



**WORLD HEALTH ORGANIZATION**

GENEVA

1974

Specifications and monographs containing summaries of relevant data and toxicological evaluations will be issued separately by FAO and WHO under the titles :

*Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives*

FAO Nutrition Meetings Report Series No. 55

WHO Food Additives Series No. 6

*Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents, and certain other food additives*

FAO Nutrition Meetings Report Series No. 56

WHO Food Additives Series No. 7

ISBN 92 4 120557 1

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PRINTED IN SWITZERLAND

## CONTENTS

	Page
1. Introduction . . . . .	7
2. General considerations . . . . .	8
2.1 Modification of the agenda . . . . .	8
2.2 Need for adequate information . . . . .	8
2.3 General principles for establishing acceptable daily intakes . . . . .	8
2.4 Hypersensitivity reactions to food additives . . . . .	10
2.5 Comments on evaluation of natural food colours . . . . .	10
3. Principles governing the establishment of specifications . . . . .	11
3.1 Scope . . . . .	11
3.2 General criteria for limits of lead, arsenic, and heavy metals . . . . .	11
3.3 Criteria for purity of food colours . . . . .	11
3.4 Methods of analysis . . . . .	12
4. Revision of certain specifications . . . . .	12
5. Comments on substances on the agenda . . . . .	13
5.1 Flavouring substances and flavour enhancers . . . . .	13
5.2 Food colours . . . . .	15
5.3 Food enzymes . . . . .	19
5.4 Thickening agents . . . . .	20
5.5 Miscellaneous substances . . . . .	21
6. Recommendations to FAO and WHO . . . . .	28
Annex 1. Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives . . . . .	30
Annex 2. Acceptable daily intakes and information on specifications . . . . .	33
Annex 3. Further toxicological studies and information required or desirable . . . . .	36

## JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 4-13 June 1974

### *Members invited by FAO*

- Mr D. F. Dodgen, Director, Food Chemicals Codex, National Academy of Sciences, Washington, D.C., USA
- Dr H. Eich, Food Colour Commission, Besigheim, Rossertweg 8, Federal Republic of Germany
- Dr S. W. Gunner, Head, Food Additive Unit, Division of Additives and Pesticides, Bureau of Chemical Safety, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada
- Mr A. W. Hubbard, Head, Food Science Division, Ministry of Agriculture, Fisheries and Food, London, England (*Vice-Chairman*)
- Dr K. Kojima, Director, Laboratory for Medicinal Plants, National Institute of Hygienic Sciences, Tokyo, Japan
- Dr P. L. Schuller, Head, Laboratory for Chemical Analysis of Foodstuffs, National Institute of Public Health, Bilthoven, Netherlands

### *Members invited by WHO \**

- Dr F. Berglund, Head, Food Research Department, National Food Administration, Stockholm, Sweden
- Dr J. C. Dacre, Associate Professor of Medicine, Laboratory of Environmental Medicine, Department of Medicine, Tulane University Medical School, New Orleans, La., USA
- Dr W. A. Mannell, Chief, Toxicological Evaluation Division, Foods Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada (*Rapporteur*)
- Professor P. Marquardt, Chief, Institute for Experimental Therapeutics, University of Freiburg, Freiburg-in-Breisgau, Federal Republic of Germany
- Dr P. Shubik, Director, Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, Nebr., USA
- Professor R. Truhaut, Director, Toxicological Research Centre, Department of Pharmaceutical and Biological Sciences, René Descartes University, Paris, France (*Chairman*)

### *Observers (invited by FAO)*

- Dr G. F. Wilmink, Chairman, Codex Committee on Food Additives, Ministry of Agriculture and Fisheries, The Hague, Netherlands

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\* *Unable to attend:* Professor P. Magee, Courtauld Institute of Biochemistry, The Middlesex Hospital Medical School, London, England.

Dr R. Marcuse, Chairman, IUPAC, Food Section, Swedish Institute of Food Preservation Research, SIK, Göteborg, Sweden

*Secretariat*

Dr H. Blumenthal, Deputy Director, Division of Toxicology, Bureau of Foods, Food and Drug Administration, Washington, D.C., USA (*Temporary Adviser*)

Mrs B. M. Dix, Nutrition Officer, Food Standards and Food Science Service, FAO, Rome, Italy

Dr P. S. Elias, Principal Medical Officer, Department of Health and Social Security, London, England (*Temporary Adviser*)

Dr K. O. Herz, Nutrition Officer, Food Standards and Food Science Service, FAO, Rome, Italy

Dr L. G. Lodomery, Liaison Officer, Food Standards and Food Science Service, FAO, Rome, Italy

Dr F. C. Lu, Chief, Food Additives, WHO, Geneva, Switzerland (*Joint Secretary*)

Mr R. K. Malik, Senior Officer, Food Standards and Food Science Service, FAO, Rome, Italy (*Joint Secretary*)

Dr F. Tarding, Head, Department of Biochemistry, Institute of Toxicology, National Food Institute, Søborg, Denmark (*Temporary Adviser*)

Dr G. Vettorazzi, Scientist, Food Additives, WHO, Geneva, Switzerland



# EVALUATION OF CERTAIN FOOD ADDITIVES

## **Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives**

A Joint FAO/WHO Expert Committee on Food Additives met in Rome from 4 to 13 June 1974. The meeting was opened by Dr M. Ganzin, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Ganzin, in his opening remarks, informed the Committee that the previous work of the Committee had been carefully reviewed at the Third Joint FAO/WHO Conference on Food Additives and Contaminants<sup>1</sup> held in Geneva in October 1973. He also stressed the importance of the work of the Committee in relation to that of the Codex Alimentarius Commission.

### **1. INTRODUCTION**

As a result of the recommendation of the first Joint FAO/WHO Conference on Food Additives held in September 1955<sup>2</sup> there have been 17 previous meetings of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1). The present meeting was convened on the recommendation made in the seventeenth report.<sup>3</sup> Its terms of reference were as follows: (1) to review the Report of the Third Joint FAO/WHO Conference on Food Additives and Contaminants; (2) to prepare specifications and carry out the toxicological evaluation of certain food additives; (3) to revise the specifications for certain food additives; and (4) to re-evaluate certain food additives.

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<sup>1</sup> *FAO Miscellaneous Meetings Report Series*, 1974 (document ESN: MMS 74/6); WHO/Food Add/74.43.

<sup>2</sup> *FAO Nutrition Meetings Report Series*, 1956, No. 11; *Wld Hlth Org. techn. Rep. Ser.*, 1956, No. 107.

<sup>3</sup> *FAO Nutrition Meetings Report Series*, 1974, No. 53; *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 539.

## 2. GENERAL CONSIDERATIONS

### 2.1 Modification of the agenda

The flavour enhancers L-arginine-L-glutamate, L-lysine-L-glutamate, and monosodium-L-aspartate were not dealt with at this meeting because the data on which a safety evaluation could have been based were not received in time. Starch sodium succinate was also deleted from the agenda because no relevant data were received.

### 2.2 Need for adequate information

The first meeting of the Committee held in 1956 dealt with the general principles governing the use of food additives. The report (see Annex 1, reference 1) emphasized that food additives should be used only when necessary and then not in excess of the levels required for the specific technological process. It stressed that safety for use was an all-important consideration. Guidance on the procedures for the testing of food additives to establish their safety for use was given at the second and fifth meetings (see Annex 1). These guidelines were further elaborated at later meetings, the seventeenth in particular, as well as by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives.<sup>1</sup> Once again the Joint FAO/WHO Expert Committee has been asked to evaluate a number of additives for which the available data were grossly inadequate. The Committee therefore re-emphasized the importance of adequate chemical, biochemical, and toxicological data for evaluation purposes.

### 2.3 General principles for establishing acceptable daily intakes

In following the principles stated in its previous reports and in the report of a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals<sup>2</sup> the Committee noted the comments in the report of the Third Joint FAO/WHO Conference on Food Additives and Contaminants referring to (1) the statement by the Committee that the acceptable daily intake (ADI) does not include the amounts of a substance naturally present in food, and (2) the use of the phrase "ADI not limited".

(1) The rule that the ADI should not include amounts of a substance naturally present in food has been followed since the sixth meeting of the Committee and was restated in the seventeenth report.<sup>3</sup> In principle,

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 348.

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 546.

<sup>3</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 539, p. 10.

however, the toxicity of a substance is the same whether it is naturally present in the food or added subsequently. Moreover, it is not normally possible to differentiate by chemical analysis between a substance naturally present and added quantities of the same substance. The Committee therefore agreed that, as a general rule, the ADI should include the total amount of a compound in food. However, there are exceptions, and each case should be considered individually. As a corollary, the Committee stressed the need to verify the total amount of the substance under study in the diet of experimental animals. If, however, the substance occurs in food in a chemical form different from that employed as a food additive the two quantities may have to be evaluated separately.

Certain food additives were examined by the Committee in the light of this new position.

#### *Ascorbic acid*

Since the amount of ascorbic acid naturally present in the diet is small compared with the ADI, the Committee decided that in this instance the ADI should include the former amount. The ADI of this compound is quoted as 0-15 mg/kg.

Quoted ADI ranges for essential nutrients starting at 0 are not to be interpreted literally since there is clearly a lower limit corresponding to the requirements for these nutrients. The lowest value of the range will depend on the requirements. These amounts are determined by expert committees concerned with nutritional aspects of additives.<sup>1</sup>

#### *Benzoic acid*

Precise information on levels of this substance occurring naturally in foods was not available to the Committee but it is believed that the amounts are small. The Committee therefore decided that the ADI to be allocated should include the amount present naturally in the diet.

#### *Nitrates*

When setting the ADI for nitrates those present naturally in the diet of test animals were not taken into account. However, naturally occurring nitrates contribute significantly to the total nitrate intake and the ADI therefore excludes naturally occurring nitrates. The Committee indicated that this matter should be reviewed in the near future.

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<sup>1</sup> The Committee reaffirmed, nevertheless, that it is concerned with adjusting the ADI if a food additive is shown to interfere with nutritional requirements in one form or another.

### *Certain other substances naturally present in food*

Formic acid, sorbic acid, tocopherols, free glutamic acid, and their salts evaluated by the Committee are other examples of food additives whose present ADIs are now considered to cover the amounts naturally present in food.

(2) The Committee decided, for the sake of clarity, to discontinue using the expression "ADI not limited" and to use instead the expression "ADI not specified". Each time this expression appears in a table, it should be followed by a reference mark linking it to a footnote reading as follows: "This statement means that, on the basis of available data (chemical, biochemical, and toxicological), the total daily intake of the substance arising from its use or uses at levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, and for reasons stated in the individual evaluations, the establishment of an acceptable daily intake (ADI) expressed in mg per kg of body weight is not deemed necessary."

#### **2.4 Hypersensitivity reactions to food additives**

Urticaria or asthmatic reactions have been reported in man following the oral administration of certain food colours to individuals sensitive to benzoates or salicylates. However, cutaneous tests of these colours in animals to detect hypersensitivity have not been predictive of such reactions.

In considering this problem, the Committee reaffirmed the conclusion stated in the seventeenth report that no approval would be given for the use of a substance causing serious or widespread hypersensitivity reactions. For substances capable of causing only a low incidence of, or minor, hypersensitivity reactions, the Committee should establish ADIs. However, it is hoped that such hazards could be minimized by appropriate labelling of foods containing such additives.

#### **2.5 Comments on evaluation of natural food colours**

In keeping with the principle that an ADI must take account of the quantity of a compound ingested as a normal constituent of food relative to the quantity ingested as a result of its addition to food, it is necessary to consider this relationship for food colours that are normal constituents of food. If the food additive use of these substances represents only a small proportion of the total intake, previous experience with them may compensate for the lack of formal laboratory investigations when an evaluation is made.

### 3. PRINCIPLES GOVERNING THE ESTABLISHMENT OF SPECIFICATIONS

#### 3.1 Scope

A summary of the general principles governing the establishment of specifications for food additives is contained in the tenth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>1</sup> As noted in previous reports, the primary purpose of developing such specifications is to establish criteria for the purity and identity of food additives for the use of toxicologists and others concerned with such substances. The specifications are intended to have an international application.

In drawing up specifications for a number of food colours derived from natural sources cognizance was taken of the fact that a multiplicity of uses is possible for certain substances. Turmeric, for example, may be used both as a condiment and a food colour. The Committee stressed that the scope of the specifications developed for such substances is confined to their use as food additives.

#### 3.2 General criteria for limits of lead, arsenic, and heavy metals

In reviewing the specifications for certain food additives included on the agenda, the Committee noted that it may be possible to lower the limits for arsenic, lead, and heavy metals through the application of current technology and good manufacturing practice. The Committee reiterated the views expressed in the seventeenth report that there are inconsistencies in the manner in which limits on heavy metal contaminants, arsenic, and fluorine have been applied to closely related additives, and stressed the need to review the general principles, as stated in the tenth report, concerning the levels of these impurities and various other factors.

#### 3.3 Criteria for purity of food colours

While the general criteria for setting limits for lead, arsenic, and heavy metals in food additives are applicable also to food colours, the Committee drew attention to the possibility of chromium and/or zinc residues occurring in those food colours for which certain oxidizing and/or reducing agents are employed in manufacture. While recognizing that more information on this point is desirable, the Committee nevertheless considered it advisable to recommend the establishment of limits of impurities for these two elements as indicators of good manufacturing practice. Although

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<sup>1</sup> *FAO Nutrition Meetings Report Series, 1967, No. 43; Wld Hlth Org. techn. Rep. Ser., 1967, No. 373.*

different manufacturing conditions might necessitate the application of different limits for chromium in respect of different colours, 20 mg/kg was recommended as the value not normally to be exceeded. For food colours in which zinc is used as a reducing agent, the Committee decided to set a limit of 200 mg/kg for zinc and a limit of 40 mg/kg for "heavy metals" (as defined by the test used) other than zinc.

The Committee recognized that aromatic amines may be present as contaminants in a variety of food colours synthesized from nonsulfonated aromatic amines. More information on the nature of these contaminants and their levels in these colours was requested. In the meantime, the general limit of 0.02% proposed at an earlier meeting is maintained.

#### **3.4 Methods of analysis**

As noted in the earlier reports of the Committee (see Annex 1), the methods given in the specifications are not intended to be referee methods but are generally applicable to the analysis of products available in international commerce. The Committee took note of some new and improved analytical methods. As better methods become available they will be considered and may eventually be adopted.

### **4. REVISION OF CERTAIN SPECIFICATIONS**

At its seventeenth session the Committee reviewed specifications prepared at earlier sessions for anticaking agents, antimicrobials, antioxidants, emulsifiers, thickening agents, and a number of miscellaneous substances. It also reviewed the methods of analysis for these substances, and made a number of recommendations to update and revise the specifications on a uniform basis. These recommendations were carefully considered by the Committee at its eighteenth meeting in the light of a large number of comments and suggested amendments. Certain significant changes require to be applied to all the specifications to bring them into line with one another—namely, to matters of nomenclature, description, appearance, uses, and expressions of solution strengths and solubilities. Some other specific requirements in individual specifications need to be revised on the basis of the latest information—namely, assay values, criteria for certain impurities, and methods of analysis. Finally, the specifications for a group of substances require substantial revision. It is intended that all specifications revised by the Committee should be published in due course.

The Committee recommended that for the sake of clarity and precision the earlier explanatory notes on specifications should be reviewed and updated.

## 5. COMMENTS ON SUBSTANCES ON THE AGENDA

The Committee evaluated a number of food additives for the first time and also re-evaluated several substances that had been considered at previous meetings. Points of interest arising from these evaluations are set out below. The acceptable daily intakes and information on specifications are summarized in Annex 2. Additional information about the substances is given in the monographs to be published separately (see p. 2).

### 5.1 Flavouring substances and flavour enhancers

Specifications were prepared for calcium 5'-guanylate, calcium 5'-inosinate, calcium 5'-ribonucleotides, disodium 5'-guanylate, disodium 5'-inosinate, disodium 5'-ribonucleotides, L-glutamic acid, monoammonium L-glutamate, monocalcium di-L-glutamate and monopotassium L-glutamate. Specifications also exist for ethylmethylphenyl glycidate, fumaric acid, maltol, ethyl maltol, DL-menthol and L-menthol.

#### *Ethyl maltol*

The re-evaluation of this additive was based on the results of an additional long-term study, a 2-generation reproduction study in rats, and a short-term study in the dog. The Committee confirmed the previous ADI of 0-2 mg/kg.

#### *Ethylmethylphenyl glycidate*

The Committee re-examined the monograph for ethylmethylphenyl glycidate prepared by the eleventh meeting. The study by Griepentrog reported in the monograph<sup>1</sup> was subsequently published in full in 1969<sup>2</sup> and the published paper indicates that adverse neurological effects accompanied by demyelination occurred in conjunction with the lowest levels of ethylmethylphenyl glycidate fed to animals. The Committee therefore withdrew the previously established temporary ADI. The material used in the study referred to apparently had no clear-cut specification. Since that time, an ethylmethylphenyl glycidate having well defined specifications has become available. This material is now being used in long-term rat feeding studies and in metabolism studies. Evaluation of this substance must await the completion of the new studies and the results of additional demyelination studies in the chicken required by the Committee. No monograph was prepared.

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<sup>1</sup> *FAO Nutrition Meetings Report Series*, 1967, No. 44A ; WHO/Food Add/68.33.

<sup>2</sup> Griepentrog, F. (1969) *Med. u. Ernähr.*, **10**, 89-90.

### *Fumaric acid*

The previous conditional ADI was deleted and the previous unconditional ADI confirmed as 0-6 mg/kg.

### *Maltol*

This substance was given a temporary ADI in the eleventh report of the Committee and additional biochemical studies were required in animals and man. No results of long-term studies were available at that time. Since then, some information on metabolism has become available but is considered inadequate. A short-term study in a second species was reported. The results indicate a lower no-effect level than that used for the previous estimation of the ADI. Because no long-term studies or adequate biochemical studies have been made and evidence now available from short-term studies indicates a marked species difference the Committee decided to withdraw the temporary ADI. No monograph was prepared.

### *DL-menthol and L-menthol*

To conform with the decision of the eleventh meeting, the conditional ADI for menthol was eliminated and an ADI of 0-0.2 mg/kg was established. As no new data were available, it was decided not to issue a monograph.<sup>1</sup>

### *Disodium and calcium 5'-ribonucleotides and disodium and calcium salts of guanylic acid and inosinic acid*

For the flavour enhancers calcium 5'-ribonucleotides, disodium 5'-ribonucleotides, the disodium and calcium salts of guanylic acid, and the disodium and calcium salts of inosinic acid the Committee agreed that the available data revealed no inherent toxicological problems. Studies in rats have assured the absence of general toxic effects and, combined with a knowledge of the metabolism of these substances in man, enabled the Committee to agree to designate "ADI not specified" for these substances. It was observed that their use as food additives would be small in comparison with the natural levels in certain foods. The same argument applies if these substances are considered in terms of their purine equivalents. Recommended use levels in foods were reported as 50-300 mg/kg of food on an "as served" basis. The Committee suggested that specific mention on the label of the addition of these substances to the food may be justified.

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<sup>1</sup> For a summary of the biological data see Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents, *FAO Nutrition Meetings Report Series*, 1967, No. 44A; WHO/Food Add./68.33.

## 5.2 Food colours

### *Allura red AC*

The Committee decided not to set an ADI for this colour because of a lack of metabolism studies and the unsatisfactory nature of the only long-term study in rats available for evaluation; too few animals remained at the end of the study to allow a satisfactory assessment to be made. Additional studies in these areas are essential before a definitive evaluation is made. No specification was prepared.

### *Annatto extracts*

The earlier specification was revised in the light of the latest information. The Committee was also informed that metabolism studies have been initiated on the major carotenoids as required by the thirteenth report. In view of this assurance the temporary ADI of 0–1.25 mg/kg was extended.

### *Azorubine*

A revised specification was prepared. The Committee was able to give a temporary ADI of 0–0.5 mg/kg pending completion of a long-term study in another species. Studies on the embryotoxicity, including teratology, of azorubine and its effects on metabolism are needed.

### *Beet Red*

This colour is a normal constituent of food. The Committee reviewed the earlier specification for Beet Red and Betanine and prepared a revised specification for Beet Red restricted in scope to their use as food colours. Application of the principles set out in section 2.5 and the availability of an adequate specification permit evaluation in the absence of a full range of toxicological investigations.

A “temporary ADI not specified” was agreed upon.

### *Brilliant Black PN*

The earlier designation “Brilliant Black BN” was changed to “Brilliant Black PN” and a revised specification was prepared. The Committee was able to assign a temporary ADI of 0–2.5 mg/kg. Metabolism studies, reproduction studies, and embryotoxicity, including teratology, studies are required.

### *Canthaxanthine*

The Committee prepared a new specification and established an ADI of 0–25 mg/kg for this substance.

*Caramel colours (ammonia process)*

The specifications prepared at the fifteenth and sixteenth meetings were reviewed and a revised specification providing for a method for the analysis of 4-methylimidazole was prepared. On the understanding that the studies required in the thirteenth report will be forthcoming, the temporary ADI of 0–100 mg/kg<sup>1</sup> was extended.

*Carotenes (natural)*

Further information is required before the Committee can proceed with the development of a specification for carotenes derived from natural sources. The Committee was therefore unable to evaluate the natural carotenes. No monograph was prepared.

*β-apo-8'-carotenal*

A revised specification was prepared and a group ADI of 0–5 mg/kg<sup>2</sup> was established.

*β-carotene*

The Committee revised the earlier specification for β-carotene. Following a review of the biological data a group ADI of 0–5 mg/kg<sup>2</sup> was established.

*β-apo-8'-carotenoic acid, methyl and ethyl esters*

The Committee revised the earlier specification and established a group ADI of 0–5 mg/kg.<sup>2</sup>

*Chlorophyllin copper complex, sodium and potassium salts*

In the opinion of the Committee the method for the analysis of free ionizable copper is inadequate and it was, therefore, decided that the revised specification for these substances should remain tentative until a suitable analytical method for free ionizable copper becomes available. While reviewing these substances, the Committee also considered chlorophyll copper complex and chlorophyll. A revised tentative specification for chlorophyll copper complex was prepared. There appears to be no major commercial use of chlorophyll *per se* in the food industry, mainly because of its instability. It was therefore decided that the non-use should be confirmed and then the existing specification revoked.

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<sup>1</sup> Based on a product having a colour intensity of 20 000 EBC (European Brewery Convention) units and containing not more than 200 mg/kg (200 ppm) of 4-methylimidazole.

<sup>2</sup> Expressed as the sum of the carotenoids β-carotene, β-apo-8'-carotenal, and the methyl and ethyl esters of β-apo-8'-carotenoic acid.

Pending revision of the tentative specifications, a temporary ADI of 0–15 mg/kg was established only for chlorophyllin copper complex, sodium and potassium salts, on the basis of the data available for evaluation.

#### *Cochineal and carminic acid*

No new specification was prepared since a toxicological evaluation was not possible on the data available.

#### *Erythrosine*

A revised specification was prepared by the Committee providing for a limit of 0.1% fluoresceine. On the data available it was also possible to establish an ADI of 0–2.5 mg/kg. In the Committee's view, metabolism studies, preferably involving man, are desirable.

#### *Green S*

The previous specification for Wool Green BS was revised. The Committee felt that the nomenclature " Wool Green BS " for the food grade material was not desirable and decided to re-name the substance " Green S ", retaining, however, the name " Wool Green BS " in the list of synonyms.

The Committee decided to withdraw the temporary ADI for this colour because of the unavailability of additional data requested in the earlier evaluation.

#### *Indanthrene Blue RS*

The temporary ADI assigned at an earlier meeting was withdrawn because no additional data were available for evaluation by the Committee. No new specification was prepared.

#### *Indigotine*

A revised specification was prepared and an ADI of 0–5 mg/kg was assigned to this colour.

#### *Iron oxides and hydrated iron oxides*

A new specification was prepared by the Committee and the designation " Temporary ADI not specified " was agreed upon because of absence of information on physiological absorption and storage of iron following the use of these pigments as food additives.

#### *Lycopene*

In view of the lack of information on lycopene, it is premature to develop specifications for this food colour. Further information and comments are,

therefore, required on this additive derived from both natural and synthetic sources. The Committee was unable to establish an ADI. No monograph was prepared.

*Orange GGN*

Because of the incomplete nature of the data available it was not possible for the Committee to establish an ADI. No monograph was prepared; no revision of the specification was undertaken.

*Orange RN*

No specification was prepared and the data available did not permit the establishment of an ADI. The Committee observed that a no-effect level had not been established in the most sensitive species tested and that an adequate multigeneration study had not been made.

*Orchil and orcein*

The Committee was informed that there was no substantial use of the material as a food additive. As a consequence, the earlier specification was revoked and no ADI was established. No monograph was prepared.

*Patent Blue V*

No new data were available for toxicological evaluation. A revised specification was prepared. The Committee therefore agreed to withdraw the temporary ADI given in the thirteenth report.

*Persian Berries*

Neither a specification nor toxicological data were available for this colour to allow evaluation. No monograph was prepared.

*Ponceau 4R*

The Committee reviewed the earlier specification and prepared a revised tentative specification. Since the previous evaluation, an additional long-term study on mice has been conducted. A temporary ADI of 0-0.125 mg/kg was established. Metabolism studies, reproduction studies, and an adequate long-term study in another species are required.

*Ponceau 6R*

It was not possible to estimate an ADI on the biological data available to the Committee. No new specification was prepared.

### *Quinoline Yellow*

The Committee was aware that two types of colour—with and without a methyl group on the quinoline moiety—were in commercial use in products designated as Quinoline Yellow. The revised tentative specification prepared at this meeting provides for both types.

The Committee decided to extend the temporary ADI of 0–2.5 mg/kg. A long-term study in a second species, metabolism studies, preferably involving man, and the results of the multigeneration study now in progress are required.

### *Turmeric and curcumin*

The Committee revised the earlier specification for turmeric as a food colour and made a provision for hygienic requirements. It was noted that turmeric oleoresin is also an item of commerce. The establishment of a specification for that substance may become necessary in the future.

In relation to the toxicological evaluation, no adverse effects in animal tests have been obtained with a turmeric preparation of undefined curcumin content at the only level tested. The true no-effect level may well have been higher than the level chosen. Curcumin is known to be present in turmeric at average levels of 3%. In the light of this information and according to the principles stated in section 2.5, the Committee decided to allocate a temporary ADI of 0–2.5 mg/kg to turmeric and to establish a temporary ADI of 0–0.1 mg/kg for curcumin based on an average content of 3% in turmeric.

### *Yellow 2G*

It was not possible to establish an ADI for Yellow 2G at this meeting and no specification was prepared. The Committee was informed that new data may soon become available.

## **5.3 Food enzymes**

In the evaluation of food enzymes derived from various microorganisms, the Committee considered the possibility of mutations occurring in the organism which could affect the food enzyme adversely. It was pointed out that specifications for these enzymes could not offer an assurance that mutations would not occur. In the view of the Committee, however, such a possibility does not present a serious problem in the evaluation of food enzymes since maintaining a constant strain is a paramount requirement in the successful use of microorganisms to produce enzymes for food applications.

#### *Microbial lipase (Aspergillus oryzae)*

In the fifteenth report, the Committee drew attention to a suspicion that  $\beta$ -nitropropionic acid, a metabolite of *Aspergillus oryzae*, was potentially carcinogenic. No information has become available to substantiate this concern. Furthermore, a suitable method of assay for  $\beta$ -nitropropionic acid is now available and analyses of food have shown that this metabolite is present in very few foods and then only in minute amounts. The Committee decided to designate an "ADI not specified" for this food enzyme. No monograph was prepared.

#### *Other microbial enzymes*

For microbial carbohydrase (*Aspergillus niger*), microbial glucose oxidase (*Aspergillus niger*), microbial rennet (*Endothia parasitica*), microbial rennet (*Mucor miehei*), and microbial rennet (*Mucor pusillus*) the Committee agreed to designate an "ADI not specified".

### **5.4 Thickening agents**

#### *Carrageenans*

The Committee prepared a tentative new specification for carrageenans to embrace substances covered by the previous separate specifications for carrageenans and furcellaran. The toxicological evaluation of these substances appears in the seventeenth report.

#### *Enzyme-treated starches*

Reiterating the comments made in the seventeenth report, the Committee, in developing specifications for enzyme-treated starches, stressed that the enzymes used in their manufacture should be restricted to those for which specifications have been prepared by the Expert Committee. The Committee established a tentative general specification. The toxicological evaluations were made during the seventeenth meeting.

#### *Hydroxypropyl distarch phosphate*

A specification exists for this compound and the available data permitted the designation of an "ADI not specified".

#### *Pectins*

The Committee reviewed the tentative specification for pectins, including amidated pectin, prepared at the seventeenth meeting, and prepared a revised specification. The evaluation of the toxicity studies submitted on amidated pectin showed them to be incomplete and further work is in pro-

gress. The temporary ADI of 0–25 mg/kg assigned at the seventeenth meeting was extended.

#### *Tara gum (Peruvian carob bean gum)*

The Committee was able to prepare a tentative specification. It also considered the suggestion that tara gum, carob bean gum, and guar gum be evaluated as a group of chemically closely related substances. It was not possible, however, to proceed in this manner because of significant differences in the physicochemical and biological characteristics of these three gums. The Committee therefore agreed to evaluate tara gum separately from the available data but was unable to establish an ADI. No monograph was prepared.

#### *Xanthan gum*

A specification was prepared for this substance. This, and the adequacy of the biochemical and toxicological data, enabled the Committee to estimate an ADI of 0–10 mg/kg.

### **5.5 Miscellaneous substances**

#### *Aluminium potassium sulfate and aluminium sulfate*

Specifications were prepared by the Committee but it decided to defer the toxicological evaluation of these additives because of insufficient data on these and related aluminium compounds used, or proposed for use, in foods. In particular, there is no precise information on the aluminium content of the diet derived from the food itself and from cooking utensils. No monographs were prepared.

#### *Ammonium salts of phosphatidic acid*

A specification was available to the Committee. Additional toxicological studies have been provided since the previous evaluation. An ADI of 0–30 mg/kg was estimated. The phosphate contribution to total dietary phosphate intake from this additive must be included in the ADI for phosphates.

#### *Asbestos*

(1) Asbestos is a generic term for a number of hydrated silicates that can be processed into flexible fibres made up of fibrils. These silicates are divided into two large groups, *serpentine* (chrysotile) and *amphibole*, which contains as subgroups the minerals anthophyllite, amosite (ferroanthophyllite), crocidolite, temolite, and actinolite.

There is a fundamental difference between the chrysotile and amphibole asbestos. For example, the chrysotile fibrils are exceedingly small in cross-section and tubular whereas the amphibole fibrils are large in cross-section, appear as straight narrow sheets, and are solid. Chrysotile fibrils are approximately 0.02–0.03  $\mu\text{m}$  in diameter and amphibole fibrils are approximately 0.1  $\mu\text{m}$  in diameter. In general, the amphiboles are harsh, hard, and springy, and not as flexible and soft as chrysotile.

According to the information available to the Committee, the chrysotile variety of fibre alone is used in the food industry on account of its good flexing and tensile strengths, great surface area, and good absorption characteristics.

(2) Chrysotile can be identified by its refractive index or the characteristic electron diffraction pattern and morphology. Quantitative estimates are obtained by counting the number of fibrils visible on an electron micrograph. In principle, a single fibril 1  $\mu\text{m}$  in length and 0.03  $\mu\text{m}$  in diameter (approximate mass,  $2 \times 10^{-15}$  g) can be identified by its electron diffraction pattern. In practice, the methodology requires a concentration of about 60 000 fibrils ( $10^{-10}$  g/litre). The experimental blanks reported ranged from  $10^{-9}$  g/litre to  $10^{-8}$  g/litre. Reported levels of chrysotile fibril residues in water, wine, and beer have ranged from  $10^{-8}$  g/litre to  $10^{-10}$  g/litre. In this situation there is clearly a need for further work to establish unequivocally data on fibril levels in food and whether the use of asbestos filter pads introduces additional fibrils into the food filtrate.

(3) Some information was available to the Committee about the types of asbestos filter pad used in the food industry. Details of the treatment given to asbestos before the manufacture of filter pads was, however, not available. For instance, it is not known to what extent asbestos is acid washed, the types of impurity that may remain in filter pads made from asbestos not so treated, and to what extent these impurities could pass into food. Similarly, information is not available on the extent of treatment given to filter pads to prevent the asbestos fibres being dispersed into food. If such treatment were universal it would go a considerable way towards eliminating or reducing the asbestos contamination of food from this source.

The serpentine mineral chrysotile is considered harmless to health by many authorities; crocidolite and amosite, both of them amphibole minerals, are considered to be associated with asbestosis and cancer. A current view holds that the carcinogenic effects of asbestos are associated with the physical form of the fibres. Although it has not been proved conclusively, this possibility could justify a certain degree of control.

Considerable concern has been expressed in several countries about the presence of asbestos fibres in manufactured beverages, drinking-water,

and foods. It is well known that inhalation of certain forms of asbestos presents an occupational hazard leading to a chronic fibrosing pulmonary disease known as asbestosis, and certain forms of cancer. There is also little doubt that inhalation of certain types of asbestos fibres results in the occurrence of mesotheliomas, usually seen in the pleura sometimes in the peritoneum; an increased incidence of bronchogenic cancer is also observed; however, this is very frequently, but not invariably, associated with heavy cigarette smoking as well. It has been claimed that occupational exposure to certain varieties of asbestos can lead to an increased incidence of cancer of the gastrointestinal tract, but this association has been less studied.

Experimental studies in animals have reproduced the effects of asbestos in the lung but the few investigations of ingestion of asbestos in chronic feeding studies are so far reported to have produced negative results. It is believed that further studies are being made but the results are not yet available.

A major advance in the study of asbestos in recent years has been the use of the electron microscope for identifying fibres; this method has been particularly useful when newer instruments incorporating an electron probe and X-ray diffraction have been used. The introduction of these sensitive techniques has revealed the presence of various types of asbestos at a very wide range of concentrations in many sources of drinking-water, as well as in beverages filtered through asbestos filters. There is no unequivocal evidence for associating these findings with human health problems at the present time.

Although it is prudent to reduce human exposure to asbestos in food to a minimum, it is not possible, for practical reasons, to recommend monitoring for asbestos fibres as a general procedure. Neither the instruments nor the expertise are generally available at present. This problem requires much more research, and a group of experts should be convened to formulate a practical approach when new information becomes available during the next few years.

#### *Calcium aluminosilicate*

The Committee was informed that the term "sodium calcium silicoaluminate" is inaccurate since the sodium ion does not constitute a significant portion of this molecule. The name was therefore changed to calcium aluminosilicate in the tentative specification. The toxicological evaluation of this material was made at the seventeenth meeting.

#### *Calcium, potassium, sodium ferrocyanides*

The Committee considered calcium, potassium, and sodium ferrocyanides in the light of the evaluation made by the seventeenth meeting and noted

that specifications were available. The data available from human metabolism studies have been substantiated by the results of studies in the rat and the dog. The additional metabolism studies requested by the previous meeting would provide only limited additional information and would require use of high levels of radioactive materials in human subjects, which was not warranted. An ADI of 0–0.025 mg/kg was established for this material. A larger safety factor than is normally employed was used to compensate for the absence of a long-term feeding study.

#### *Dimethylpolysiloxane*

The Committee was informed that a variety of commercial preparations and mixtures are available. Insufficient data are available on these products to justify changes in the existing specification, and the Committee recommended retaining the specification but requested additional information. New toxicological data were available for evaluation and an ADI of 0–1.5 mg/kg was estimated.

#### *Diethyl sodium sulfosuccinate*

The Committee prepared a specification and assigned a temporary ADI of 0–2.5 mg/kg pending an adequate long-term study in rats of both sexes. Clarification of an apparent effect of this substance on suckling rats due to its presence in the mothers' milk is also required.

#### *Glucono- $\delta$ -lactone*

A revised specification was prepared and an ADI of 0–50 mg/kg<sup>1</sup> was established; it includes the previous unconditional and conditional ADIs.

#### *Glycerol esters of wood rosin*

Glycerol esters of wood rosin are produced by the esterification of pale coloured rosins derived from pine stump wood; rosin is also obtained by tapping the gum from the pine tree (gum rosin) or by separation from tall oil — a mixture of rosin and fatty acids recovered from the chips of pine wood used in the sulfate or kraft paper manufacturing process (tall oil rosin). The acid fraction of all three types of rosin is a complex mixture of mono-carboxylic derivatives of alkylated hydrophenanthrenes known as resin acids. These acids differ primarily in the number and location of sites of unsaturation in their molecules. In the formation of the glycerol esters, these rosin acids are esterified with food-grade glycerol.

The composition of the neutral fraction of the rosins is only partly known. It contains resin and fatty acid esters, plant sterols, 3,5-dimeth-

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<sup>1</sup> Expressed as total gluconic acid from all sources.

oxystilbene, terpenes, and other materials. When good manufacturing practice is followed, the conditions for esterification of refined rosins do not significantly alter the internal structure of the resin acids and neutral bodies. When intended for use in chewing gum base, the product is usually purified by steam stripping but when intended for adjusting the density of citrus oils for beverages it is purified by counter-current steam distillation.

More information is required on the exact sources of rosin used to prepare individual glycerol esters, the actual composition of the product defined within the colour range of the rosin used, and the acid number and drop softening point of the product. A tentative specification was prepared that does not, however, provide a means of differentiating between products derived from the three main sources of rosin.

The Committee decided to postpone the toxicological evaluation of glycerol esters of wood rosin because they are not sufficiently characterized.

#### *DL-Lactic Acid and its calcium, potassium, and sodium salts*

In regard to the specifications for DL-lactic acid and its calcium, potassium and sodium salts, the Committee was informed that L(+)-lactic acid and its salts are also used in food. The Committee decided to delete all references to stereochemistry in the specifications. However, in foods for infants less than 3 months old neither the racemic mixture nor the D(-) isomer should be used. The toxicological evaluation was made at the seventeenth meeting.

#### *Mannitol*

A revised specification was prepared for this food additive and its re-evaluation was also on the agenda because it had been given an unconditional and conditional ADI at a previous meeting, but new data of a preliminary nature indicate that rats fed mannitol over long periods suffer adverse effects. Although details of the study were not available, the Committee decided to make the ADI temporary. Additional studies to resolve the situation are required. No monograph was prepared.

#### *Monoglyceride citrate*

This substance, being only a monoglyceride, does not fall within the existing specification for citric and fatty acid esters of glycerol. As the substance has specific uses and is an item of commerce, a specification was prepared. It was evaluated toxicologically at the seventeenth meeting.

#### *Potassium tartrate*

No use of this substance in food is known to the Committee and a specification was therefore not prepared.

### *Saccharin and its sodium and calcium salts*

The Committee also considered the calcium and sodium salts of saccharin in connexion with the specifications for the parent substance and was able to prepare a revised specification for saccharin and specifications for sodium and potassium salts of saccharin. The limit of impurity for toluenesulfonamides noted in these specifications is intended to include isomeric forms. The question of establishing a limit for other foreign substances was discussed; further information about the nature of such substances and the quantities used was requested.

Many toxicological studies have been performed with saccharin since the previous monograph was published. These investigations have resulted in several pertinent findings.

(1) The earlier conclusion that saccharin is not metabolized, either in experimental animals or man, but is excreted unchanged, is confirmed.

(2) Two feeding studies employing high concentrations of saccharin (5% or 7.5%) in the rat have resulted in the induction of bladder cancer. The results of several other long-term feeding studies in the mouse, rat, and hamster are negative but only one of these studies (in the mouse) involved more than one generation.

(3) Variation in the purity of saccharin made by the two main commercial syntheses (Remsen-Fahlberg or Maumee) has become apparent. In particular, the presence of the impurity *o*-toluenesulfonamide at levels up to 6 000 ppm has been reported; however, other impurities have also been reported and the search is continuing.

(4) Several epidemiological studies, particularly in diabetics, have shown no association between the ingestion of saccharin and the occurrence of bladder cancer.

In the report of a WHO Scientific Group on the Assessment of the Carcinogenicities and Mutagenicity of Chemicals<sup>1</sup> it is stated that "The action of the majority of carcinogenic compounds is associated with preliminary changes (e.g., hyperplasia, cirrhosis) the role of which is not clear. However, there are some chemicals that give rise to neoplasms only after the induction of particular pathological effects. For example, the cancers of the urinary bladder observed in rats treated with Myrj 45 (polyoxyethylene monostearate) are thought to have been caused by the presence of bladder calculi induced by the chemical rather than by its direct action. A no-effect level for chemicals that produce tumours in this way may be

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 546.

established.” Saccharin may have induced some bladder cancers in rats, but at high concentrations only. It seems reasonable to suppose that a secondary effect may have occurred, such as a change in urinary pH resulting in calculus formation brought about by the compound itself or by an impurity. Further studies will permit specific conclusions to be drawn. For the time being, an overall assessment of the toxicological evaluation of saccharin does not lead to any modification of the prior recommendations of the Committee. The ADI is 0-5 mg/kg as previously recommended; for dietetic purposes only, the ADI is 0-15 mg/kg. No monograph was prepared.

#### *Sodium and calcium cyclamates*

Specifications for these substances are available. The Committee considered several extensive long-term studies in a number of strains of rats and mice reported since the last evaluation of cyclamates. All were negative. A study in hamsters was also negative with regard to the induction of tumours of the urinary bladder. The original rat study<sup>1</sup> reporting the occurrence of bladder cancer in rats cannot readily be interpreted since any of the three compounds tested (saccharin, cyclohexylamine, and cyclamate), the presence of parasites in the bladder, calculus formation, or impurities in the saccharin could have caused the effects observed.

It is now possible to conclude that cyclamate has been demonstrated to be noncarcinogenic in a variety of species.

Cyclohexylamine, a metabolite of cyclamate, has been reported to cause atrophy of the testis in the rat and a pressor-amine-like effect in man. Several studies are in progress on both these effects. At the present time data are not available to permit the determination of a no-effect level. It was therefore not possible for the Committee to arrive at an acceptable daily intake, even on a temporary basis. No monograph was prepared.

#### *Sorboyl palmitate (mixed anhydride or sorbic and palmitic acids)*

Since the information on specifications available to the Committee was inadequate the Committee did not prepare a specification.

The data submitted on this anhydride did not fully support the claim that the compound is completely hydrolyzed to sorbic acid and palmitic acid in bread baking. The Committee noted that because of the sensitivity of the method employed and the proposed level of use, up to 3 ppm of sorboyl palmitate could remain undetected in bread. It also considered it

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<sup>1</sup> J. M. Price et al. (1970), *Science*, **167**, 1131-1132.

prudent not to ignore effects that might possibly result from treatment of bread dough with 3 000 ppm of an acid anhydride such as sorboyl palmitate.

For these reasons, and because a staple food is involved in the proposed use of this additive, the Committee decided to postpone a decision until toxicological investigations have been carried out on bread treated with sorboyl palmitate. No monograph was prepared.

#### *Other substances*

Specifications were also prepared for the following substances :

butyl *p*-hydroxy benzoate  
calcium gluconate  
calcium lactate  
ferrous gluconate  
potassium acetate  
potassium chloride  
sodium acetate.

## **6. RECOMMENDATIONS TO FAO AND WHO**

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

2. The methods and procedures for the testing of food additives should be comprehensively reviewed and brought into line with advances in food science, toxicology, and related disciplines.

3. There is a need to review the general principles governing the establishment of food additive specifications, and for reasons of clarity and precision it would also be useful to prepare appropriate explanatory notes on these specifications. This should be undertaken as soon as possible.

4. The toxicological evaluation of food additives that also occur in nature now takes into account the quantity of the natural compound in the diet. Adequate information should be provided on the natural distribution of such materials before evaluations by the Committee are requested.

5. Certain substances, such as nitrates and asbestos, are widely distributed in the environment. They often occur in drinking-water and, in the case of asbestos, in the air also. Additional monitoring is required and

some analytical methods may have to be developed. More detailed monitoring of the total environment, including food, for specific substances should be encouraged if these substances raise toxicological problems in relation to food safety.

6. Food additives should properly be evaluated for mutagenic potential. However, as stated by a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals,<sup>1</sup> *in vitro* mutagenicity tests alone cannot yield definitive results applicable to man ; mammalian test systems are more promising but still require further development and experience. The development of such methods should be encouraged.

7. The WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals<sup>1</sup> considered it “ logical that tumour induction be considered as a manifestation of toxicity to be studied as an individual problem in each case ” and “ recognized that there are certain instances of cancer induction that may be secondary to an initial noncarcinogenic effect of a chemical ”. It is therefore recommended that further attention be paid to these matters and that practical approaches to the conclusion of the Scientific Group<sup>1</sup> that “ the possible existence of a threshold to the effect of both chemical carcinogens and mutagens should be envisaged ”, should be formulated.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 546.

## Annex 1

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

1. General Principles Governing the Use of Food Additives. First Report. *FAO Nutrition Meetings Report Series*, 1957, No. 15 ; *Wld Hlth Org. techn. Rep. Ser.*, 1957, No. 129.
2. Procedures for the Testing of Intentional Food Additives to Establish their Safety for Use. Second Report. *FAO Nutrition Meetings Report Series*, 1958, No. 17 ; *Wld Hlth Org. techn. Rep. Ser.*, 1958, No. 144.
3. Specifications for Identity and Purity of Food Additives (Antimicrobial Preservatives and Antioxidants). Third Report. These specifications were subsequently revised and published as *Specifications for Identity and Purity of Food Additives*, vol. I. *Antimicrobial Preservatives and Antioxidants*, Rome, Food and Agriculture Organization of the United Nations, 1962.
4. Specifications for Identity and Purity of Food Additives (Food Colours). Fourth Report. 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.
5. Evaluation of the Carcinogenic Hazards of Food Additives. Fifth Report. *FAO Nutrition Meetings Report Series*, 1961, No. 29 ; *Wld Hlth Org. techn. Rep. Ser.*, 1961, No. 220.
6. Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants. Sixth Report. *FAO Nutrition Meetings Report Series*, 1962, No. 31 ; *Wld Hlth Org. techn. Rep. Ser.*, 1962, No. 228.
7. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Emulsifiers, Stabilizers, Bleaching and Maturing Agents. Seventh Report. *FAO Nutrition Meetings Report Series*, 1964, No. 35 ; *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 281.
8. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Food Colours and Some Antimicrobials and Antioxidants. Eighth Report. *FAO Nutrition Meetings Report Series*, 1965, No. 38 ; *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 309.
- \*9. Specifications for Identity and Purity and Toxicological Evaluation of Some Antimicrobials and Antioxidants. *FAO Nutrition Meetings Report Series*, 1965, No. 38A ; WHO/Food Add/24.65.
- \*10. Specifications for Identity and Purity and Toxicological Evaluation of Food Colours. *FAO Nutrition Meetings Report Series*, 1966, No. 38B ; WHO/Food Add/66.25.

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\* These documents can be obtained on request from : Food Additives, World Health Organization, 1211 Geneva 27, Switzerland, or Food Policy and Food Science Service, Food and Agriculture Organization of the United Nations, 00100 Rome, Italy.

11. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases. Ninth Report. *FAO Nutrition Meetings Report Series*, 1966, No. 40 ; *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 339.
12. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Emulsifiers and Stabilizers and Certain Other Substances. Tenth Report. *FAO Nutrition Meetings Report Series*, 1967, No. 43 ; *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 373.
- \*13. Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-treatment Agents, Acids and Bases. *FAO Nutrition Meetings Report Series*, No. 40A, B, C ; WHO/Food Add/67.29.
14. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Flavouring Substances and Non-Nutritive Sweetening Agents. Eleventh Report. *FAO Nutrition Meetings Report Series*, 1968, No. 44 ; *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 383.
- \*15. Toxicological Evaluation of Some Flavouring Substances and Non-Nutritive Sweetening Agents. *FAO Nutrition Meetings Report Series*, 1968, No. 44A ; WHO/Food Add/68.33.
- \*16. Specifications and Criteria for Identity and Purity of Some Flavouring Substances and Non-Nutritive Sweetening Agents. *FAO Nutrition Meetings Report Series*, 1969, No. 44B ; WHO/Food Add/69.31.
17. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Antibiotics. Twelfth Report. *FAO Nutrition Meetings Report Series*, 1969, No. 45 ; *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 430.
- \*18. Specifications for the Identity and Purity of Some Antibiotics. *FAO Nutrition Meetings Report Series*, 1969, No. 45A ; WHO/Food Add/69.34.
19. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Food Colours, Emulsifiers, Stabilizers, Anticaking Agents, and Certain Other Substances. Thirteenth Report. *FAO Nutrition Meetings Report Series*, 1970, No. 46 ; *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 445.
- \*20. Toxicological Evaluation of Some Food Colours, Emulsifiers, Stabilizers, Anticaking Agents and Certain Other Substances. *FAO Nutrition Meetings Report Series*, No. 46A ; WHO/Food Add/70.36.
- \*21. Specifications for the Identity and Purity of Some Food Colours, Emulsifiers, Stabilizers, Anticaking Agents and Certain Other Food Additives. *FAO Nutrition Meetings Report Series*, No. 46B ; WHO/Food Add/70.37.
22. Evaluation of Food Additives. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Extraction Solvents and Certain Other Substances ; and a Review of the Technological Efficacy of Some Antimicrobial Agents. Fourteenth Report. *FAO Nutrition Meetings Report Series*, 1971, No. 48 ; *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 462.
- \*23. Toxicological Evaluation of Some Extraction Solvents and Certain Other Substances. *FAO Nutrition Meetings Report Series*, 1971, No. 48A ; WHO/Food Add/70.39.
- \*24. Specifications for the Identity and Purity of Some Extraction Solvents and Certain Other Substances. *FAO Nutrition Meetings Report Series*, 1971, No. 48B ; WHO/Food Add/70.40.

- \*25. A Review of the Technological Efficacy of Some Antimicrobial Agents. *FAO Nutrition Meetings Report Series*, 1971, No. 48C; WHO/Food Add/70.41.
26. Evaluation of Food Additives. Some Enzymes, Modified Starches, and Certain Other Substances: Toxicological Evaluations and Specifications and a Review of the Technological Efficacy of Some Antioxidants. Fifteenth Report. *FAO Nutrition Meetings Report Series*, 1972, No. 50; *Wld Hlth Org. techn. Rep. Ser.*, 1972, No. 488.
27. Toxicological Evaluation of Some Enzymes, Modified Starches and Certain Other Substances. *FAO Nutrition Meetings Report Series*, 1972, No. 50A; *WHO Food Additives Series*, 1972, No. 1.
28. Specifications for the Identity and Purity of Some Enzymes and Certain Other Substances. *FAO Nutrition Meetings Report Series*, 1972, No. 50B; *WHO Food Additives Series*, 1972, No. 2.
29. A Review of the Technological Efficacy of Some Antioxidants and Synergists. *FAO Nutrition Meetings Report Series*, 1972, No. 50C; *WHO Food Additives Series*, 1972, No. 3.
30. Evaluation of Certain Food Additives and the Contaminants Mercury, Lead and Cadmium. Sixteenth Report. *FAO Nutrition Meetings Report Series*, 1972, No. 51; *Wld Hlth Org. techn. Rep. Ser.*, 1972, No. 505.
31. Evaluation of Mercury, Lead, Cadmium and the Food Additives Amaranth, Diethylpyrocabonate and Octyl Gallate. *FAO Nutrition Meetings Report Series*, 1972, No. 51A; *WHO Food Additives Series*, 1972, No. 4.
32. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives, *FAO Nutrition Meetings Report Series*, 1974, No. 53; *Wld Hlth Org. techn. Rep. Ser.*, 1974, No. 539.
33. Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents. *FAO Nutrition Meetings Report Series*, No. 53A; *WHO Food Additives Series*, 1974, No. 5.

## Annex 2

### ACCEPTABLE DAILY INTAKES AND INFORMATION ON SPECIFICATIONS

	<i>Specification</i> <sup>a</sup>	<i>ADI</i> (mg/kg body weight)
<i>Flavouring substances and flavour enhancers</i>		
calcium-5'-ribonucleotide	N	ADI not specified <sup>b</sup>
disodium-5'-ribonucleotide	N	ADI not specified <sup>b</sup>
ethylmaltol	S	0-2
ethylmethylphenyl glycidate	S	No ADI allocated <sup>c</sup>
fumaric acid	S	0-6
guanylic acid, sodium and calcium salts	N	ADI not specified <sup>b</sup>
inosinic acid, sodium and calcium salts	N	ADI not specified <sup>b</sup>
maltol	S	No ADI allocated <sup>c</sup>
D,L-menthol and L-menthol	S	0-0.2
<i>Food colours</i>		
Allura Red AC	O	No ADI allocated <sup>d</sup>
Annatto extracts	R	0-1.25 <sup>e, f</sup>
azorubine	R	0-0.5 <sup>f</sup>
Beet Red	R	ADI not specified <sup>b, f</sup>
Brilliant Black PN	R	0-2.5 <sup>f</sup>
canthaxanthine	R	0-25
caramel colours (ammonia process) <sup>g</sup>	R	0-100 <sup>f</sup>
carotenes (natural)	S	No ADI allocated <sup>d</sup>
β-apo-8'-carotenal <sup>h</sup>	R	0-5
β-carotene <sup>h</sup>	R	0-5
β-apo-8'-carotenoic acid, methyl and ethyl esters <sup>h</sup>	R	0-5
chlorophyllin copper complex, sodium and potassium salts	RT	0-15 <sup>f</sup>
cochineal and carminic acid	S	No ADI allocated <sup>d</sup>

<sup>a</sup> O, Specification not prepared ; N, new specification prepared ; R, existing specification revised ; S, a specification exists, revision not considered ; T, the new specification (NT) or revised specification (RT) is tentative and comments are invited.

<sup>b</sup> The statement "ADI not specified" means that, on the basis of the available data (toxicological, biochemical, and other), the total daily intake of the substance, arising from its use or uses at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, and for the reasons stated in individual evaluations, the establishment of an acceptable daily intake (ADI) in mg per kg of body weight is not deemed necessary.

<sup>c</sup> The additional information requested in the earlier evaluation was not made available. The previous temporary ADI was withdrawn.

<i>Food colours (continued)</i>	<i>Specification<sup>a</sup></i>	<i>ADI</i> (mg/kg body weight)
curcumin	S	0-0.1 <sup>f</sup>
erythrosine	R	0-2.5
Green S	R	No ADI allocated <sup>c</sup>
Indanthrene Blue RS	S	No ADI allocated <sup>c</sup>
indigotine	R	0-5
iron oxides (and hydrated iron oxides)	R	ADI not specified <sup>b,f</sup>
lycopene	O	No ADI allocated <sup>d</sup>
Orange GGN	S	No ADI allocated <sup>d</sup>
Orange RN	O	No ADI allocated <sup>d</sup>
orchil and orcein	S	No ADI allocated <sup>d</sup>
Patent Blue V	R	No ADI allocated <sup>c</sup>
Persian Berries	O	No ADI allocated <sup>d</sup>
Ponceau 4R	RT	0-0.125 <sup>f</sup>
Ponceau 6R	S	No ADI allocated <sup>d</sup>
Quinoline Yellow	RT	0-0.5 <sup>f</sup>
turmeric	R	0-2.5 <sup>f</sup>
Yellow 2G	O	No ADI allocated <sup>d</sup>
 <i>Food enzymes</i>		
microbial carbohydrase ( <i>Aspergillus niger</i> )	S	ADI not specified <sup>b</sup>
microbial glucose oxidase ( <i>Aspergillus niger</i> )	S	ADI not specified <sup>b</sup>
microbial lipase ( <i>Aspergillus oryzae</i> )	S	ADI not specified <sup>b</sup>
microbial rennet ( <i>Endothia parasitica</i> )	S	ADI not specified <sup>b</sup>
microbial rennet ( <i>Mucor miehei</i> )	S	ADI not specified <sup>b</sup>
microbial rennet ( <i>Mucor pusillus</i> )	S	ADI not specified <sup>b</sup>
 <i>Thickening agents</i>		
hydroxypropyl distarch phosphate	S	ADI not specified <sup>b</sup>
oxidized starches	S	ADI not specified <sup>b</sup>
pectin (amidated)	R	0-25 <sup>f</sup>
tara gum	NT	No ADI allocated <sup>d</sup>
xanthan gum	N	0-10

<sup>d</sup> Evaluation not possible from the data provided.

<sup>e</sup> Expressed as bixin.

<sup>f</sup> Temporary acceptance.

<sup>g</sup> Based on a product having a colour intensity of 20 000 EBC (European Brewery Convention) units and containing not more than 200 mg/kg (200 ppm) of 4-methylimidazole.

<sup>h</sup> As the sum of  $\beta$ -carotene,  $\beta$ -apo-8'-carotenal, and  $\beta$ -apo-8'-carotenic acid, methyl and ethyl esters.

<sup>i</sup> The phosphorus content is to be included in the ADI for phosphates.

<sup>j</sup> Calculated as sodium ferrocyanide.

<sup>k</sup> Calculated as total gluconic acid from all sources.

<sup>l</sup> For dietetic uses the ADI is 0-15 mg/kg body weight.

<i>Miscellaneous food additives</i>	<i>Specification <sup>a</sup></i>	<i>ADI (mg/kg body weight)</i>
aluminium potassium sulfate	N	Decision postponed
aluminium sulfate	N	Decision postponed
ammonium salts of phosphatidic acid <sup>i</sup>	S	0-30
calcium, potassium, and sodium ferrocyanides <sup>j</sup>	R	0-0.025
cyclamates, sodium and calcium salts	S	No ADI allocated <sup>d</sup>
dimethylpolysiloxane	S	0-1.5
dioctyl sodium sulfosuccinate	N	0-2.5 <sup>f</sup>
glucono- $\delta$ -lactone <sup>k</sup>	R	0-50
glycerol esters of wood rosins	NT	Decision postponed
mannitol	R	0-50 <sup>f</sup>
saccharin and its sodium and calcium salts	R	0-5 <sup>l</sup>
sorboyl palmitate	O	No ADI allocated <sup>d</sup>

#### Specifications only

<i>Substance</i>	<i>Specification <sup>a</sup></i>
chlorophyll copper complex	RT
calcium 5'-guanylate	N
calcium 5'-inosinate	N
disodium 5'-guanylate	N
disodium 5'-inosinate	N
L-glutamic acid	N
monoammonium L-glutamate	N
monocalcium di-L-glutamate	N
monopotassium L-glutamate	N
butyl <i>p</i> -hydroxybenzoate	N
enzyme-treated starches	N
carrageenans	RT
calcium gluconate	N
ferrous gluconate	N
calcium lactate	R
potassium acetate	R
sodium acetate	R
potassium chloride	N
aluminium calcium silicate	RT
potassium lactate (solutions)	R
sodium lactate (solutions)	R
monoglyceride citrate	N

**FURTHER TOXICOLOGICAL STUDIES AND INFORMATION  
REQUIRED OR DESIRABLE**

(1) *Food colours*

*Annatto extracts.* Completion of metabolic studies at present in progress.<sup>1</sup>

*Azorubine.* Adequate long-term studies in another species ; investigation of embryotoxicity, including teratogenicity ; and adequate metabolic studies in several species preferably including man.<sup>1</sup>

*Beet Red.* Metabolic studies, preferably involving man, and an adequate long-term study in one suitable species.<sup>1</sup>

*Brilliant Black PN.* Metabolic studies, preferably involving man, and adequate reproduction and embryotoxicity, including teratological studies.<sup>1</sup>

*Caramel colours (ammonia process).* Results of long-term and reproduction studies on caramel colours prepared by the ammonia or ammonium sulfate process and containing different proportions of 4-methylimidazole.<sup>1</sup>

*Chlorophyllin copper complex, sodium and potassium salts.* Revision of tentative specifications.<sup>2</sup>

*Curcumin.* Metabolic studies, preferably involving man ; adequate long-term studies in a rodent species ; reproduction and embryotoxicity, including teratogenicity.<sup>1</sup>

*Erythrosine.* Metabolic studies preferably involving man.<sup>2</sup>

*Iron oxides and hydrated iron oxides.* Adequate information on the absorption and storage of iron following the use of these pigments as food additives.<sup>1</sup>

*Ponceau 4R.* Metabolic studies in several species, preferably including man, an adequate long-term study in another species, and reproduction studies.<sup>1</sup>

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<sup>1</sup> Required by June 1978.

<sup>2</sup> Desirable.

*Quinoline Yellow*. Metabolic studies in several species, preferably including man, an adequate long-term study in another species, and results of multigeneration studies.<sup>1</sup>

*Turmeric*. Adequate short-term study in a non-rodent species ; a long-term study at higher levels in a rodent species to establish a no-effect level, using turmeric with a well-defined curcumin content.<sup>1</sup>

(2) *Thickening agents*

*Pectin (amidated)*. The results of histological examinations in the long-term study and adequate reproduction and embryotoxicity, including teratological studies.<sup>1</sup>

(3) *Miscellaneous food additives*

*Diethyl sodium sulfosuccinate*. Effects on neonatal animals, particularly those exposed to diethyl sodium sulfosuccinate through the milk, an adequate long-term study in a rodent species, and investigation of pulmonary circulatory effects including pulmonary hypertension.<sup>1</sup>

*Mannitol*. Submission of final report on long-term study in rats, which is in progress.

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<sup>1</sup> Required by June 1978.

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