Evaluation of certain food additives and contaminants

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

World Health Organization Technical Report Series 751

World Health Organization, Geneva 1987
Monographs containing summaries of relevant data and toxicological evaluations are available under the title:


Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives
FAO Food and Nutrition Paper, No. 37

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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

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

ISBN 92 4 120751 5
© World Health Organization 1987

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. For rights of reproduction or translation of WHO publications, in part or in toto, application should be made to the Office of Publications, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

ISBN 0512-3254
PRINTED IN SWITZERLAND
87/7147 – Schätler S.A. – 7300
## CONTENTS

1. Introduction ............................................................................................................. 8
2. General considerations ........................................................................................... 9
   2.1 Principles governing the toxicological evaluation of compounds on the agenda ........ 9
      2.1.1 Natural items of food .................................................................................. 9
      2.1.2 Flavours ...................................................................................................... 10
      2.1.3 Interaction with nutritional factors ............................................................... 10
      2.1.4 General considerations ............................................................................... 11
   2.2 Principles governing the establishment and revision of specifications ..................... 11
      2.2.1 General ....................................................................................................... 11
      2.2.2 Revision of Guide to Specifications ............................................................ 11
      2.2.3 Sensitivity of limit tests ............................................................................... 11
      2.2.4 Feasibility and applicability of methods of analysis ..................................... 12
3. Comments on specific food additives and contaminants ............................................. 12
   3.1 Antioxidants ..................................................................................................... 12
   3.2 Flavouring agents ............................................................................................. 19
   3.3 Food colours ..................................................................................................... 20
   3.4 Sweetening agents ........................................................................................... 25
   3.5 Thickening agents ............................................................................................ 26
   3.6 Miscellaneous food additives ........................................................................... 29
   3.7 Contaminants .................................................................................................. 35
4. Establishment and revision of certain specifications and general methods ................. 38
   4.1 Specifications ................................................................................................... 38
   4.2 General methods ............................................................................................... 40
5. Principles for the safety assessment of food additives and contaminants in food ............ 41
6. Future work .............................................................................................................. 41
7. Recommendations to FAO and WHO ........................................................................ 42
   Annex 1. Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives ............................... 45
   Annex 2. Acceptable daily intakes, other toxicological recommendations, and information on specifications ................................................................. 50
   Annex 3. Further toxicological studies and information required or desired ................ 53
   Annex 4. Matters arising from the reports of sessions of the Codex Committee on Food Additives ................................................................. 56
JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 2-11 June 1986

Members invited by FAO

Dr S.W. Gunner, Director-General, Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, Canada
Mr J. Howlett, Principal Scientific Officer, Food Science Division, Ministry of Agriculture, Fisheries and Food, London, England
Professor K. Kojima, College of Environmental Health, Azubu University, Sagamihara-Shi, Kanagawa-Ken, Japan (Chairman)
Dr R. Mathews, Director, Food Chemicals Codex, National Academy of Sciences, Washington, DC, USA
Mrs I. Meyland, Scientific Officer, Central Laboratory, Nutrients and Food Additives, National Food Agency, Soborg, Denmark
Dr J.P. Middelmen, Division of Food Chemistry and Technology, Food and Drug Administration, Department of Health and Human Services, Washington, DC, USA
Professor F. Pellerin, Faculty of Pharmacy of the South Paris University, Corentin-Celton Hospital, Issy-les-Moulinaux, France
Dr S.A. Slorach, Head, Food Research Department, The National Food Administration, Toxico logical Department, Uppsala, Sweden

Members invited by WHO

Dr H. Blumenthal, Director, Division of Toxicology, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA
Dr Barbara MacGibbon, Senior Principal Medical Officer, Division of Toxicology and Environmental Protection, Department of Health and Social Security, London, England
Dr G. Nazario, Scientific Adviser, National Secretariat of Sanitary Surveillance, Ministry of Health, Sao Paulo, Brazil
Dr K. Oduose, Associate Professor of Medicine, Department of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria (Rapporteur)
Professor M.J. Rand, Chairman, Department of Pharmacology, University of Melbourne, Victoria, Australia (Vice-Chairman)
Dr P. Shubik, Senior Research Fellow, Green College, Oxford, England
Dr V.A. Tuteleyan, Deputy Director, Institute of Nutrition, Academy of Medical Sciences of the USSR, Moscow, USSR

Secretariat

Dr Y.K. Al-Mutawa, Head, Division of Public Health Laboratory, Ministry of Public Health, Safat, Kuwait (WHO Temporary Adviser)
Dr J.R. Cabral, Scientist, Unit of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyons, France (WHO Temporary Adviser)
Professor Indira Chakravarty, Head, Department of Biochemistry and Nutrition, All India Institute of Hygiene and Public Health, Calcutta, India (WHO Temporary Adviser)
Mr. A. Feberwee, Chairman, Codex Committee on Food Additives, Deputy Director, Nutrition and Quality Affairs, Ministry of Agriculture and Fisheries, The Hague, Netherlands (Member of FAO Secretariat)

Professor C.L. Galli, Head, Toxicology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy (WHO Temporary Adviser)

Mr. R. Haigh, Principal Administrator, Commission of the European Communities, Brussels, Belgium (WHO Temporary Adviser)

Dr. Y. Hayashi, Chief, Division of Pathology, National Institute of Hygienic Sciences, Biological Safety Research Center, Setagaya-Ku, Tokyo, Japan (WHO Temporary Adviser)

Dr. J.L. Herrman, Division of Food and Color Additives, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (WHO Consultant)

Dr. R.W. Moch, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (WHO Temporary Adviser)

Dr. E. Poulsen, Chief Adviser in Toxicology, Ministry of the Environment, Søborg, Denmark (WHO Temporary Adviser)

Dr. A.W. Randell, Food Policy and Nutrition Division, FAO, Rome, Italy (Joint Secretary)

Dr. N. Rao Maturu, Food Standards Officer, Joint FAO/WHO Food Standards Programme, FAO, Rome, Italy

Dr. S. Shibko, Associate Director for Toxicological Evaluation, Division of Toxicology, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (WHO Temporary Adviser)

Professor A. Somogyi, Director, Department of Drugs, Animal Nutrition and Residue Research, Institute for Veterinary Medicine, Berlin (West) (WHO Temporary Adviser)

Professor K. Truhaut, Emeritus Professor of Toxicology, Faculty of Pharmaceutical and Biological Sciences, Université René Descartes, Paris, France (WHO Temporary Adviser)

Dr. G. Vettorazzi, Senior Toxicologist, International Programme on Chemical Safety, Division of Environmental Health, WHO, Geneva, Switzerland (Joint Secretary)

Dr. R. Walker, Professor, Department of Biochemistry, University of Surrey, Guildford, Surrey, England (WHO Temporary Adviser)
EVALUATION OF CERTAIN
FOOD ADDITIVES AND CONTAMINANTS

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

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 2 to 11 June 1986. The meeting was opened by Dr P. Lunven, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Lunven noted that this thirtieth meeting of the Expert Committee had come during the fortieth anniversary year of FAO and coincided almost exactly with the fortieth anniversary of the establishment of the WHO Interim Commission. He briefly reviewed the origins and history of the Expert Committee and noted that both FAO and WHO had recognized since 1949 that the increasing use of various chemical substances in the food industry called for special considerations in the areas of public health, nutrition, and food production and distribution. Dr Lunven also drew attention to the close linkages within the framework of FAO and WHO with other Committees and Programmes, most particularly the Joint FAO/WHO Food Standards Programme and the International Programme on Chemical Safety.

Dr Lunven referred to the Principles for the safety assessment of food additives and contaminants in food,¹ which would be under review at the present meeting. He drew attention to its importance in providing guidance to developing countries in setting out broad principles for future assessments of the safety of chemical substances in foods, allowing toxicologists, nutritionists and food scientists freedom to meet new challenges with new ideas and new initiatives, while still retaining the basic principles of the previous Committees. Dr Lunven drew attention to the fact that most of the substances which the Committee had considered at its previous meetings were those that had been of most interest to the countries of the industrialized world. Although these were the countries where the use of food additives was greatest and whose international

marketing activities affected the intake of food additives in populations around the world, it was perhaps appropriate to consider further the special problems presented by food additives and contaminants in developing countries. Traditional and small-scale food industries provided a significant part of the food supply; plant extracts were used to provide rich and exciting colours and flavours, but very little was known about these materials, and still less about what constituted a quality acceptable for use in food. Dr Lunven requested that special attention should continue to be paid to the problems of countries that do not have the resources to conduct toxicological studies or to prepare specifications of identity and purity of food-grade materials, and whose exposure to some contaminants may be significantly higher than that experienced in the industrialized world.

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,¹ there have been twenty-nine previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the twenty-ninth meeting (Annex 1, reference 70). The tasks before the Committee were: (a) to prepare specifications for the identity and purity of certain food additives and to evaluate their toxicological properties; (b) to review specifications for selected food additives; (c) to undertake toxicological evaluations and re-evaluations of certain food additives and contaminants; (d) to consider the methodology for testing and assessing chemicals in food; and (e) to discuss and provide advice on matters arising from the report of the eighteenth session of the Codex Committee on Food Additives.²

2. GENERAL CONSIDERATIONS

2.1 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (Annex 1) and those established by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives\(^1\) and the WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.\(^2\) In addition, the Committee reaffirmed the need to take into consideration recent developments in toxicological techniques, as stated in its seventeenth report (Annex 1, reference 32). The Committee also reviewed and endorsed a draft document produced by the International Programme on Chemical Safety in response to the Committee's repeated recommendations to study "the application of advances in methodology to the toxicological evaluation of food additives and contaminants" (Annex 1, references 56, 59, and 62).

2.1.1 Natural items of food

From time to time the Committee is faced with the need to evaluate the toxicological properties of substances that are traditionally consumed as items of food in some parts of the world. This has been the situation with some flavours, colours, and thickening agents. At the present meeting the colour turmeric and the thickening agent processed *Eucheuma* seaweed fall into this category.

The Committee considered two extremes:

(a) that such substances be considered foods, in the same sense as vegetables and fruits, and should therefore be acceptable with no need for toxicological studies and no need to specify an acceptable daily intake (ADI); or

(b) that they be considered food additives, requiring toxicological evaluation.

The Committee concluded that this issue cannot be generalized to such an extent that simple guidelines can be established for deciding whether such substances should be considered foods or

---


food additives. Therefore, each substance should be considered separately. Because food consumption patterns vary from country to country, national governments may differ in how they wish to treat these substances.

Whenever a substance is considered to be a food additive, toxicological evaluation is required to ensure its safety and establish an ADI. The assurance of safety may be based on toxicological studies performed on more highly purified products, provided that information is available showing that other substances likely to be toxic are not present in the native product. A determination of safety may also be facilitated by sound epidemiological evidence of safety. In some situations, a substance acceptable as food may be considered a food additive to allow the setting of specifications in order to ensure microbiological purity and control of chemical contaminants.

2.1.2 Flavours

The Committee was informed that the Codex Committee on Food Additives had temporarily endorsed the use of natural flavours and those prepared synthetically but identical to natural flavours in Codex Food Standards. In view of this action, the Committee reiterated the view expressed in the twentieth report that "naturalness per se is no guarantee of safety" (Annex 1, reference 41), and reaffirmed recommendations made in previous reports of the Committee (Annex 1, references 47, 50 and 62) to establish priorities for the testing and evaluation of food additives, including flavouring agents. The Committee recommended that the Codex Committee on Food Additives set the priority-setting programme in motion by providing consumption patterns of flavours for consideration by future committees. The Committee also stressed that it could evaluate only substances for which adequate toxicological data were available, and stated that it would welcome data on flavours that have not yet been evaluated.

2.1.3 Interaction with nutritional factors

In considering the effects of α-tocopherol and butylated hydroxytoluene (BHT) in inducing vitamin K-responsive haemorrhage, the Committee recommended that, for full evaluation of possible toxic effects, compounds that interact with essential
nutrients (such as vitamin K) should be tested with and without appropriate nutrient supplementation of the diet.

2.1.4 General considerations

Group ADIs have been applied to substances closely related chemically and toxicologically. However, when information is available to show that these compounds have different biological properties, then a group ADI is no longer applicable and separate ADIs should be set (e.g., see section on antioxidants).

2.2 Principles governing the establishment and revision of specifications

2.2.1 General

The specifications for the identity and purity of food additives prepared by the Committee have two purposes: (a) to ensure that the substances tested for toxicological properties are the same as those used in food; and (b) to ensure that substances used as food additives conform to the identity and purity requirements of the specifications.

The Committee reiterated the importance of the specifications for protecting the consumer, for regulatory control, for industry, and for ensuring food safety, as originally stated in its first and third reports (see Annex 1, references 1 and 3, respectively).

2.2.2 Revision of Guide to Specifications

The Committee noted that the general methods contained in the Guide to Specifications (Annex 1, reference 65) had not been revised since 1983, and recommended that attention be given to reviewing and updating them to take account of changes in specifications, methodology, and analytical techniques. For example, the Committee recommended that the separate Annex of Methods of Analysis for Colours (Annex 1, reference 68) be incorporated into the general methods section along with certain other new methods developed at this meeting (see section 4.2).

2.2.3 Sensitivity of limit tests

Certain specifications have limits designated as “passes test”. The application of such specifications is dependent on the limits inherent in the use of these tests, and the Committee considered that the
understanding of such limits would be enhanced if an approximate sensitivity for the test method were provided. A test may be suitable for the analysis of a group of chemical substances, but the sensitivity of the test method may differ for different members of the group. Consequently, a single sensitivity value cannot always be provided for such limit tests. In such situations, the lower limit of reliable measurement for a certain member of the group could be provided as an indicator of the sensitivity of the specification, where applicable.

2.2.4 Feasibility and applicability of methods of analysis

It is important to ensure that the methods included in the specifications achieve a degree of accuracy consistent with the specified limits. At the same time, however, there is a need to ensure that the methods are practicable for routine use wherever needed. The Committee takes into account both of these requirements in order to ensure that specifications are fully useful. However, for certain specifications, the most accurate method may require the use of highly specialized analytical equipment which may not be easily available everywhere (see, for example, section 3.6.6 on talc).

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

3.1 Antioxidants

The Committee noted significant differences in the toxicity of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tertiary butylhydroquinone (TBHQ) and considered that a group ADI for these compounds, as established earlier (Annex 1, reference 44), was no longer appropriate. Accordingly, BHA, BHT, and TBHQ were evaluated separately (see section 2.1.4).

3.1.1 Butylated hydroxyanisole (BHA)

Butylated hydroxyanisole was last evaluated at the twenty-seventh meeting of the Committee (Annex 1, reference 62), when the temporary ADI of 0–0.5 mg/kg of body weight (group ADI with BHT and TBHQ) was maintained pending adequate studies to
determine whether the induction of hyperplasia, papilloma, and carcinoma by BHA in the forestomach of the rat and hamster is relevant for evaluating the safety of BHA for man. It was specifically requested that studies be submitted to show whether or not BHA induces hyperplasia in the stomach of species that do not have a forestomach, such as the dog, pig and monkey, and to determine the mechanism of BHA's effect on the forestomach. A multigeneration reproduction study was also requested.

Studies have since been conducted that provide additional information on the proliferative changes observed in the forestomach of rats fed BHA, and on the effect of BHA on the stomach and oesophagus of species that do not have a forestomach. The data show that induction of hyperplasia in the forestomach of the rat is dose dependent and can be reversed when BHA is removed from the diet. In one species that does not have a forestomach, the dog, levels of BHA that produced effects in the forestomach of the rat had no effect on either the stomach or the oesophagus. However, in monkeys and pigs, there was some evidence that BHA produced effects on the oesophagus. In monkeys, an increased mitotic rate was reported, and in pigs hyperkeratoses were diagnosed, largely by macroscopic methods.

The Committee believes that the studies in monkeys and pigs should be repeated; in particular, dietary administration of BHA should be tested in the monkey (currently only gavage data are available).

The results of several tests on the genotoxicity of BHA, involving both bacterial and mammalian cells, lend additional support to the previously held view (based on evaluation of several in vitro and in vivo systems) that BHA is not mutagenic.

The Committee was informed that no new data had been submitted to meet the requirements for a multigeneration reproduction study.

The Committee based its evaluation of BHA on the no-effect level found in a long-term toxicity study in rats, in which it was shown that 1.25 g/kg of BHA in the diet produced no significant changes. A temporary ADI of 0–0.3 mg/kg of body weight was established. An addendum to the toxicological monograph was prepared.

The Committee was asked to consider including a test for specific absorption in the specifications for BHA. However, because the substance is a mixture of two isomers, which may vary in proportion,
specific absorption would not be an appropriate indicator of purity and the Committee did not feel its inclusion was warranted. The existing specifications were revised with respect to methodology.

The Committee requested that the following studies be carried out before the re-evaluation of BHA in 1988:

1. Studies to explore the potential for BHA to cause oesophageal hyperplasia in pigs and monkeys. The studies should be carried out with dietary BHA. The Committee recognizes the technical difficulties in carrying out the study in monkeys due to potential diet rejection, but emphasizes that it should nevertheless be attempted.

2. Multigeneration reproduction study.

In addition, it would be desirable to carry out studies to determine the mechanism of action of BHA on the forestomach.

3.1.2 Butylated hydroxytoluene (BHT)

Butylated hydroxytoluene (BHT) was last evaluated at the twenty-seventh meeting of the Committee (Annex 1, reference 62) when a group ADI with BHA and TBHQ of 0–0.5 mg/kg of body weight was established.

As requested in the twenty-seventh report of the Committee (Annex 1, reference 62), data from a lifetime feeding study in rats (including a single-generation reproduction study) were submitted to the Committee for review. The data indicated that lifetime (including in utero) exposure to BHT caused a dose-related increase in the number of hepatocellular adenomas and carcinomas in Wistar rats. Most of the hepatocellular tumours occurred when the rats were more than two years old. The Committee noted that previously reported single-generation carcinogenicity studies with BHT in Fischer 344 and Wistar rats were negative, as were conventional carcinogenicity studies with BHT in B6CF1 mice and mutagenicity tests. On the other hand, in one study, male and female C3H mice fed semi-synthetic diets containing BHT for 10 months showed a higher incidence of hepatocellular tumours than did concurrent controls. However, it was noted that in this study the dose-response relationship was inverted, and in other studies with the same inbred strain, tumour incidence was not significantly different from that in controls of similar age.

The Committee concluded that BHT has been shown to be hepatocarcinogenic only in an in utero study in rats. The toxicological significance of the hepatocarcinogenicity may relate to
the differences is design between this study and the previous (negative) studies. In particular, the positive study lasted for 144 weeks, and the test animals were exposed to BHT in utero and had low body weights. The Committee felt, therefore, that the reasons for the in utero effects of BHT should be studied as a matter of priority.

The Committee was also informed that several studies from one laboratory had reported that the feeding of BHT caused haemorrhage in rats. Such haemorrhage can be prevented by feeding a vitamin K analogue, which suggests that it may be due to the presence of anti-vitamin K activity, possibly associated with diets containing low amounts of vitamin K. The Committee concluded that further studies were required on the mechanism of the haemorrhagic effect.

The Committee also reviewed a one-generation reproduction study in rats. BHT had no effect on the gestation rate, but showed a dose-related effect on litter size, number of males per litter, and gain in body weight during the lactation period. The Committee based its evaluation of BHT on the no-effect level in this study; since 25 mg/kg of body weight BHT produced no significant toxicological effect, a temporary ADI of 0–0.125 mg/kg of body weight was established. An addendum to the toxicological monograph was prepared. The existing specifications were revised. Further studies or information required for the re-evaluation of BHT in 1990 include:

1. Investigation of the hepatocarcinogenicity of BHT in rats after in utero exposure.
2. Studies on the mechanism of the haemorrhagic effect of BHT in susceptible species.

3.1.3 Gallates (dodecyl, octyl and propyl)

These compounds were previously evaluated at the twenty-fourth meeting of the Committee in 1980 (Annex 1, reference 53), when a group ADI of 0–0.2 mg/kg of body weight was established. It was noted that in setting this ADI the Committee had used a larger than usual safety factor (250), because of concern for adverse effects shown in the reproduction studies.

In reviewing the gallates, the Committee noted that the metabolic studies that had shown that the gallates are hydrolysed to gallic acid and the corresponding alcohols were not wholly satisfactory. In addition, data from extensive reproduction studies of octyl gallate,
in which the progeny of the treated female rats were exchanged with the progeny of the control females, and a very limited reproduction study with dodecyl gallate, suggest that the milk of female rats treated with these gallates contains potentially toxic substances. Similar effects were not observed with propyl gallate. On the basis of these considerations and the fact that the amount of data available for each of these gallates was quite different, the Committee concluded that for the purpose of setting an ADI each gallate should be considered individually.

**Dodecyl gallate.** The Committee noted that the available information on this compound is limited and for the most part derived from studies that do not meet present-day standards. In a two-generation reproduction study in rats there was retardation in growth at the highest concentration fed, and some litters were lost in the second generation. This perinatal effect appeared to be due to the young rejecting mothers' milk. In a recent short-term study, in which dodecyl gallate was administered by gavage, the no-effect level was 10 mg/kg of body weight. There are no long-term, carcinogenicity, metabolism, or mutagenicity studies for this compound. The Committee also noted that sensitivity to dodecyl gallate could be a problem in people exposed to it in an industrial environment. Therefore, the Committee did not establish an ADI. No toxicological monograph was prepared.

The Committee requested that studies be carried out on the metabolism of dodecyl gallate. However, if sufficient toxicity data became available on the known hydrolysis products of dodecyl gallate, there would be no need for additional studies on metabolism. It would also be desirable that the identification of metabolites be extended to include those present in the milk of lactating animals.

**Octyl gallate.** Acute toxicity studies are available in a wide range of species. Short-term studies in rats showed no effects related to octyl gallate at levels up to 5 g/kg of the diet. Reproduction studies, also in rats, showed that high dose levels of octyl gallate (6 g/kg) have a marked effect on the survival of the offspring through weaning. Further studies in rats showed that the mortality among suckling rats observed at the highest levels tested (2.5 g/kg and 5 g/kg in the diet) was due to perinatal effects, and must have been caused by a factor entering the mothers' milk. No long-term, carcinogenicity, metabolism, or mutagenicity studies are available for evaluating this substance. The Committee could not establish an ADI.
The Committee requested that studies be carried out on the metabolism of octyl gallate. However, if sufficient data became available on the toxicity of the known hydrolysis products of octyl gallate, then additional studies on the metabolism of octyl gallate would not be needed. It would also be desirable that the identification of metabolites be extended to include those present in the milk of lactating animals. No toxicological monograph was prepared.

The Committee also noted that n-octyl gallate can cause reactions in the buccal mucosa of individuals previously sensitized by cutaneous contact with this compound. Because of this observation, the use of n-octyl gallate in beer and other widely consumed beverages is not recommended.

Propyl gallate. The acute and long-term studies are extensive and cover a wide range of animal species. Several long-term studies have been reported. Propyl gallate has been shown to be non-mutagenic in a number of in vivo or in vitro tests. In a recent study, propyl gallate was not shown to be carcinogenic in Fischer 344 rats or B6C3F1 mice of either sex.

In a reproduction study in rats, no adverse effects were reported when the concentration of propyl gallate in the diet was 5 g/kg. The Committee based its evaluation on this study, since studies with other gallates indicate that reproductive processes may be the most sensitive indicator of toxicity. An ADI of 0–2.5 mg/kg of body weight was established. No toxicological monograph was prepared.

The existing specifications were revised for dodecyl gallate, octyl gallate, and propyl gallate.

3.1.4 Tertiary butylhydroquinone (TBHQ)

Tertiary butylhydroquinone (TBHQ) was previously evaluated at the nineteenth and twenty-first meetings of the Committee (Annex 1, references 38 and 44). The ADI for man was set at 0–0.5 mg/kg of body weight on the basis of the dietary no-effect level in the dog of 1500 mg/kg. This was a group ADI with BHA and BHT.

At the present meeting, the Committee reviewed mutagenicity data for TBHQ. The available data were from studies involving both bacterial and mammalian cell test systems. When all the data were considered, there was some, though conflicting, evidence that TBHQ had genotoxic activity. Thus, the Committee felt that additional
studies would be desirable to resolve questions relating to the mutagenicity of TBHQ.

The Committee re-examined a 20-month feeding study in rats. Although no adverse effects were noted in this study, it was considered to be inadequate as a test for carcinogenicity by present-day standards because: (a) there was no evidence that the level of TBHQ fed was the maximum tolerated dose; (b) the duration of test was inadequate for a carcinogenicity study; and (c) some animals died during the study. The Committee was informed that lifetime studies in two rodent species will be carried out according to current standards for testing chemicals for carcinogenicity.

The present evaluation is based on a long-term feeding study in dogs in which a no-effect level of 1.5 g of TBHQ per kg of diet was found. A temporary ADI of 0.0.2 mg/kg of body weight was established. The following additional information is required for the re-evaluation of TBHQ in 1990:

Results of lifetime feeding studies in two rodent species. Feeding studies should take into account the normal degradation products of TBHQ in food.

It would be desirable for additional studies to be carried out to resolve questions related to the genotoxicity of TBHQ.

An addendum to the existing toxicological monograph was prepared. The existing specifications were revised.

3.1.5 Tocopherols

α-Tocopherol and mixed tocopherol concentrate were evaluated for an ADI by the Committee in 1961 and 1973 (Annex 1, references 6 and 32). At the meeting in 1973, an ADI of 0–2 mg/kg of body weight was allocated based on clinical experience in man.

At the present meeting, the Committee evaluated new data, including results of short-term tests, a long-term carcinogenicity study, tests for mutagenicity/clastogenicity, and reproduction and teratology studies. Further human data from clinical and controlled studies were also considered.

α-Tocopherol was non-mutagenic and non-carcinogenic, and the results of reproduction/teratology studies did not indicate that α-tocopherol had adverse effects on reproductive function. However, in a long-term study in rats, a no-effect level could not be established for effects on blood clotting and liver tissue, and there was evidence from human studies that excessive intakes of α-tocopherol could
cause haemorrhage. Other adverse effects noted in clinical studies at
dietary doses of ≥ 720 mg α-tocopherol/day included weakness,
fatigue, and creatininuria and effects on steroid hormone metabolism.

The Committee noted that α-tocopherol (vitamin E) may be an
essential nutrient and that a recommended dietary allowance of
0.15 mg/kg of body weight per day was allocated by the National
Research Council of the USA National Academy of Sciences.
However, excessive intakes of α-tocopherol produce adverse clinical
and biochemical effects, and self-medication with large doses of
vitamin E preparations could present a hazard.

The previously allocated ADI of 0–2 mg/kg of body weight for
dl-α-tocopherol was amended to 0.15–2 mg/kg of body weight on the
basis of clinical experience in man and the fact that α-tocopherol
may be an essential nutrient. The new ADI is a group ADI for both
dl-α-tocopherol and d-a-tocopherol concentrate.

The Committee felt that further work is desirable on the
mechanisms by which α-tocopherol interferes with vitamin K-
dependent blood-clotting factors and noted that further long-term
studies on α-tocopherol are planned. A toxicological monograph
was prepared for α-tocopherol.

The Committee recognized that a number of different commercial
products can be characterized according to the isomeric form and
degree of purity of the α-tocopherol they contain. The existing
specifications for dl-α-tocopherol were therefore revised and two
new specifications were prepared for d-α-tocopherol concentrate and
tocopherol concentrate, mixed.

3.2 Flavouring agents

3.2.1 d-Carvone and l-carvone ((+)-carvone and (−)-carvone)

(+)-Carvone and (−)-carvone were evaluated at the twenty-third
and twenty-fifth meetings (Annex 1, references 50 and 56). A
temporary ADI of 0–1.0 mg/kg of body weight was allocated to (+)-
and (−)-carvone (as sum of the isomers) at the twenty-third meeting
pending the submission of biochemical and metabolic studies in
several animal species, preferably including man. At the twenty-
seventh meeting (Annex 1, reference 62), the Committee extended
the temporary ADI since it was informed that lifetime feeding
studies with (+)-carvone in rats and mice were in progress.
Although at the present meeting the Committee was aware that several long-term and/or carcinogenicity studies in mice and rats had been completed, the results had not been submitted for evaluation. The Committee therefore extended the temporary ADI of 0–1.0 mg/kg of body weight up to 1988, pending submission of the results of these studies.

No toxicological monograph was prepared. The existing specifications for (−)-carvone were revised and the name was changed to “l-carvone”. The existing specifications for (+)-carvone were revised and the name was changed to “d-carvone”.

3.3 Food colours

3.3.1 Brown FK

Brown FK was evaluated and a new monograph was prepared at the twenty-ninth meeting of the Committee (Annex 1, reference 70). A temporary ADI of 0–0.075 mg/kg of body weight was allocated to Brown FK until 1986, pending the results of a complete histological examination of the low- and intermediate-dose groups in a long-term study in rats. These data were required in order adequately to establish a no-effect level in this study, which could be used as a basis for estimating an ADI for man.

Since no further data were available to the Committee, the temporary ADI was not extended. No toxicological monograph was prepared. The existing specifications were revised in order to facilitate the identification of appropriate materials to be used in further toxicological studies.

3.3.2 Curcumin and turmeric

Turmeric and curcumin (the main colouring component of turmeric) were evaluated at the eighteenth meeting of the Committee when temporary ADIs of 0–2.5 and 0–0.1 mg/kg of body weight for turmeric and curcumin, respectively, were allocated (see Annex 1, reference 35), pending: (a) an adequate short-term feeding study on turmeric in a non-rodent species; (b) an adequate long-term feeding study on curcumin in a rodent species and on turmeric with a well-defined curcumin content; and (c) a multigeneration reproduction/teratogenicity study on curcumin.
At the twenty-second meeting, the Committee extended the temporary ADIs up to 1980 (Annex 1, reference 47). At the twenty-fourth meeting (Annex 1, reference 53), the Committee reviewed new studies on the metabolism of curcumin and acute, short-term, long-term, reproduction, and mutagenicity studies on turmeric and on an alcoholic extract of turmeric. The Committee decided to extend the temporary ADIs up to 1982, pending the results of an adequate long-term study in a rodent species and teratogenicity studies on curcumin, and an adequate short-term study in a non-rodent species on turmeric. At the twenty-sixth meeting, the Committee (Annex 1, reference 59) reviewed further data and was informed of other studies in progress in response to the Committee’s request for those studies in previous reports; at the same time the temporary ADIs were extended up to 1986.

At the present meeting, the Committee was aware that turmeric and curcumin are used in three major forms, namely: (a) ground turmeric powder; (b) turmeric oleoresin, including preparations used as both colours and flavouring agents, containing a broad range (5 to 55%) of curcuminoids; and (c) curcumin (an extract containing at least 90% curcuminoids).

Since the specifications and properties of these materials are sufficiently different, toxicological data obtained for one of them cannot be used to interpret the toxicology of the others. Thus, the Committee considered that these materials should be evaluated independently of each other.

Curcumin. The Committee reviewed new metabolic studies, mutagenicity tests, and acute and short-term toxicological studies on curcumin (turmeric extract containing 790 g/kg curcumin). The Committee was informed that the required long-term carcinogenicity study in a rodent species was nearing completion.

The Committee extended the existing temporary ADI of 0–0.1 mg/kg of body weight for curcumin up to 1989 and requested the submission of results of a carcinogenicity study and a reproduction/teratogenicity study.

Turmeric oleoresin. The Committee reviewed new studies on turmeric oleoresin, in which the material studied conformed to the specifications for turmeric oleoresin. One of the studies was a short-term one in pigs, which had been conducted in response to the Committee’s request for such a study in a non-rodent species. The oleoresin used in this study had a curcumin content of 175 g/kg. Histopathological changes were observed in the liver, kidney,
bladder, and thyroid of animals in the two highest dose-groups, including hyperplasia of thyroid follicular cells; an increase in the weight of the thyroid glands was recorded at the lowest dose tested (60 mg/kg of body weight per day). It was not possible to establish a no-effect level in this study.

The Committee allocated a temporary ADI of 0.0–0.3 mg/kg of body weight for turmeric oleoresin, based on the minimal changes in the short-term study in pigs. Further data required by 1989 include the results of a short-term study in the pig or another non-rodent species. If such a study is performed in a species other than the pig, the design of the study should be such that it allows the sensitivity of the test species to be compared with that observed in the pig in the earlier study. Also, a clear no-effect level should be established.

Turmeric (ground turmeric powder). The Committee concluded that, because turmeric (ground turmeric powder) is often regarded as a food rather than as a food additive, it is not appropriate to allocate an ADI.

An addendum to the toxicological monograph covering both turmeric oleoresin and curcumin was prepared.

The Committee stressed that extraction solvent residues in turmeric oleoresin and curcumin should be the minimum consistent with good manufacturing practice and that the materials should comply with specifications relating to solvent residues. It was noted that several different extraction solvents could be used in the preparation of turmeric oleoresins and curcumin, and the Committee indicated that solvents such as acetone would be preferred to chlorinated hydrocarbons where they serve the same technological function.

Colouring materials containing curcumin, the principal colouring agent in turmeric, are available in varying degrees of purity. The existing specifications for curcumin were revised and new, tentative specifications were prepared for turmeric colour. The Committee noted the existence of specifications for turmeric oleoresin prepared at an earlier meeting which covered materials used for both colouring and flavouring purposes, but these were not considered in depth at the present meeting. These specifications should be revised to conform with those for turmeric colour.
3.3.3 *Erythrosine*

Erythrosine was evaluated in 1964, 1969, 1974 and 1984 (Annex 1, references 8, 19, 35, and 66). In 1984, the previous ADI was reduced to 0–1.25 mg/kg of body weight and made temporary (Annex 1, reference 66). The Committee requested the following information for re-evaluation of erythrosine in 1986:

1. The results of histopathological examination (including assessment of diffuse hyperplasia) of all thyroid glands from the most recent long-term studies in rats.

2. The mechanism of the effects of erythrosine on the thyroid gland in terms of the biochemical and histopathological parameters, the existence of a threshold level for these effects, and the extent of their reversibility.

It was also considered desirable for the Committee to have information on the pharmacokinetics of erythrosine and its effect on the thyroid function of human subjects.

The Committee considered the results of further studies addressing these issues. Metabolic studies confirmed that erythrosine is absorbed only to a small extent from the gastrointestinal tract in rats and man. Biochemical studies of thyroid function and of the metabolism of thyroid hormones indicated that erythrosine inhibits the deiodination of thyroxine to triiodothyronine, and, at high dose levels, activates secretory mechanisms for thyrotropin in the pituitary.

It was noted that further studies on mutagenicity had confirmed that erythrosine was non-genotoxic and that no effects on thyroid function or regulatory mechanisms had been observed in human studies at dose levels up to 80 mg (single dose) or 25 mg daily for seven days.

The previously established temporary ADI was withdrawn and a new temporary ADI of 0–0.6 mg/kg of body weight was allocated based on the results of studies of the biochemical effects of erythrosine on thyroid hormone metabolism and regulation, in which a no-effect level of 2.5 g/kg of the diet, equivalent to 125 mg/kg of body weight, was established.

The Committee required the results of pharmacokinetic studies which relate the amount of absorption to the amount ingested and which would enable a correlation to be established between blood/tissue levels of erythrosine and effects on the thyroid. These data should be made available for re-evaluation of erythrosine in 1988.
A toxicological monograph was prepared. The existing specifications were revised.

3.3.4 Fast Green FCF

Fast Green FCF was evaluated at the twenty-fifth and twenty-ninth meetings of the Committee and on both occasions toxicological monographs were prepared (Annex 1, references 56 and 70). At the twenty-ninth meeting, the Committee noted that the results of oral carcinogenicity tests in mice were negative but equivocal results were obtained in rats. The previously allocated temporary ADI of 0–12.5 mg/kg of body weight was extended until 1986 to permit the completion of histological examination of all groups of rats from a carcinogenicity study and biometric examination of the data.

The Committee evaluated the data from a detailed review of the histopathological effects of the compound in the long-term rat study and concluded that these indicated that Fast Green FCF is non-carcinogenic in rats.

An ADI of 0–25 mg/kg of body weight was allocated on the basis of the no-effect level in the long-term rat study.

An addendum to the existing toxicological monograph was prepared. The existing specifications were revised.

3.3.5 Lithol rubine BK

Lithol rubine BK was considered by the Committee in 1977 and 1982 (Annex 1, references 44 and 59) but insufficient data were available for evaluation and for establishing an ADI. At the present meeting the Committee considered the results of two long-term studies in mice and rats. In the mouse study, there was a dose-related increase in mortality and renal damage, but no detailed histopathological examination was conducted on the low- and intermediate-dose groups. The long-term study in rats was complicated by high mortality rates which led to a premature termination of the study for males, and limited histopathological examinations were carried out. In view of these limitations the Committee did not find it possible to determine an unequivocal no-effect level in either study and no ADI could be established.

Before the Committee can re-evaluate lithol rubine BK for the purpose of establishing an ADI, the following data will be required:
1. Results of a complete histopathological examination of all
dose-groups in the long-term mouse study.
2. Results of a new long-term study in rats.
3. An adequate reproduction/teratology study.
A toxicological monograph was prepared and the existing
specifications were revised in order to facilitate the identification of
appropriate materials to be used in further toxicological studies.

3.4 Sweetening agents

3.4.1 Mannitol

Mannitol was reviewed previously by the Committee at its
eighteenth meeting in 1974 (Annex 1, reference 35). A temporary
ADI of 0–50 mg/kg of body weight was established on the basis of
human data. In 1985 the Committee extended the temporary ADI
up to 1986, pending the submission of the results of a number of
long-term studies that had already been completed (Annex 1,
reference 70). This sugar alcohol is dehydrogenated to fructose and
then metabolized through the mammalian glycolytic pathway.
Mannitol occurs endogenously in humans. No mutagenic or
cytotoxic effect was found when mannitol was tested *in vitro* and *in vivo*. Teratogenic studies in several species did not reveal any
mannitol-related adverse effects. Mannitol was not carcinogenic in
rats and mice maintained on diets containing up to 50 g/kg.
Retinopathy and cataract formation occurred at an increased rate
in male rats in an early carcinogenicity study, but such effects were
not seen in four subsequent studies. An increase in the number of
benign thymomas was noted in female Wistar rats in a lifetime
feeding study, but this effect was not seen in three other studies
designed to determine whether the response was species specific. One
of the species tested (female Fischer rats) had an increased incidence
of adrenal medullary hyperplasia plus phaeochromocytoma
(Annex 1, reference 62). On the basis of these studies, the Committee
decided to allocate an ADI “not specified”.

Clinical experience with this substance as a therapeutic agent in
man has indicated no adverse effects. Mannitol is poorly absorbed
and exerts a laxative effect in man and animals, a common feature
of all polyols. This factor should be taken into account when
considering the levels of use of all polyols, either singly or in
combination (Annex 1, reference 62).
A toxicological monograph was prepared. The existing specifications were revised.

3.5 Thickening agents

3.5.1 Ethylhydroxyethyl cellulose

This substance was considered at the twenty-seventh meeting of the Committee in 1983 (Annex 1, reference 62). At that time, the Committee reviewed the general data available on ethylhydroxyethyl cellulose and decided to include it, on a temporary basis, in the group ADI of 0–25 mg/kg of body weight for modified cellulosics, pending the results of a 90-day feeding study, which were required by 1985. In 1985 the ADI was extended up to 1986 because the Committee was informed that the study was still in progress (Annex 1, reference 70).

At the present meeting, the Committee reviewed the results of the 90-day study in rats, which showed that ethylhydroxyethyl cellulose was not toxic when fed at high dietary levels. The Committee decided that ethylhydroxyethyl cellulose should continue to be included in the group ADI of 0–25 mg/kg of body weight for modified cellulosics.

A toxicological monograph was prepared. The existing tentative specifications were maintained.

3.5.2 Gums

The Committee recognized the limitations to feeding these substances at very high doses to animals because of their physical properties. The Committee decided to recommend an ADI “not specified” if no toxic effects were observed in animal feeding studies at the highest dose level possible, and if the findings were supported by appropriate human studies, provided that the Committee was satisfied that these studies were adequate.

Karaya gum. This substance was last evaluated at the twenty-ninth meeting of the Committee (Annex 1, reference 70), when the existing temporary ADI of 0–20 mg/kg of body weight was extended up to 1986, pending additional information on feeding studies in a non-rodent species. At the present meeting, a preliminary report of such a study was submitted to the Committee for review, but it lacked the detailed information needed for a proper evaluation. However, the Committee was informed that a feeding study in monkeys is in progress.
The Committee therefore agreed to extend the existing temporary ADI of 0–20 mg/kg of body weight and requested the submission of detailed information by 1988. No toxicological monograph was prepared. The existing specifications were maintained.

*Tara gum.* This substance was evaluated for the allocation of an ADI for man by the Committee in 1975, 1981, and 1984 (Annex I, references 38, 56, and 66, respectively). A temporary ADI of 0–12.5 mg/kg of body weight was allocated in 1981. Since the previous evaluation, additional data have become available and were considered at the present meeting.

Studies in rats on *in vivo* digestibility and caloric bioavailability show that tara gum is not digested by mammalian intestinal enzymes but is partially hydrolysed by the rat gut flora. Human gut enzymes do not hydrolyse this gum *in vitro*. Short-term studies in rats and dogs showed no evidence of adverse effects at a concentration of 50 g/kg of diet, and a long-term study in rats demonstrated no significant toxicity. No carcinogenic effects were observed in studies in mice and rats fed on diets containing 50 g/kg of tara gum. A reproduction study reviewed at an earlier meeting of the Committee indicated a possible effect of tara gum on lactation, since body weights and viability tended to be lower in the pups of rats given tara gum (50 g/kg of diet) than in the pups of controls given cellulose. A new study made available to the Committee indicated no evidence of embryonic or teratogenic effects. Consequently, the Committee allocated an ADI “not specified” for this substance. A toxicological monograph was prepared. The existing specifications were revised.

*Xanthan gum.* This gum was evaluated for the allocation of an ADI for man by the Committee in 1974 and 1985 (Annex I, references 35 and 70). An ADI of 0–10 mg/kg of body weight was established in 1974 and maintained in 1985. Since 1985, new information has become available and was considered at the present meeting.

In response to the Committee’s request, data were provided on the nature of the nitrogenous constituents of xanthan gum (equal to about 1% nitrogen by weight). About half of the nitrogenous matter is proteinaceous, and contains amino acid residues in the same proportions as in other food-grade gums. The rest is present as aminosugars, nucleic acids, and nucleotides.

A two-year study in rats failed to show any carcinogenic or other toxic effects attributable to the gum, and a reproduction study in rats also revealed no untoward effects. In addition, no toxic effects were
observed in the several short-term studies done in rats, rabbits, guinea pigs, and dogs. Several recent studies in man indicated no adverse effects at levels up to 10–13 g daily. The Committee, in keeping with the principles stated in section 2.2.3 in the twenty-ninth report regarding allocation of an ADI when no toxicity has been observed (Annex 1, reference 70), established an ADI "not specified" for this compound.

However, because of the potential for high exposure to xanthan gum and the fact that it is prepared from a microbial source not normally used in food, the Committee considers that an adequate long-term study in a second rodent species is desirable.

A new toxicological monograph was prepared. The existing specifications were revised.

3.5.3 Processed *Eucheuma* seaweed (semi-refined carrageenan)

The Committee recognized that simply processed seaweeds are used as a food in certain parts of the world. However, processed *Eucheuma* seaweed was brought to the attention of the Committee to be evaluated for proposed food additive use.

The Committee had no toxicological data to evaluate processed *Eucheuma* seaweed as a food additive, and no ADI was set. Further information is required before a toxicological evaluation can be made (see section 2.1.1). A toxicological monograph was not prepared.

In drawing up specifications for this substance the Committee recognized that a spectrum of products, ranging from native washed seaweeds to extracted and purified products such as carrageenan, are consumed in foods. The Committee considered it important to maintain clear distinctions between these products. It concluded that the name "semi-refined carrageenan" was inadequate to describe the true nature of the product and drew up new, tentative specifications under the name "processed *Eucheuma* seaweed" to assist in the identification of appropriate materials to be used in further toxicological studies.
3.6 Miscellaneous food additives

3.6.1 Glucono δ-lactone

This compound was evaluated for the establishment of an ADI by the Committee in 1966 and 1974 (Annex 1, references 13 and 35). The Committee allocated an ADI of 0–50 mg/kg of body weight in 1974. The Committee noted that, in an aqueous medium, glucono δ-lactone readily forms an equilibrium mixture of the lactone and gluconic acid. These are intermediates in the oxidation of glucose through the pentose phosphate cycle.

A long-term test in rats with a single level of glucono δ-lactone in the diet showed no evidence of carcinogenicity. Teratogenic tests have shown no abnormalities in several species. Glucono δ-lactone was not mutagenic in microbial tests.

Since glucono δ-lactone makes an insignificant contribution to the normal carbohydrate diet and it is metabolized into normal body constituents, the Committee decided to establish an ADI “not specified” for this compound. The Committee noted that single doses of glucono δ-lactone above 20 g exert a laxative effect in man. This fact should be taken into account when considering levels of use.

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

3.6.2 Mineral oil (food-grade) and hydrocarbon waxes

The Committee had evaluated mineral oil (food-grade) at its twentieth meeting (Annex 1, reference 41) and allocated an ADI “not specified”. The Committee was informed that some mineral oils in use at present are manufactured using new techniques and inadequate information was available on the safety and detailed specifications of these substances.

The Committee was informed that toxicity data were available for certain hydrocarbon waxes. The data included long-term feeding studies in rats, implantation studies in mice, and skin-painting studies in rabbits and mice. The Committee was not supplied with any data on other hydrocarbon waxes that are currently in use and that are manufactured using new techniques.

The Committee was also informed that, in a lifetime feeding study in rats, a blend of petroleum jelly (petrolatum) did not show any adverse effects.
The Committee noted that substances currently produced may differ from those for which toxicological data are available, since the toxicological tests were carried out on substances in commercial use in the 1960s. The Committee concluded that a thorough review of all food-grade mineral oil and hydrocarbon waxes, and petroleum jelly, including toxicological evaluation and detailed specifications, should be undertaken in 1988.

The Committee changed the present ADI for food-grade mineral oil to a temporary ADI “not specified”. No ADI was established for hydrocarbon waxes (food-grade) or petroleum jelly. No toxicological monograph was prepared.

This group of compounds includes products of both petroleum and synthetic origin. The Committee did not consider the synthetic hydrocarbon waxes at this meeting. The products derived from petroleum have variable paraffinic and naphthenic fractions and sulfur content and the Committee considered that better characterization of the products could be achieved if methods were developed for the routine identification of the various hydrocarbon species present. Information on the identity of the sulfur-containing compounds should be made available. The existing specifications for mineral oil, food-grade, were revised and made “tentative” and the name was changed to “mineral oil”. New, tentative specifications were prepared for petroleum jelly and paraffin wax.

3.6.3 Polyvinylpyrrolidone (PVP)

Polyvinylpyrrolidone was reviewed by the Committee at its twenty-ninth meeting in 1985 (Annex 1, reference 70), when the previous concerns about the toxicity of this substance per se were resolved and the question of contamination of polyvinylpyrrolidone with low levels of hydrazine was discussed. Although it was considered that the probability of adverse effects arising from such low levels of hydrazine was remote, the Committee at that time maintained the temporary ADI of 0–25 mg/kg of body weight, pending the submission of data to establish the lowest technically attainable level of hydrazine in the final product.

At the present meeting, the Committee was informed that current levels of hydrazine in the final product were 1 mg/kg or less. It was considered that this level of hydrazine did not represent a significant risk. The previous temporary ADI was changed to an ADI of 0–50 mg/kg of body weight. No toxicological monograph was
prepared. The existing tentative specifications were revised and the "tentative" qualification was deleted.

3.6.4 Sodium aluminium phosphate (acidic and basic)

Sodium aluminium phosphate was evaluated by the Committee in 1982 (Annex 1, reference 59), when concern was expressed that there was: (a) insufficient information on the aluminium content of the diet; and (b) a need for additional safety data, including absorption and metabolic studies in man, short-term feeding studies, and a multigeneration reproduction study. At the twenty-ninth meeting of the Committee (Annex 1, reference 70), limited new data from absorption studies, including a study in man, were considered, and it was noted that: (a) the accumulation of aluminium ions was increased in individuals with chronic renal disease; (b) aluminium had been implicated in the etiology of certain neurotoxic disorders, but definitive studies relating diet to these conditions were lacking; and (c) other dietary factors affected the absorption of aluminium. At that time the Committee concluded that the temporary ADI of 0–6 mg/kg of body weight (equivalent to 0–0.6 mg/kg of body weight expressed as aluminium) allocated to sodium aluminium phosphate until its review in 1986 should apply to all aluminium salts added to food. It was recommended that aluminium be reviewed in detail at a future meeting.

At the present meeting, the Committee reviewed several further studies on the absorption of aluminium from sodium aluminium phosphate and certain other aluminium compounds. These studies indicated that aluminium is poorly absorbed and, in the short term, does not accumulate in the body to a significant extent. On this basis the Committee considered that the temporary ADI for sodium aluminium phosphate (acidic and basic) could be extended, and confirmed that the temporary ADI of 0–0.6 mg/kg of body weight for aluminium should be applied to all aluminium salts added to food. The Committee reiterated the previous recommendation that aluminium (in all its forms) be reviewed in detail at a future meeting.

The Committee considered that, if data from adequate absorption/metabolic studies and short-term feeding studies demonstrated that there was no bioaccumulation of aluminium in the tissues, there would be no need for the previously required multigeneration reproduction study.
No toxicological monograph was prepared. The existing specifications for sodium aluminium phosphate (acidic) and sodium aluminium phosphate (basic) were maintained.

3.6.5 Sulfur dioxide and sulfites

These compounds were evaluated by the Committee in 1961, 1964, 1965, and 1973 (Annex 1, references 6, 8, 11, and 32). An ADI of 0–0.7 mg/kg of body weight was allocated in 1973 to sulfur dioxide and to sulfur dioxide equivalents arising from sodium metabisulfite, potassium metabisulfite, sodium sulfite, and sodium hydrogen sulfite. At subsequent reviews, calcium hydrogen sulfite, sodium thiosulfate, and potassium hydrogen sulfite were included in the group ADI (Annex 1, references 41, 47, and 62).

The present Committee considered earlier data in the light of the results of new studies performed since the last review. These included studies on the chemistry of sulfur dioxide in foods and its reactions with nutrients, and on metabolism, teratogenicity, mutagenicity, carcinogenicity, and effects on the gastric mucosa. In particular, the Committee gave consideration to adverse reactions (bronchoconstriction, anaphylactic-type reactions) in man.

In reviewing case studies and challenge tests relating to idiosyncratic sensitivity to sulfiting agents, the Committee noted the serious, life-threatening nature of the adverse effects in some cases and that several deaths associated with sulfate-treated foods had been reported. Such adverse reactions appear to occur principally, but not exclusively, in a subpopulation of sulfate-sensitive asthmatics and to be associated with consumption of salads treated with sulfate preparations; other vegetable products with high residual free-sulfite levels and sulfate-treated acidic beverages have less commonly been implicated. Many sulfate-treated processed foods contain a substantial proportion of their residual sulfur dioxide equivalents in bound form, but it is not known whether bound sulfur dioxide contributes to adverse reactions.

Although sulfiting agents can interact with DNA and may induce mutations in bacteria, in vivo mutagenicity studies in mammals were negative, as were long-term carcinogenicity studies on potassium and sodium metabisulfite in mice and rats, respectively. Sulfur(IV) oxoanions are normal intermediates in the metabolism of endogenous sulfur compounds in mammals and are oxidized enzymically to sulfate before urinary excretion. In general there is
a large reserve capacity of sulfite oxidase and the systemic toxicity of sulfites is low. This conclusion is supported by clinical experience with total parenteral nutrition solutions preserved with sulfiting agents.

While recognizing the utility and versatility of sulfiting agents as food additives, the Committee recommended that, where a suitable alternative method of preservation exists, its use should be encouraged, particularly in those applications (e.g., control of enzymic browning in fresh salad vegetables) in which the use of sulfites may lead to high levels of acute exposure and which have most commonly been associated with life-threatening adverse reactions. The Committee expressed concern about the use of sulfiting agents in foods in which such use may be unexpected by the consumer, particularly when there is no indication of their presence. The Committee also reiterated the view expressed at the twenty-seventh meeting (Annex 1, reference 62, section 2.4) that appropriate labelling was the only feasible means of offering protection to individuals who are intolerant of certain food additives.

The ADI of 0–0.7 mg/kg of body weight for sulfur dioxide and sulfur dioxide equivalents was retained. The Committee recommended that the situation with regard to the frequency of idiosyncratic adverse reactions and the relative toxic effects of free and bound sulfur dioxide should be kept under review. In addition, it requested information on the chemical forms of sulfur dioxide in food, and on the levels of gaseous impurities (such as hydrogen sulfide, sulfur trioxide) in sulfur dioxide. A toxicological monograph was prepared. The existing specifications for sulfur dioxide were revised and designated as tentative.

3.6.6 Talc

Magnesium silicates (including talc and magnesium trisilicate) were considered at the thirteenth meeting of the Committee in 1969 (Annex 1, reference 19). The Committee decided not to limit the use of these materials in food, provided that the amounts used were consistent with good manufacturing practice.

In 1973, at the seventeenth meeting, the Committee (Annex 1, reference 32) changed the “not limited” ADI for magnesium silicate (talc and magnesium trisilicate) to a temporary “not limited” ADI until 1976, pending: (a) studies to investigate the kidney damage
reported to be produced in dogs by magnesium trisilicate, (b) long-term studies on talc demonstrated to be free from asbestos-like particles; and (c) the development of a satisfactory method for estimating asbestos-like particles in talc and magnesium trisilicate.

In 1976, at the twentieth meeting, the Committee reiterated the need for a long-term study on talc of an acceptable specification before an ADI could be recommended (Annex 1, reference 41). The Committee required short-term studies by 1980 to differentiate between the medicinal magnesium trisilicate and the insoluble magnesium silicate used in food processing, and allocated magnesium silicate a temporary ADI “not specified”.

In 1980 (Annex 1, reference 53), the Committee extended the previous temporary ADI “not specified” for talc (Annex 1, reference 32) and requested a long-term study for 1983. Also in 1980, studies available to the Committee showed that talc was not mutagenic in vitro or in vivo. The temporary ADI “not specified” of magnesium silicate was extended to 1982 because certain short-term studies requested were not available. In 1982 (Annex 1, reference 59), no additional information was made available on magnesium silicate. However, the existing tentative specifications were revised to exclude the presence of magnesium trisilicate. Thus, in 1982, the Committee reallocated the ADI “not specified” for magnesium silicate. This decision was confirmed in 1985 (Annex 1, reference 70, section 2.2.2).

In 1983 (Annex 1, reference 62), talc was removed from the agenda since no new data were available. Revised specifications on talc were available to the Committee at the present meeting, indicating a satisfactory method for estimating asbestos-like particles in the talc used in food processing by the use of transmission electron microscopy. The Committee was informed that food-grade talc has a solubility of less than 10 g/litre in water and does not contain magnesium trisilicate.

In view of these clarifications, the Committee decided to withdraw the previous request for a lifetime feeding study, provided that the talc used in food processing complied with the new specifications. The Committee allocated an ADI “not specified”.

No toxicological monograph was prepared.

The Committee was aware that there is usually a requirement for asbestiform particles to be excluded from food-grade talc. However, the Committee received information suggesting that the light microscopy method previously specified for detecting asbestos in talc was incapable of achieving the degree of accuracy required by the
limit specified. The Committee was not able to identify a reliable but simple alternative method, with the exception of transmission electron microscopy, as identified above. Therefore, the Committee stressed the need to develop a practical method that can be used to detect asbestos in talc on a routine basis at the levels required (see section 2.2.4).

The existing specifications were revised and designated as "tentative".

3.7 Contaminants

3.7.1 Lead (evaluation of health risk to infants and children)

Lead was previously evaluated by the Committee at the sixteenth meeting (Annex 1, reference 30). A Provisional Tolerable Weekly Intake (PTWI) of 3 mg of lead per person, equivalent to 50 μg/kg of body weight, was established at that time. The Committee had indicated that this level did not apply to children. Because of the special concern for children and infants, the Committee at the present meeting evaluated the health risks of lead to this group. The Committee noted that valuable guidelines for evaluating these risks were provided by the previous principles governing the toxicological evaluation of metal contaminants (Annex 1, reference 30, section 3.1), as well as by the principles contained in a recent report on the needs for a special approach to evaluating health risks during infancy and early childhood.1

The reason for special concern for children and infants relates to a number of factors, including: (a) higher metabolic rate than adults; (b) rapid rate of growth of the body; (c) individual differences in body composition; (d) immaturity of the kidneys, liver, nervous system, and immune systems; and (e) incomplete development of organs and tissues such as bones and brain. Since infants and children have higher energy requirements than adults, their intake of food, and hence of contaminants, per unit body weight is greater than that of adults. In addition, particular behavioural characteristics of children, such as heightened hand-to-mouth activity and the ingestion of non-food items (pica), may result in significant exposure to lead from non-food sources. Social and

cultural attitudes related to child rearing may influence exposure to non-food sources. Because the evaluation of the health effects of lead relates to exposure from all sources, any increase in the intake of lead from non-food sources (e.g., water and air) will reduce the amount that can be tolerated from food. It is important to identify the sources of exposure that may be of greater significance to infants and children than to adults, so that strategies for control may be developed.

Detailed information on sources of lead exposure is available.\(^1\)\(^2\) Sources include the general environment, the domestic environment, food, air, and drinking-water. The domestic environment is a particularly important source of lead exposure for children and infants, and includes indoor dust, top soil, and paint. The two publications below also provide detailed information on levels of lead in food and total intake for infants and children.\(^1\)\(^2\)

There is a large amount of information on the toxic effects of lead. The information used by the Committee for its evaluation has been largely derived from studies with infants and children. Adults normally absorb 5–10% of dietary lead, but children absorb lead from the diet with greater efficiency. Children with lead intakes of 5 µg/kg of body weight per day are in positive balance and retain lead. The net absorption of dietary lead at this level averages 40% of the lead intake, and the net retention has been estimated to be about 30% of the intake. However, metabolic studies indicate a negative balance when lead intake is less than 4 µg/kg per day. The relationship between oral lead intake and blood lead levels is nonlinear, with the greatest increases in blood lead levels occurring at the lower range of exposure.

The Committee considered the available information and, on the basis of evidence that a mean daily intake of 3–4 µg/kg of body weight of lead by infants and children is not associated with an increase in blood lead levels, established a PTWI of 25 µg/kg of body weight. This level refers to lead from all sources. A toxicological monograph was prepared.

The Committee recognizes that in some situations the PTWI may be exceeded and blood lead may reach a level of more than

250 μg/litre. In such circumstances, the major source(s) of exposure should be determined and all possible steps taken to ensure that lead levels in food and contributions from other environmental sources are minimized. The following are possible strategies for achieving this.

The reduction or elimination of the use of lead solder and other lead-containing materials in equipment and containers coming into contact with food during its processing and handling can reduce lead contamination of foodstuffs.

Lead contamination of foods in tinplate cans with lead-soldered side-seams originates mainly from the solder. Such contamination can be reduced by operating the can-making equipment in such a way as to minimize the contamination of the inside of the can with the solder,1 replacing high-lead solder by low-lead or lead-free solder, and lacquering the cans after soldering. Other ways of reducing lead contamination of canned foods include: (a) using electro-welding or other techniques instead of soldering to manufacture the can; (b) using two-piece cans instead of three-piece cans; (c) limiting the level of lead permitted in the tin used to manufacture tinplate for food cans; and (d) replacing tinplate cans by other types of container.

Certain glazes used on ceramic foodware contain appreciable levels of lead. If such foodware is not fired correctly, it may release large amounts of lead into foods that come into contact with it, especially if they are acidic. The contamination of foods with lead from this source can be reduced by using lead-free glazes. Foodware can be checked for levels of leachable lead using one of the standardized methods now available.

Contamination of drinking-water with lead from plumbing systems can be eliminated by replacing the lead in such systems with other materials. If this cannot be done, contamination of soft water (pH 4.5–5.5) with lead from plumbing systems can be reduced by increasing the pH of the water to about pH 8.5 by the addition of lime.

In some circumstances, tetra-alkyl lead used as a petrol additive is a major source of environmental lead pollution. Lead in motor vehicle exhausts increases lead exposure of infants and young

---

children in several ways. Elevated lead levels in air directly increase lead exposure via inhalation. Atmospheric deposition of lead on growing crops or the use of sewage sludge contaminated with lead from highway runoff as fertilizer on agricultural land can result in increased lead levels in foodstuffs and animal fodder, and thus can indirectly increase dietary exposure. This type of lead pollution can be reduced by decreasing or eliminating the use of lead compounds as petrol additives.

House paints manufactured in the past sometimes contained high levels of lead, and therefore it is prudent to warn the parents of young children about the serious health hazards associated with the ingestion of flakes of such paint. Similar considerations apply to the use of lead in cosmetics and toys.

The discharge of lead into the environment by industry (e.g., lead ore mines and primary and secondary lead smelters) and from waste disposal may give rise to high levels of pollution locally. If such pollution cannot be reduced, careful attention should be given to the problems inherent in the consumption of heavily lead-contaminated food produced in areas affected by such pollution.

High lead levels from environmental sources in dust and soil can result in increased ingestion of lead by young children due to sucking of contaminated fingers and mouthing or swallowing of other non-food items contaminated with dust. Simple measures, such as teaching young children to wash their hands before eating, can help reduce lead exposure from contaminated dust.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS AND GENERAL METHODS

4.1 Specifications

4.1.1 Anthocyanins (other than grape-skin)

Although detailed information had been received only for anthocyanins derived from blackcurrants, the Committee noted the existence of products extracted from a variety of other materials and recognized the need to develop specifications that would cover all of them. New, tentative specifications were prepared for the product derived from blackcurrants and a request was made for information on: (a) the use of antioxidants in this product; (b) the level
and method of assay; (c) degradation products; and (d) a chromatographic identification test.

4.1.2 Calcium disodium ethylenediaminetetraacetate

The existing tentative specifications were revised and the "tentative" qualification was deleted.

4.1.3 Carob bean gum

The Committee was asked to consider the inclusion of limits on solvent residues in the specifications for carob bean gum. However, no information was provided on the use of solvents or their residues. The existing tentative specifications were revised and maintained as tentative, pending receipt of information on solvents.

4.1.4 Citric and fatty acid esters of glycerol

The Committee requested information on the assay procedure for determining the sum of citric acid, fatty acids, and total glycerol present. It also requested information on the method for measuring fatty acids. The existing tentative specifications for citric and fatty acid esters of glycerol were revised and the "tentative" qualification was maintained.

4.1.5 Heptane

The Committee noted that the product formerly referred to as heptane is in fact a mixture of hydrocarbons with the predominant general formula C₇H₁₆. The existing tentative specifications were revised and the name was changed to "heptanes". The "tentative" qualification was deleted.

4.1.6 Lecithins

The Committee received a request to make provision for hydrolysed lecithin within the specifications for lecithins. Insufficient information on the precise method of manufacture and identity of the hydrolysed product was provided to justify the request. The existing tentative specifications for lecithins were revised, the name was changed to "lecithin", which is the name in common use, and
the “tentative” qualification was retained pending receipt of information on the “peroxide value” appropriate to bleached lecithin. New tentative specifications were prepared for partially hydrolysed lecithin and a request was made for information on: (a) the type of enzyme used for its preparation; (b) its composition; and (c) tests for residual enzyme activity and for distinguishing hydrolysed lecithin from lecithin.

4.1.7 Potassium DL-malate solution

The Committee was unaware of any commercial use of this product. The existing tentative specifications were withdrawn.

4.1.8 Sodium dihydrogen citrate, sodium fumarate, and sodium DL-malate

The existing tentative specifications for sodium dihydrogen citrate, sodium fumarate, and sodium DL-malate were revised and the “tentative” qualifications were deleted.

4.2 General methods

4.2.1 Limit test for solvent residues

The Committee considered it necessary to unify the methods included in the specifications of individual additives for the analysis of solvent residues. A new single method was drawn up for inclusion in the list of general methods.

4.2.2 Test for the identification of gum constituents

Certain practical difficulties are associated with the existing general method for the identification of gum components. The existing general method was revised.

4.2.3 Analysis of food colours

The Committee recognized the desirability of having available an alternative rapid method (or methods) for verifying the identity of food colours and for limit tests on subsidiary colours. A tentative alternative general method was prepared and the Committee invited comments on its applicability.

40
5. PRINCIPLES FOR THE SAFETY ASSESSMENT OF FOOD ADDITIVES AND CONTAMINANTS IN FOOD

The Committee reviewed a draft of a monograph on the principles for the safety assessment of chemicals in food, prepared by a group of experts under the auspices of the International Programme on Chemical Safety in response to the Committee's repeated recommendations (Annex 1, references 56, 59, and 62). The Committee had discussed the preparation of this monograph at its twenty-eighth meeting (Annex 1, reference 66) and had reviewed an earlier draft at its twenty-ninth meeting (Annex 1, reference 70).

After discussion and minor modifications, the monograph was approved by the Committee. It will be published by the World Health Organization. The Committee recommended that the document be published at the earliest possible date and that arrangements be made for a wide distribution.

6. FUTURE WORK

1. The list of general methods of tests for the Committee's specifications (Annex 1, reference 65) should be updated, especially with reference to food colours and cellulose derivatives, and methods adopted by the Committee since the previous publication should be included.

2. The Committee adopted the recommendation of the Codex Committee on Food Additives to place tin on the priority list of substances for consideration when new significant data become available.

3. The intakes of arsenic and cadmium should be reviewed, especially regarding their presence in foods for infants and children.

4. The Committee over previous years has allocated to many substances an ADI "not specified". The intakes of these substances, particularly as regards their use in foods for infants and children, should be studied to establish whether these ADIs remain appropriate.

5. Several of the Committee's specifications provide for the use of solvents in the production of food additives. For consistency, these specifications need to be reviewed as a group, with a

---

toxicological evaluation of the solvent residues being undertaken as appropriate.

6. The Committee noted that several substances are being used as chewing-gum bases, most of which have not been evaluated. These substances should be reviewed as a group.

7. The Committee recommended that a thorough review of waxes, oils, and other petroleum products be carried out, and that all available data on specifications and toxicity studies of these substances be submitted for evaluation in 1988.

8. The composition of and specifications for glycerol esters of fatty and other organic acids should be reviewed as a group.

9. The Committee had previously expressed the opinion that a full ADI could be allocated only to those substances for which full specifications were available. The Committee noted that this principle had not been applied uniformly and recommended that the situation be reviewed.

10. In view of the lack of information regarding the chemical forms of sulfur dioxide responsible for adverse reactions in man, the Committee recommended that the chemical forms and levels of sulfur dioxide in various foods and beverages and their relationship with adverse reactions should be reviewed at a future meeting.

11. Aluminium, in all its forms, should be the subject of a detailed review at a future meeting.

7. RECOMMENDATIONS TO FAO AND WHO

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

2. A number of specifications remain tentative because of lack of data on certain chemical-purity criteria, microbiological criteria, or methods of analysis. FAO and WHO should take all steps necessary to obtain the data necessary to complete these specifications.

3. In addition to other criteria, it is recommended that FAO and WHO obtain evidence that substances are actually used or proposed for use as food additives before including them in the list for evaluation by the Committee. For all substances to be evaluated, the Committee reiterated that all data should be submitted well in advance of the meeting.
4. The Committee reiterated the need to establish priorities for testing and evaluating food additives and for reviewing the data requirements for toxicological evaluations, in particular for flavouring agents, as recommended in the Principles for the safety assessment of food additives and contaminants in food.¹

5. The Committee was not provided with information on the manufacture or use in foods of several substances on its agenda, despite requests for such information. Specifications should be withdrawn for substances for which essential information is not submitted within a reasonable time.

6. FAO and WHO should encourage governments through the Joint FAO/WHO Food Contamination Monitoring Programme to include routine checks for lead in foods for infants and young children as part of their national programmes for monitoring food contamination.

7. FAO and WHO should take action to provide governments, through the Joint FAO/WHO Food Contamination Monitoring Programme, with information on the exposure of infants and young children to lead contamination in foods, and on lead intakes, in order to allow them to take the necessary action to reduce such contamination.

8. Since the report of the Committee is vital to the work of the Joint FAO/WHO Food Standards Programme, and in order to expedite the dissemination of the information it contains to member states, FAO and WHO should take the necessary steps to ensure the distribution of a summary of the report as soon as possible after each meeting.

9. In order to generate the information needed for the toxicological examination of seaweeds and their products used as food additives, FAO and WHO should consider ways and means of providing assistance to developing countries in which revenues from food additives prepared from seaweed products are an important part of the economy. The assistance could be in the form of strengthening the research capabilities in the developing countries concerned or the provision of funds to evaluate the substances elsewhere.

10. During its review of specifications for food colours the Committee was aware that several methods required the use of

standard reference materials. The Committee recommends that FAO and WHO encourage manufacturers of food colours, national governments, and international bodies to make such standards available, in order to facilitate the use of the specifications.
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 RECOMMENDATIONS, AND INFORMATION ON SPECIFICATIONS**

<table>
<thead>
<tr>
<th>Specifications¹</th>
<th>ADI for man (mg/kg of body weight) and other toxicological recommendations</th>
</tr>
</thead>
</table>

### A. Food Additives

#### Antioxidants
- Butylated hydroxyanisole (BHA) R 0.3³
- Butylated hydroxytoluene (BHT) R 0.125²
- Dodecyl gallate R No ADI allocated³
- Octyl gallate R No ADI allocated³
- Propyl gallate R 2.5
- Tertiary butylhydroquinone (TBHQ) R 0.2³
- Tocopherol, d-α R 0.15
- Tocopherol, d-a-concentrate N 2.4 ⁵

#### Flavouring agents
- d-Carvone R 1.1⁵
- l-Carvone R 0.14³

#### Food colours
- Brown FK R No ADI allocated³
- Curcumin R 0.1³
- Erythrosine R 0.6²
- Fast Green FCF R 0.25
- Lithol rubine BK R No ADI allocated³
- Turmeric oleoresin O 0.3²

#### Sweetening agents
- Mannitol R ADI "not specified"⁶

#### Thickening agents
- Ethylhydroxyethyl cellulose S 0.25³
- Karaya gum S 0.2⁰
- Processed *Eucheuma* seaweed N, T No ADI allocated³
- Tara gum R ADI "not specified"⁶
- Xanthan gum R ADI "not specified"⁶
<table>
<thead>
<tr>
<th>Specifications(^1)</th>
<th>ADI for man (mg/kg of body weight) and other toxicological recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscellaneous food additives</strong></td>
<td></td>
</tr>
<tr>
<td>Glucono δ-lactone</td>
<td>R</td>
</tr>
<tr>
<td>Hydrocarbon waxes</td>
<td>N, T(^8)</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>R, T</td>
</tr>
<tr>
<td>Petroleum jelly</td>
<td>N, T</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP)</td>
<td>S</td>
</tr>
<tr>
<td>Sodium aluminium phosphate, acidic S</td>
<td>S</td>
</tr>
<tr>
<td>Sodium aluminium phosphate, basic S</td>
<td>R, T(^10)</td>
</tr>
<tr>
<td>Sulfur dioxide and sulfites</td>
<td>R, T</td>
</tr>
<tr>
<td>Talc</td>
<td></td>
</tr>
</tbody>
</table>

**B. Contaminants**

- Lead (children and infants) \([25 \mu g/kg of body weight]\(^{11}\)

<table>
<thead>
<tr>
<th>Specifications only(^2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackcurrant extract</td>
<td>N, T</td>
</tr>
<tr>
<td>Calcium disodium ethylenediaminetetraacetate</td>
<td>R</td>
</tr>
<tr>
<td>Carob bean gum</td>
<td>R, T</td>
</tr>
<tr>
<td>Citric and fatty acid esters of glycerol</td>
<td>R, T</td>
</tr>
<tr>
<td>Heptanes</td>
<td>R</td>
</tr>
<tr>
<td>Lecithin</td>
<td>R, T</td>
</tr>
<tr>
<td>Lecithin, partially hydrolysed</td>
<td>N, T</td>
</tr>
<tr>
<td>Potassium malate solution, DL-</td>
<td>W</td>
</tr>
<tr>
<td>Sodium dihydrogen citrate</td>
<td>R</td>
</tr>
<tr>
<td>Sodium fumarate</td>
<td>R</td>
</tr>
<tr>
<td>Sodium malate, DL-</td>
<td>R</td>
</tr>
<tr>
<td>Tocopherol concentrate, mixed</td>
<td>N</td>
</tr>
<tr>
<td>Turmeric colour</td>
<td>N, T</td>
</tr>
</tbody>
</table>

\(^1\) 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; W, previously established specifications withdrawn.

\(^2\) Temporary acceptance (see Further Toxicological Studies and Information Required or Desired).
3 Insufficient information available to establish an ADI.
4 The lower value represents the daily dietary allowance recommended by the USA National Academy of Sciences/National Research Council. The upper value represents the maximum value for the ADI.
5 ADI applies to the two listed compounds, alone or in combination.
6 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 ADI expressed in numerical form is not deemed necessary.
7 Group ADI for modified celluloses.
8 New tentative specifications for paraffin wax were prepared.
9 Group temporary ADI for aluminium salts expressed as aluminium.
10 Revised tentative specifications for sulfur dioxide were prepared.
11 Provisional tolerable weekly intake (PTWI).
Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

Antioxidants

*Butylated hydroxyanisole (BHA)*¹

Submission of results of:
1. Studies to explore the potential of BHA to cause oesophageal hyperplasia in pigs and monkeys. The studies should be conducted with dietary BHA. The Committee recognizes the technical difficulties in carrying out the study in monkeys due to potential diet rejection, but emphasizes that it should nevertheless be attempted.
2. Multigeneration reproduction study.

*Butylated hydroxytoluene (BHT)*²

1. Investigation of the hepatocarcinogenicity of BHT in rats after *in utero* exposure.
2. Results of studies on the mechanism of the haemorrhagic effect of BHT in susceptible species.

*Tertiary butylhydroquinone (TBHQ)*²

1. Results of lifetime feeding studies in two rodent species. The feeding studies should take into account the normal degradation products of TBHQ in food.
2. It would be desirable for additional studies to be carried out to resolve questions related to the genotoxicity of TBHQ.

Flavouring Agent

*d–Carvone and l–carvone*¹

Submission of the results of long-term and/or carcinogenicity feeding studies in mice and rats known to be in progress or completed.

¹ Information required by 1988.
² Information required by 1990.
Food colours

*Curcumin*¹

Submission of results of:
1. A long-term carcinogenicity study in a rodent species; this study is known to be nearing completion.
2. A reproduction/teratogenicity study on curcumin.

*Erythrosine*²

Results of pharmacokinetic studies that relate the amount of absorption to the amount ingested, which would enable a correlation to be established between blood/tissue levels of erythrosine and its effects on the thyroid.

*Turmeric oleoresin*³

Results of a short-term study in the pig or another non-rodent species. A clear no-effect level should be established. If the study is performed in a species other than the pig, the design of the study should be such that it allows the sensitivity of the test species to be compared with that observed in the pig in the earlier study reviewed by the Committee.

Thickening agents

*Karaya gum*²

Results of a feeding study in monkeys that is known to be in progress.

Miscellaneous food additives

*Mineral oil (food-grade)*²

Data on all food-grade mineral oils and hydrocarbon waxes and petroleum jelly, including toxicological information and detailed specifications, should be made available to the Committee for a thorough review.

¹ Information required by 1989.
² Information required by 1988.
Sodium aluminium phosphate

Data on aluminium, in all its forms, including sodium aluminium phosphate, should be made available to the Committee for a detailed review at a future meeting.
MATTERS ARISING FROM THE REPORTS OF SESSIONS OF THE CODEX COMMITTEE ON FOOD ADDITIVES

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

1. Acute toxicity of tin

The Committee was informed that CCFA was concerned about the observation that canned fruit-based beverages containing 200 mg of tin per kg of beverage may result in acute gastric irritation. CCFA requested the Committee to provide further information on this observation as well as on the health significance of the 200 mg/kg threshold level in relation to setting maximum levels of tin in food.

The Committee noted that this observation, which appeared in the report of its twenty-sixth meeting (Annex 1, reference 59), was based on certain reports available to the Committee at that meeting, and expressed the view that the observation should be considered ancillary to other toxicological information. The Committee held the view that the allocated provisional value for maximum tolerable daily intake of tin of 2 mg/kg of body weight should not be exceeded. The Committee agreed to the recommendation of CCFA to place tin on the priority list of substances for consideration when new significant data become available.

2. Intake of arsenic and cadmium by infants and children

CCFA inquired whether the tolerance levels established for arsenic and cadmium apply to infants and children. The Committee expressed the view that the provisional tolerable intake for man for these contaminants is equally applicable to infants and children and to adults, as stated at the twenty-first meeting (Annex 1, reference 44). The Committee, however, recalled the discussions at the twenty-first meeting on the problems of exposure of infants and children to contaminants, and the recommendation that the intake of contaminants by infants and children should be limited to as low a
level as possible. The Committee agreed that the problem of arsenic and cadmium intake by infants and children is worthy of consideration at a future meeting.

3. Setting priorities for evaluation of flavours

CCFA emphasized the need to establish priorities for the evaluation of flavouring agents. The Committee reiterated the recommendations contained in its twenty-ninth and earlier reports and suggested that CCFA should, as an initial step, collect relevant data, including information on the patterns of use of the flavouring agents (see section 2.1.2).

4. Residues of sulfur dioxide in food

The Committee was informed of the concern of CCFA about sulfur dioxide and sulfiting agents and was asked to consider the following issues:
(a) idiosyncratic sensitivity to sulfur dioxide;
(b) the fact that the ADI is regularly exceeded by some population subgroups;
(c) the relative toxicity of free and bound sulfur dioxide residues in food, and their ability to provoke idiosyncratic reactions.
Sulfur dioxide and sulfites were considered by the Committee at the present meeting (see section 3.6.5 on page 32).

5. Thickening agents

CCFA had requested guidance regarding the effect of thickening agents on the gut flora and on the absorption of nutrients. The Committee had no information to suggest that thickening agents affect nutrient absorption when they are used according to good manufacturing practices and when the ADI is not exceeded.

57
Recent reports:

No.  | Title                                                                 | Pages   | Price (Sw. fr.) |
---  |----------------------------------------------------------------------|---------|-----------------|
705  | The role of food safety in health and development                      | 79 pages| 7.               |
706  | The use of epidemiology in the study of the elderly                    | 84 pages| 8.               |
707  | Recommended health-based occupational exposure limits for respiratory irritants |         |                  |
708  | Education and training of nurse teachers and managers with special regard to primary health care | 154 pages| 14.              |
709  | WHO Expert Committee on Rabies                                         | 104 pages| 9.               |
710  | Evaluation of certain food additives and contaminants                 | 44 pages| 5.               |
711  | Advances in malaria chemotherapy                                       | 218 pages| 20.              |
712  | Malaria control as part of primary health care                        | 73 pages| 8.               |
713  | Prevention methods and programmes for oral diseases                   | 46 pages| 5.               |
714  | Identification and control of work-related diseases                   | 71 pages| 7.               |
715  | Blood pressure studies in children                                    | 36 pages| 5.               |
716  | Epidemiology of leprosy in relation to control                        | 60 pages| 6.               |
717  | Health manpower requirements for the achievement of health for all by the year 2000 through primary health care | 92 pages| 8.               |
718  | Environmental pollution control in relation to development            | 63 pages| 6.               |
719  | Arthropod-borne and rodent-borne viral diseases                       | 116 pages| 10.              |
720  | Safe use of pesticides                                               | 60 pages| 6.               |
721  | Viral haemorrhagic fevers                                             | 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.—
<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
<th>Pages</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>The biology of malaria parasites</td>
<td></td>
<td>32.—</td>
</tr>
<tr>
<td></td>
<td>Report of a WHO Scientific Group (229 pages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Hospitals and health for all</td>
<td></td>
<td>12.—</td>
</tr>
<tr>
<td></td>
<td>Report of a WHO Expert Committee on the Role of Hospitals at the First Referral Level (82 pages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>WHO Expert Committee on Biological Standardization</td>
<td></td>
<td>20.—</td>
</tr>
<tr>
<td></td>
<td>Thirty-sixth Report (149 pages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Community-based education for health personnel</td>
<td></td>
<td>12.—</td>
</tr>
<tr>
<td></td>
<td>Report of a WHO Study Group (89 pages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Acceptability of cell substrates for production of biologics</td>
<td></td>
<td>5.—</td>
</tr>
<tr>
<td></td>
<td>Report of a WHO Study Group (29 pages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td></td>
<td>9.—</td>
</tr>
<tr>
<td></td>
<td>Thirtieth Report (50 pages)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>