EVALUATION OF FOOD ADDITIVES
SPECIFICATIONS FOR THE IDENTITY AND PURITY OF
FOOD ADDITIVES AND THEIR TOXICOLOGICAL EVALUATION:
SOME EXTRACTION SOLVENTS AND CERTAIN OTHER SUBSTANCES;
AND A REVIEW OF THE TECHNOLOGICAL EFFICACY
OF SOME ANTIMICROBIAL AGENTS

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

Geneva, 24 June–2 July 1970

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Specifications for the substances considered in this report, monographs containing summaries of relevant biological data and toxicological evaluations, and a review of the technological efficacy of some antimicrobial agents will be issued by FAO and WHO in separate publications entitled:

1. *Toxicological evaluation of some extraction solvents and certain other substances*
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2. *Specifications for the identity and purity of some extraction solvents and certain other substances*
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— 2 —
# CONTENTS

1. Introduction ............................................. 5

2. Principles governing the establishment of specifications .... 6
   2.1 Scope .............................................. 6
   2.2 Microbiological requirements .......................... 6
   2.3 Analytical methods .................................. 7

3. Principles governing toxicological evaluations ............... 7
   3.1 General guidelines and acceptable daily intakes .......... 7
   3.2 Special considerations ............................... 7

4. Special considerations relating to solvents ................. 9
   4.1 Chemical aspects ................................... 9
   4.2 Toxicological aspects ................................ 9
   4.3 Solvent residues .................................... 10
   4.4 Impurities in solvents ............................... 11
   4.5 Interaction with food ................................ 11

5. Comments on substances on the agenda ..................... 12
   5.1 Items not considered further .......................... 12
   5.2 Items briefly considered ............................. 12
   5.3 Evaluation .......................................... 13
      5.3.1 Miscellaneous food additives ................. 13
      5.3.2 Filtration aids and clarifying agents ......... 16
      5.3.3 Heavy metal contaminants and related additives 17
      5.3.4 Extraction solvents ............................ 20
      5.3.5 Miscellaneous items ............................ 23

6. Review of technological efficacy of some antimicrobial agents 24
   6.1 Methods of analysis in food .......................... 24
   6.2 Review of efficacy .................................. 24

7. Estimation of food additive intake .......................... 25

8. Recommendations ......................................... 26
   8.1 Recommendations to FAO and WHO ..................... 26
   8.2 General recommendations ............................. 26

Annex 1. Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives .............. 27
Annex 2. List of food additives on the agenda ................ 29
Annex 3. Impurities in solvents ............................. 31
Annex 4. Resolution WHA23.50 of the Twenty-third World Health Assembly 33
Annex 5. Toxicological evaluations: miscellaneous food additives and contaminants ............................. 34
Annex 7. Toxicological evaluations: extraction solvents ........ 36
JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Geneva, 24 June - 2 July 1970

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

A Joint FAO/WHO Expert Committee on Food Additives met in
Geneva from 24 June to 2 July 1970. The meeting was opened by
Dr. L. Bernard, Assistant Director-General, WHO, on behalf of the
Directors-General of the Food and Agriculture Organization of the United
Nations and of the World Health Organization.

1. INTRODUCTION

As a result of the recommendations of the Joint FAO/WHO Conference
on Food Additives held in September 1955, a thirteen Joint FAO/WHO
Expert Committees on Food Additives have met (see Annex 1).

The present meeting was convened on the recommendations made in
the thirteenth report of the Joint FAO/WHO Expert Committee on Food
Additives. Its terms of reference were: (1) to draw up specifications for
and to make a toxicological evaluation of certain food additives, and
(2) to review the technological efficacy of certain antimicrobial agents
(see Annex 2). Most of the substances considered had been suggested by
the Codex Committee on Food Additives, to which the Expert Committee
acts as an advisory body on questions of toxicity, specifications for identity
and purity, and methods of analysis. Some of these substances, notably
cyclamates, monosodium glutamate, and mercury, have achieved so much
notoriety that the delegates to the Twenty-third World Health Assembly
adopted a resolution concerning the health hazards of food additives
(see Annex 4).

Series*, 1956, No. 11.
In order to facilitate the discussions, the Committee constituted itself into two groups, one of which gave major attention to toxicological evaluation and the other to chemical specifications and technological efficacy.

2. PRINCIPLES GOVERNING THE ESTABLISHMENT OF SPECIFICATIONS

As stressed in previous reports, the specifications of a food additive play an important role in its toxicological evaluation.

2.1 Scope

As in the past, the specifications have been developed for use by toxicologists and others concerned with the identity and purity of food additives, their purpose being to prescribe an adequate degree of purity that should be met by the substances. The specifications are not necessarily suitable for commercial use, since they may not take into account all the criteria that are of interest to the commercial user. However, references are made in the individual specifications to some of the criteria that may be of interest in commerce. Since the specifications for additives are intended for use at an international level, each specification should be drawn up in such a way as to encompass suitable products of manufacturers all over the world.

As in previous meetings,¹ the Committee agreed that specifications would be developed for those substances that are manufactured commercially and that have been recognized by the Committee as being used in food processing. The specifications for identity and for purity, together with the methods of analysis where applicable, will be set out in a separate publication (see page 2). Where a complete specification cannot be developed owing to lack of information, a tentative specification will be given, indicating the additional information required.

2.2 [Microbiological requirements]

Attention is drawn to the recommendation made in the thirteenth report ² regarding microbiological contamination of food additives produced from natural sources. The Committee agreed to include some criteria for microbiological quality when considering proteinaceous substances, such as gelatin and sodium caseinate.


2.3 Analytical methods

Although newer analytical methods are being continually developed and the sensitivity and reliability of existing methods are being improved, the methods cited, or others based on similar principles, should be considered adequate at present for international purposes.

3. PRINCIPLES GOVERNING TOXICOLOGICAL EVALUATIONS

3.1 General guidelines and acceptable daily intakes

The Committee again adopted the same general principles for the establishment of acceptable daily intakes (ADI) set out in previous relevant reports of the Joint FAO/WHO Expert Committee on Food Additives. The definitions of ADIs have already been stated in the thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives.\(^1\) Emphasis was placed on the more recent advances in toxicological and biochemical methodology and interpretation set forth in the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives.\(^2\)

3.2 Special considerations

A number of items on the agenda gave rise to consideration of matters of principle.

3.2.1 Evaluation of a toxic metabolite formed by intestinal microflora

The formation of cyclohexylamine from cyclamate again exemplifies the possibility of the generation of toxic metabolites from food additives. In this instance, the microflora of the alimentary tracts of man and of the animal species used in toxicological testing behave similarly. In other instances, however, it is possible that the different micro-organisms colonizing human and animal intestinal tracts could generate different toxic metabolites from the same food additive.

3.2.2 Food additives that are also natural constituents of the diet

Since no general principles could be formulated in connexion with the evaluation of glutamates, phosphates and copper, each substance had to be evaluated on an individual basis.

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3.2.3 Extrapolation to man of animal data indicating a "vulnerable age" of toxicological reactivity

The possibility exists that high doses of glutamate produce brain lesions in newborn animals. Any attempt to interpret these data in terms of human neonates and infants involves the problem of how far developmental stages in animal species and in man can be considered equivalent in relation to vulnerability to possible effects of food additives. Relevant information would be of considerable value.

3.2.4 Relationship between chemical and biological reactivity of food additives

The suggestion has sometimes been made that because a food additive was chemically inert it would be without long-term toxic effects. There is, however, sufficient experimental evidence to demonstrate that such assumptions are not always valid and therefore adequate toxicological studies are always indispensable.

3.2.5 Formation of toxic products by interaction between an additive and a food constituent

If a toxic reaction product arising from interaction between an additive and a food constituent can be identified, then it can be subjected to appropriate toxicological investigation and the results can be evaluated. Furthermore, it is possible that unidentified toxic products may be formed. In this case, foodstuffs treated with the additive should be used in experiments. A number of such experiments with foodstuffs extracted with solvents are described in the monographs.

3.2.6 The significance of results of mutagenicity studies on food additives

This question was considered in 1966 by a WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives, which pointed out the difficulties in extrapolating such experimental results to man, and mentioned also the mutagenic effects of some foods. During the evaluation of cyclamates, the Committee drew attention to the possibility that chromosomal breaks might be produced by physical changes as well as by chemical agents. These observations cannot yet be interpreted in terms of human health hazards.

3.2.7 Data derived from unconventional studies

Some of the toxicological data in the monographs considered by the present Committee were obtained from experiments in which non-oral

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routes of administration, unusual species, or unconventional procedures were used. Although these data were not of direct value in making toxicological assessments, they provided useful background information and, while of little prospective use, may contribute in retrospect to the understanding of toxic effects.

3.2.8 The need for priorities in the testing of food additives

The Committee had before it a plethora of experimental evidence relating to some food additives, but there was a paucity of data on which to evaluate solvents used in food processing. It would therefore be desirable to apply a more balanced judgement when commissioning toxicological studies, having regard to the expense of toxicological testing, the shortage of suitable facilities and competent personnel, and the need for protection of the health of the public. Priority should be given to investigations on solvents and other substances which are valuable in food technology and beneficial to the public.

4. SPECIAL CONSIDERATIONS RELATING TO SOLVENTS

The solvents used in the food industry can be divided into two broad groups according to their function: (a) Carrier solvents, used to aid the dispersion of colours, flavours, emulsifying agents and other intentional food additives. Such solvents were not on the agenda, but it was noted that some of them are also used as extraction solvents. (b) Extraction solvents, used principally for extracting oils and fats from unprocessed and semi-processed produce, for defatting of fish and other meals in the preparation of protein concentrates, and for the decaffeination of coffee.

4.1 Chemical aspects

For a number of solvents, the Committee was able to draw on information provided in an interim report prepared by the Food Additives and Contaminants Commission of the Food Section of the International Union of Pure and Applied Chemistry.

Specifications were drawn up covering identity and freedom from impurities, but they do not necessarily call for chemically pure compounds since some of the solvents are mixtures of homologous compounds.

Stabilizers may be added to some solvents (see page 22), but there were insufficient data to permit their inclusion in the specifications.

4.2 Toxicological aspects

The use of solvents in food technology raises 4 toxicological issues:

(a) Treatment with solvents may affect the nutritive value of foodstuffs.
(b) Residues of solvents may have toxic effects.

(c) Impurities in solvents and additives to solvents may remain in the extracted food and have toxic effects.

(d) A solvent may react with the constituents of a foodstuff to form toxic products.

The present usage of certain solvents could be accepted only tentatively in the light of what is known about their toxicity, even bearing in mind their limited use. Further information on the uses of solvents, the levels of residues, and the nature and the levels of stabilizers is required. The Committee considered that as more toxicological data became available the solvents should be re-evaluated and, as far as possible, acceptable daily intakes should be assigned.

In considering the safety of extraction solvents, some recognition was given to the Threshold Limit Values (TLV) for the vapour phase set out by the American Conference of Governmental and Industrial Hygienists, although the Committee was aware of the limitations inherent in the application of data on inhalation to any assessment of safety of residues in foods. In addition to the obvious differences arising because inhaled substances do not pass into the portal vein and immediately through the liver, there is a paucity of data about rates of absorption, preferential storage sites and the like. It was also recognized that TLVs were industrial standards designed to apply to healthy adults subject to exposure during working hours. For this reason, TLVs could be regarded as providing only a rough guide to potential oral toxicity.

4.3 Solvent residues

With good manufacturing practice, extraction solvents would, in most cases, be largely recovered after use, and residues in foodstuffs would be expected to be reduced to a minimum, but there are a few exceptions, such as ethanol. Minimization of residues of solvents to toxicologically negligible amounts was considered by the Committee to be of particular importance with halogenated hydrocarbons and methanol.

The term “good manufacturing practice” allows considerable latitude in interpretation. The Committee believed that the level of solvent residues should be reduced below that required by purely economic considerations.

A number of methods have been published for the detection and measurement of residues of the various solvents under consideration. Not all of them, however, are suitable for the detection and measurement of residues in food.

It is necessary to consider these methods in relation to the technological use of the solvent; separate methods for residue analysis or separate modifications of a common basic method may be necessary for the same
solvent where it has two or more distinct extraction uses. For the chlorinated solvents and carbon disulfide the problem of solvent residue estimation is virtually identical to that of fumigant residue estimation. For these, general gas chromatographic “multidetection” systems of residue analysis are being developed. A multidetection system developed specifically for solvent residues has been used for hexane and chlorinated hydrocarbons.\(^1\)

### 4.4 Impurities in solvents

The main problem centres on petroleum hydrocarbon fractions that may contain aromatics and polynuclear hydrocarbons. These impurities raise a toxicological problem, particularly as some polynuclear aromatic hydrocarbons are carcinogenic. They may become concentrated in the extracted oil or may be transferred to the residual material when the solvent is removed from the processed food.

Little information is available at present about the carcinogenic constituents of polynuclear aromatic hydrocarbons. Some work is now in progress and more precise information may become available in the near future. In the meantime, it was decided to develop only tentative specifications for hexane and heptane.

Some additional information on this important problem is given in Annex 3.

### 4.5 Interaction with food

Although solvents do not normally react with food, there are particular circumstances in which an interaction is possible between chlorinated solvents (e.g., dichloroethane, trichloroethylene, dichloromethane, trichloroethane) and the protein or other food constituents. For example, cysteine can react with trichloroethylene to form dichlorovinylcysteine,\(^2\) and dichloroethane can react with trimethylamine to form choline chloride (a reaction that has been observed in the extraction of fish-meal).\(^3\) The alcohols and acetone may denature protein. No interaction with food has been detected when petroleum hydrocarbon fractions are used. The products formed by the interaction of certain halogenated hydrocarbons with certain food constituents are toxic. The principles of toxicological assessment are discussed elsewhere (see section 3.2.4).

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5. COMMENTS ON SUBSTANCES ON THE AGENDA

5.1 Items not considered further

A number of items were briefly considered but were not evaluated for the reasons given below, and no monographs were prepared for them.

(a) Carbon disulfide and 1,1,1-trichloroethane (methylchloroform)

These two substances were on the agenda but there was no evidence that they were used for food extraction; therefore the toxicological data available were not considered and specifications were not prepared.

(b) Ethyl acetate

Although this is a solvent, there was no evidence of its use as such in food processing. The specification for and the toxicological evaluation of ethyl acetate as a flavouring agent remained unchanged.

(c) 2-Methylpropan-1-ol (isobutyl alcohol)

Although a request was received to consider this substance as a potential extraction solvent for fish protein concentrates, the data submitted were inadequate for preparation of a specification and for toxicological evaluation.

5.2 Items briefly considered

(a) Caseinates

Casein is recognized as the major nutritional component in milk. When isolated according to good manufacturing practice employing food-grade reagents, it is essentially unchanged and may be regarded as a food. Therefore a toxicological evaluation was deemed unnecessary. A specification for sodium caseinate was prepared.

(b) Edible gelatin

It was recognized by the Committee that edible gelatin is a protein of low nutritive value. As such, its use should be limited to foodstuffs constituting a trivial portion of the diet unless supplemented to achieve nutritional adequacy. In view of these facts the Committee recognized that edible gelatin is a food and could be used in accordance with good manufacturing practice. A specification was prepared.

(c) Curcumin

No significant information was available on which to base an evaluation. Revised specifications were prepared for turmeric and curcumin.

(d) Carrageenan and furcellaran

New evidence suggests a need to re-evaluate carrageenan; however, since a number of studies are known to be in progress, the Committee decided to postpone consideration until their completion.

5.3 Evaluation

5.3.1 Miscellaneous food additives

A number of substances were assessed in the light of toxicological data. The results of the evaluation are summarized in Annex 5.

(a) Brominated vegetable oils

Although these substances have been used for some years in soft drinks and fruit juices, no evaluation was made at the ninth committee meeting in 1966 because of lack of suitable data. Since then short-term studies in animals have demonstrated that high doses cause degenerative cardiac lesions. Furthermore, accumulation of lipid and lipid-bound bromine has been demonstrated in adipose tissue and in intracellular fat of various other tissues, both in man and in experimental animals. This evidence suggests that a human epidemiological problem could arise from the use of brominated vegetable oils. It was concluded that they should not be used as food additives in the absence of evidence indicating their safety; therefore, specifications are limited to an identification test.

(b) Cyclamates

The evaluation of cyclamates by the eleventh committee led to the assignment of only a temporary ADI because of reservations concerning their safety, and further work was requested by 1970. The publicity given to results indicating a possible toxicological hazard led to much anxiety amongst the public.

Consideration of cyclamates encompassed cyclohexylamine and mixtures of cyclamates and saccharin, since some relevant toxicological studies have been carried out with these substances. The data are included in the body of the monograph on cyclamates.

Although there has been a considerable amount of further work, some questions have still not been fully answered.

(i) The laxative action of high doses of cyclamates has been attributed to an osmotic effect, but other mechanisms have not been excluded: in
the absence of a definitive study the question of its long-term toxic effect on the intestinal tract remains open.

(ii) Because cyclamates are converted to cyclohexylamine by intestinal flora, this metabolite has been extensively studied. This phenomenon also poses a fundamental problem which is considered elsewhere (see section 3.2.1).

(iii) The mutagenic effects of cyclamates and cyclohexylamine were regarded as indications for further experiments, but their immediate relevance in toxicological evaluation is not clear. The question is discussed elsewhere (see section 3.2.6).

(iv) The Committee discussed the production of tumours of the urinary bladder following implantation of cholesterol pellets containing cyclamate. It held that these results were not in themselves definitive for the assessment of a toxic effect, since ingestion of the substance is the only route of administration of food additives: they may, however, provide a warning sign justifying further studies. A similar approach had been employed in assessing the significance of findings of tumours in studies carried out with subcutaneous injections of certain food colours.\(^1\)

Since tumours were also found in experiments in which cyclamate alone or in combination with saccharin was given orally, no ADI was assigned to cyclamates. Attention is drawn to numerous studies, in progress or planned, on cyclamates and cyclohexylamine. These studies will be evaluated as they become available. The Committee's evaluation recognizes that there are benefits in the use of cyclamates in the management of diabetics and the grossly obese, against which possible risks have to be balanced.

The Committee also reviewed the specifications for calcium cyclamate and sodium cyclamate prepared at the eleventh meeting.\(^2\) After taking into consideration the quality of the products commercially available it was agreed that the limit of cyclohexylamine should be reduced from 100 mg/kg to 25 mg/kg. The Committee further felt that the same limit of cyclohexylamine should be prescribed for cyclohexylsulfamic acid, which was also considered at the eleventh meeting. A method for the estimation of cyclohexylamine in cyclamates and in cyclohexylsulfamic acid was developed. Analytical methods now available for the detection and estimation of dicyclohexylamine are sensitive to 1–2 mg/kg.


(c) Monosodium glutamate

At the thirteenth meeting of the Committee consideration of monosodium glutamate was deferred, and it was noted that its use as a condiment raised a problem for its assessment as a food additive. As with cyclamate, considerable publicity has been given to laboratory data purporting to have toxicological significance for the addition of glutamate to food, generally without a balanced consideration of all the available evidence. The papers referred to in the monograph on glutamate were selected from the extensive literature on this compound because of their relevance to its evaluation as an additive. As a result of the publicity given to glutamate, a considerable amount of work is now in progress.

Much of the recent work on the effects of glutamate is concerned with high doses which produce acute pharmacological reactions, but there is little in these data to suggest a long-term toxic hazard. A more serious potential toxic hazard of glutamate is the finding that it produced brain damage in new-born animals.¹ Although the weight of the evidence does not support the contention that glutamate as an additive in the diet can lead to brain damage, caution is desirable in the use of glutamate as an additive in infant diets.

It has been suggested that the main reason for the addition of monosodium glutamate to baby food is to improve the taste from the mother's point of view; there is, however, no evidence that infants like the taste—which would provide a more cogent reason for its use. The sixth report suggested that foods prepared specifically for infant diets require special consideration, urging that food additives should be avoided where possible and that great care should be exercised both in the choice of additive and the level of use.

The Committee concluded that monosodium glutamate could be given an unconditional ADI of 0–120 mg/kg applicable to the general population except infants under one year of age.

A tentative specification had been prepared for monosodium glutamate at the thirteenth meeting. This was reviewed and a final specification was developed. The Committee felt that similar specifications should also be prepared for other glutamates, such as potassium or calcium glutamate. This could not be done, however, as they were not on the agenda and no information on these substances was available.

(d) Phosphoric acid and phosphates

The Committee is aware of the need to revise the specifications for phosphoric acid and a number of phosphates that had been developed in earlier meetings.

A new monograph on biological data was prepared to replace the previous individual monographs on phosphoric acid and the various phosphates of sodium, potassium, calcium, and magnesium. There are no toxicological grounds for treating these substances separately. Phosphoric acid itself carries no special hazards that distinguish it from other acids used in foods.

5.3.2 Filtration aids and clarifying agents

Consideration was given to a filtration medium (asbestos), a filtration aid and decolourizer (activated vegetable carbon), and a flocculant (tannin). The results of the evaluations are summarized in Annex 6.

(a) Asbestos

It was not possible to prepare a specification since information concerning the physical forms of asbestos used in the food industry was lacking; there is a need for methods to distinguish between these forms. Information is also required concerning any significant changes in the chemical or physical properties of asbestos that may occur if it is exposed to acidic or alkaline media in food processing.

It was noted that asbestos is a contaminant in some tales. It was recommended that new methods of detection should be used to eliminate contamination of food by asbestos from this source.

The many industrial uses of asbestos have made it a ubiquitous environmental contaminant. There was some discussion on the possibility that the ingestion of foods contaminated with asbestos fibres might add to the risk of carcinogenicity.

Evidence was considered on persorption and lymphatic transport of asbestos fibres injected subcutaneously. It was felt that there was a real possibility of persorption of asbestos fibres ingested with foods that had been exposed to asbestos-containing filter pads during their processing. It was decided that no definitive evaluation could be made until relevant experimental data concerning this possibility had been submitted.

In spite of these reservations, it was concluded that the use of asbestos in processes in which it is essential would cause no hazards to the consumer, provided that crocidolite is not used and that residues in food are kept at negligible levels in accordance with good manufacturing practice. Nevertheless, it was felt that suitable alternative filtration media ought to be developed.

(b) Activated vegetable carbon (food grade)

Activated vegetable carbon differs from carbon blacks in that the latter are derived from the incomplete combustion of hydrocarbons from fossil fuels, whereas the former is derived from vegetable matter or lignites.
Certain carbon blacks are used as food colours,¹ and activated vegetable carbons are largely used as clarifying agents or decolourizers. Virtually no activated vegetable carbon is present in the finished food product, and the data on this type of carbon did not demonstrate toxicity. A specification for activated vegetable carbon was prepared.

(c) Tannins (food grade)

A tentative specification for tannins prepared by the Committee relates only to tannins that yield gallotannins (derivatives of gallic acid) on hydrolysis. Many other kinds of tannin also occur in nature, including those that on hydrolysis yield ellagittannins (derivatives of hexahydroxy d-dibenzoic acid) and condensed (non-hydrolysable) tannins (e.g., in the Douglas fir). The hydrolysable tannins can also be distinguished from the condensed tannins: on dry distillation the former yield pyrogallol (1,2,3-trihydroxybenzene) whereas the latter yield catechol (1,2-dihydroxybenzene). Hydrolysable gallotannins may be obtained from nutgalls, the excrescences that form on young twigs of various Quercus spp. (e.g., Q. infectoria, Q. illiniae); these include Chinese and aleppo tannins. They may also be obtained from the leaves of various sumac species (e.g., Rhus cotaria, R. glabra, and R. typhina; these include Sicilian and American sumac). All consist of the polydigalloyl esters of glucose. A further source of hydrolysable gallotannins is the seed pods of tara (Caesalpinia spinosa); these consist essentially of the polydigalloyl esters of quinic acid. Recognizing that the Committee was recommending two types of ADI, one for tannins derived from Peruvian tara and the other from Turkish aleppo, Chinese tara, and Sicilian sumac, it was considered necessary to collect more information to distinguish between tannins derived from these various sources.

Evaluation of the toxicity of tannins was complicated by the fact that they are naturally occurring constituents of many foods, such as wine and brewed tea. It was also noted that the addition of tannins as floculants in food processing should result in virtually no residues in finished foods, providing good manufacturing practices are followed.

5.3.3 Heavy metal contaminants and related additives

Three heavy metals were considered, namely copper, mercury, and tin. Mercury is always a contaminant, never an additive. However, copper and tin may be both additives and contaminants. The Committee considered that the intentional addition of small amounts of tin and copper for technological purposes would not significantly increase the total intakes of

these metals and would therefore not be objectionable from a toxicological point of view (see also Annex 5).

(a) Copper and cupric sulfate

Copper is recognized as an essential trace element and a required dietary constituent. In the past a major source of dietary copper was from utensils used in food processing. When stainless steel vessels are used less copper appears in the food, but the presence of copper is sometimes necessary, as for example in controlling fermentation in the manufacture of Emmentaler cheese. The addition of copper has also been proposed for colour fixation in some processed vegetables. Another source of dietary copper arises from its use as a pesticide.

Toxicological data before the Committee were not amenable to the assignment of an ADI, since a no-effect level could not be determined. Data on the use of copper as a food supplement for growth promotion in pigs were considered of little relevance in assessing toxicity, and therefore were not included in the monograph. It was noted that toxicity at 30 mg/kg body weight in rats was minimal. The Committee concluded that reliance could be placed on the long human exposure to background levels of copper and, provided that intake does not exceed 0.5 mg/kg/day (as indicated in the tenth report), no deleterious effects would be expected. In this connexion, the Committee was presented with recent data indicating that certain foodstuffs naturally have a high content of copper which has not apparently produced any toxic effects.

A specification for cupric sulfate has been prepared.

(b) Mercury

Analyses in certain countries have shown that some foods are contaminated with mercury to an extent liable to cause human intoxication. The source of the mercury is environmental pollution, the major sources being chloralkali industries using mercury cells, paper pulp factories using phenylmercury salts as slimicides, wood pulp factories using phenylmercury salts as fungicides, the industrial use of inorganic mercurials, and the agricultural use of various organomercurial fungicides. Whatever the source of pollution, most mercury compounds can be converted in nature to methylmercury, traces of which may then occur in fish and other foods of animal origin.

The methylmercury radical is very stable. It is only slowly excreted after ingestion by man and its elimination by fish is even slower, the half-life exceeding one year.

Surveys of mercury levels in foods have been carried out in only a few countries.\(^1\) There is urgent need for such surveys, especially in regard to

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fish and shellfish. It would also be desirable to have analytical data on the level of total mercury and, where possible, the forms in which it occurs. As a guide to the choice of analytical methods, it should be noted that fish from uncontaminated areas usually contain less than 0.1 ppm and in other foods there is less than 0.05 ppm; in contrast, fish and shellfish from areas contaminated by mercury may contain more than 1 ppm.

Methylmercury compounds produce serious and sometimes fatal neurotoxicity and embryopathy. Over 200 cases of methylmercury intoxication have been reported in the literature. Of these more than 100 occurred in Minamata and Niigata in Japan, during the last two decades, due to ingestion of contaminated fish and shellfish: the syndrome of intoxication has been termed Minamata disease. Approximately 20 cases of “congenital” Minamata disease were due to consumption of contaminated fish and shellfish by pregnant women, who themselves were usually asymptomatic.

The biological data available to the Committee do not allow an ADI for methylmercury to be established. The Committee has, however, taken notice of a number of alarming points: (1) the epidemics of poisoning, (2) the high sensitivity of the fetus, (3) the occurrence, among fish-eaters in non-epidemic areas, of mercury levels in blood and hair approaching those associated with symptoms of poisoning, and (4) a correlation in man between exposure to mercury as a contaminant of fish and the incidence of chromosome breaks in circulating lymphocytes.

Although a considerable amount of data were available, the Committee thought it would be premature to prepare a monograph, especially as publication of a detailed review of the risks associated with mercury in fish was expected within a few months. This review should prove of value in putting the problem in perspective and may stimulate further work.

There are no data on which to assign an ADI to mercury: this is urgently required as a guide to the levels of contamination above which food should be discarded. It is strongly urged that environmental pollution by mercury should be reduced to the minimum possible. Such measures have already been put into effect in some countries.

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(e) Tin and stannous chloride

A specification on stannous chloride was prepared. The Committee noted that the substance had only a limited application as a food additive: it is used as an additive when asparagus and peas are packed in glass containers or in lacquered cans, and it is also used in soda waters.

The presence of tin in foods may be due either to contamination or its use as an additive. Stannous ions prevent the migration of other heavy metals into canned food, inhibit the oxidation of ascorbic acid, and may impart a characteristic flavour.

In solid foods, tin is mostly protein bound and in the quantities likely to occur it has no apparent toxic effect. However, in acidic liquid food and beverages, high levels may occur which have occasionally produced acute toxic effects.

The absence of chronic or severe toxic effects due to tin in man, despite a long history of consumption of canned foods, indicates that there is no need to depart from the limits set by good manufacturing practice as recommended in the tenth report. Work at present in progress could lead to evaluation and the assignment of an ADI in future.

5.3.4 Extraction solvents

The results of evaluations are summarized in Annex 7.

(a) Alcohols and acetone

The solvents in this group are hydrophilic and are used in the extraction of oils and fats from wet materials. Specifications for them have been prepared for publication.

Ethanol. This substance, being the principal non-aqueous constituent of alcoholic beverages and a common constituent of the diet, is subject to different considerations from most of the other solvents. In certain countries, the economic penalties, in the form of excise duty, attached to the use of ethanol have led to the use of alternative solvents whose residues pose greater problems than those of ethanol. The relaxation of restraints on the use of ethanol in food technology therefore seems desirable.

Methanol. This substance is present in certain spirits and liqueurs in concentrations of up to 200 ppm. The intake of high doses of methanol is known to produce severe ocular damage in susceptible individuals.

When used as an extraction solvent in food technology the residues of methanol should be reduced to a minimum by observing good manufacturing practice. The Committee was informed that methanol was used only for extracting spice oils and hop oils, and that residues from these sources are insignificant in the diet.
Propan-2-ol (isopropyl alcohol). This is a minor constituent of some alcoholic beverages. It is used in certain countries as a substitute for ethanol as an extraction and carrier solvent, and as a substitute for halogenated hydrocarbon solvents in the processing of fish-protein concentrate. There have been a number of short-term human studies with propan-2-ol, and long-term animal studies are in progress. The results of these studies may lead to the assignment of an ADI when they become available. Meanwhile, with good manufacturing practice, the residues in foodstuffs should be negligible.

Acetone. This substance is formed in human intermediary metabolism and small amounts are readily metabolized. As a solvent it apparently has only minor uses in food technology. Since it has a high vapour pressure it was considered that, with good manufacturing practice, residues should be toxicologically negligible. Traces of acetone have been detected in ground pepper.

(b) Petroleum hydrocarbon fractions (hexane and heptane)

Aliphatic hydrocarbon extraction solvents, which are lipophilic, have been widely used in the food industry. While the Committee recognized that the main hydrocarbon solvent used is the hexane fraction of petroleum ether, it was felt that the specifications for commercial hexane should not exclude the use of pure n-hexane or commercial hexane with higher proportions of n-hexane than specified. The Committee did not have precise information regarding other petroleum hydrocarbon fractions used as extraction solvents, although it was reported that heptane, and certain cuts with a boiling range below that of the hexane fraction, were in use for some specific food extraction requirements. Since the Committee was not aware of any food extraction use for fractions higher than heptane, it was decided to develop a specification for heptane instead of for a general range of petroleum hydrocarbon fractions. At the same time it was understood that any lower boiling fractions used should conform to the general purity criteria prescribed for hexane and heptane.

The amounts of solvent residues in the food depend upon the desolventizing conditions and the subsequent treatment. Pritchard et al. found total hexane residues of 0.01–0.15% in extracted freshly produced palm-kernel, soya-bean, and groundnut meals. No residues were found by Watts & Holswade, using a method of detection sensitive to 10 mg/kg, in samples of cottonseed, corn, groundnut, soya-bean, and safflower oil.

There is a scarcity of information on which to base an assessment of the toxicological significance of the residues of these solvents; this is

unfortunate as they are amongst the most widely used in food technology. The argument that their chemical inertness implies biological inertness was considered to be suspect and no substitute for direct experimentation. The Committee held that data relating to oral administration of these substances were required in order to arrive at an ADI. With good manufacturing practice, the residues remaining in foods are less than 1 ppm.

(c) Halogenated hydrocarbons

These solvents are often used as alternatives to petroleum hydrocarbon fractions to avoid high fire risks, but they have the technological disadvantages that they present greater occupational health hazards and may cause more corrosion of equipment. They also have specific uses in the extraction of hops, paprika, and coffee.

A stabilizer is often added to halogenated hydrocarbons in a concentration of up to 100 mg/kg in order to prevent decomposition, particularly if they should be exposed to strong sunlight or other sources of ultraviolet radiation. Although it was not clear which stabilizers are present in the solvents used for food extraction, the following are generally added to this group of solvents: thymol and cresol, branched aliphatic hydrocarbons, triethylamine, di-isopropylamine and other amines, stearates, and ammonium carbamate. More information is needed about the nature and amount of stabilizers added to halogenated hydrocarbons used in processing foods. There are toxicological objections to the phenolic stabilizers and they should not be used: there is, however, little or no evidence on the toxicological significance of the others.

Dichloromethane (methylene chloride). This solvent can react with thiol groups of sulfur-containing amino acids, but only under extreme conditions that do not obtain in food processing. Long-term feeding studies have been carried out with hops and coffee that have been treated with the solvent, but as some of the reports of this work were available to the Committee only in an abridged form, there was insufficient information for establishing an ADI. The Committee considered that residues could be kept to toxicologically negligible levels by good manufacturing practice.

1,2-Dichloroethane (ethylene dichloride). This substance is used as a fumigant of foodstuffs and as a solvent in food processing; identical considerations apply to residues in foods arising from both uses. A toxicological evaluation of the fumigant residues is given elsewhere. New data before the Committee led to the drafting of another monograph but did not change the previous evaluation, that residues should be restricted to a minimum by observing good manufacturing practice.

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1,1,2-Trichloroethylene. The Committee noted that trichloroethylene reacts with cysteine in proteins to form a toxic product. A feeding trial with coffee extracted by the solvent has been carried out, and although no adverse effects were noted, the data were not considered adequate for establishing a formal ADI. However, it was considered that with good manufacturing practice the residues in extracted coffee are toxicologically negligible.

Specifications for the above three halogenated hydrocarbons were prepared for publication.

5.3.5 Miscellaneous items

The results of evaluations are also summarized in Annex 5.

(a) Ethyl maltol. It was noted that ethyl maltol is intended as an alternative to its homologue, maltol, which was evaluated at the eleventh meeting and for which a monograph is already available. Data on ethyl maltol were sufficient to assign an ADI and a specification has been prepared for publication.

(b) Food grade mineral oil. Since polycyclic aromatic hydrocarbons occur in mineral oils, it is important that limits be set for them in the specifications. The Committee noted that stabilizers are sometimes added to food grade mineral oil. Addition of stabilizers was likely to interfere with the test for the determination of polynuclear aromatic hydrocarbons. As the type and quantity of the stabilizers used in the product were not known, it was decided to prepare for publication a specification for "food grade mineral oil". This specification does not include other types of mineral oil used in the food industry to which stabilizers are added for certain technological purposes. It may be possible to develop a separate specification for white mineral oil containing stabilizers as more information becomes available.

The Committee noted that ingested mineral oil is absorbed and stored in tissues. However, there was no evidence that this had deleterious consequences. It was recognized that mineral oil could interfere with the absorption of fat-soluble vitamins, but with modest levels of intake the consequences are not significant. It was also noted that the use of mineral oil in food was self-limiting in that excessive amounts are laxative.

(c) Oleoresins of paprika. These are derived from a widely consumed natural foodstuff, and there were no data indicative of a toxic hazard. The use of the oleoresins as a spice was self-limiting and obviates the need for an ADI. A specification has been prepared for publication.

6. REVIEW OF TECHNOLOGICAL EFFICACY OF SOME ANTIMICROBIAL AGENTS

At previous meetings the Committee had prepared specifications for, and made toxicological evaluations of, some chemical preservatives. The Committee has now prepared monographs on the technological efficacy of the following antimicrobial agents: benzoic acid and benzoates, nitrates and nitrites, esters of p-hydroxybenzoic acid, propionic acid and propionates, sodium diacetate, sorbic acid and sorbates, sulfur dioxide and related substances, and diethylpyrocarbonate. The monographs do not contain recommendations for use, "tolerances", legal restrictions, or clearances, but constitute a review of data available in the literature. The use levels given in the monographs do not necessarily correspond to those specified by legislation or to the optimum concentrations for technological purposes.

6.1 Methods of analysis in food

Methods for assaying the pure substance are given in the monographs on specifications. Although the Committee felt that the monographs on technological efficacy should also contain methods of analysis for determining the additives in foods, it was advised that the elaboration of such methods was already being undertaken by the Joint FAO/WHO Codex Alimentarius Commission.

6.2 Review of efficacy

Only a limited number of antimicrobial agents are acceptable from a toxicological point of view. Because the antimicrobial activity of these agents is dependent on pH, their use is limited to acidic foods such as fruits, fruit juices, and jams, as well as salads and certain other foods. Even then their use may not be fully effective, as antibacterial agents used singly have a limited spectrum of antibacterial activity and may induce resistance in the flora exposed to them. Adequate chemical preservation of foods with nearly neutral pH values therefore presents difficulties pending the development of a wide-spectrum, non-pH-dependent, and organoleptically acceptable preservative of low mammalian toxicity. Meanwhile for the preservation of foods of medium and high pH one has to rely on physical methods such as drying, freezing, refrigeration, or heating. In view of the above considerations the efficacy of antibiotics such as nisin, pimaricin, and tylosin deserves full attention.

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1 The specifications for diethylpyrocarbonate and certain other antimicrobial agents that were elaborated at the ninth meeting of the Committee are attached to the monograph on technological efficacy of these compounds because they have not been previously published.
7. ESTIMATION OF FOOD ADDITIVE INTAKE

At the request of the sixth session of the Codex Committee on Food Additives, the Committee considered a study by WHO entitled "Estimation of Food Additive Intake, 1969/70 Computerized Calculation of Potential Food Additive Intake". The method employed in this study relied mainly on average food consumption data already available except in the case of beverages and confectionery products, for which high-consumption parameters were used.

The Committee considered that, with the material available, this method for assessing the potential intake of food additives was the best, even though many assumptions had to be made. It recognized that the intake of food additives by heavy consumers of particular foods cannot be accurately assessed. Nevertheless the results are useful for selecting priorities for further extensive investigation.

The Committee was aware that dietary surveys of the weekly food intake of individuals are in progress (in some cases the period is longer than one week). From these surveys, an independent assessment can be made of maximum intakes, at least in the age and sex groups surveyed. Population groups specially vulnerable to excessive intake of particular food additives should be identified. To do so will require a planned survey which takes into account sociological and economic factors as well as unusual dietary patterns.

The Committee was aware that care needs to be taken to itemize the food records so that intakes of each individual food can be identified. It also recognized that unless those responsible for the design of the study are aware of the total information needed, the basic data needed might not be collected and storage of the data might not be such as to permit ready retrieval for the calculation of food additive intake.

At the fifth session of the Codex Committee on Food Additives it had been recommended that each interested country should designate an officer for liaison with WHO on the question of the calculation of food additive intake. The Committee recommended that these liaison officers should be informed of the various aspects of the problem discussed above.

The estimated potential intake of food additives is likely to exceed the actual average intakes. This is because additives are not always present in all the foods in which their use has been proposed, and equally they may not be used to the extent of the maximum permitted. The most reliable way of determining this difference would be by sampling over an extended period and analysing the foods containing the permitted additives.

The Committee recommended that the problem of assessing high persistent consumption of additives by individuals should be the subject of further study.
8. RECOMMENDATIONS

8.1 Recommendations to FAO and WHO

(1) In view of the large numbers of food additives requiring consideration the Committee considers it desirable that further meetings of this Committee should be held annually. Future meetings should also give consideration to (a) evaluating the technological efficacy of further classes of food additives, priority to be given to certain specified antibiotics and to antioxidants, (b) preparing guidelines for evaluating the efficacy of antimicrobial food preservatives under practical conditions and (c) revising outdated specifications of food additives on a systematic basis.

(2) In view of both the seriousness and the extreme complexity of the problem of environmental pollution by mercury and mercury compounds, the Committee recommends that consideration should be given to convening a special meeting for the evaluation of the data available.

(3) The Committee reaffirmed the need for the publication of a compendium containing all its previous specifications for food additives.

8.2 General recommendations

(1) Recognizing the extreme seriousness of the problem of environmental contamination by mercury, the Committee recommends that all possible measures should be taken to reduce this form of pollution. In addition, the Committee recognized the urgent need for surveys of the levels and forms of mercury in foods.

(2) More information is needed on the level of solvent residues in some foods arising from the use of extraction solvents. More versatile, simple, and less expensive methods are desirable for detecting, and estimating the levels of, aromatic hydrocarbons and carcinogenic polynuclear aromatic hydrocarbons in the petroleum hydrocarbon solvents used for food extraction.

(3) Further information is desirable on the potential synergistic effects of antimicrobial agents previously considered by the Committee, in the hope of lowering use levels in individual foods. In addition, further work is necessary in order to develop antimicrobial agents effective at pH values greater than 6.0.

(4) Recognizing the importance of assessing food additive intake the Committee recommended that those responsible for the design and analysis of food consumption surveys should consult FAO and WHO so that the collective data can be used to the maximum extent for calculating the intake of food additives on an individual basis.
Annex 1

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


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


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Annex 2

LIST OF FOOD ADDITIVES ON THE AGENDA

CATEGORY 1

Food additives for re-evaluation

Brominated vegetable oils
Curcumin
Cyclamates
Monosodium glutamate
Phosphoric acid and phosphates

CATEGORY 2

Food additives for establishment of specifications and toxicological evaluation

Extraction solvents

Acetone
Carbon disulfide
1,2-Dichloroethane (ethylene dichloride)
Dichloromethane (methylene chloride)
Ethanol
Ethylacetate
Isobutyl alcohol
Methanol
Methylchloroform (1,1,1-trichloroethane)
n-Hexane
Petroleum ether
Propan-2-ol
1,1,2-Trichloroethylene

Other food additives

Asbestos (filtration aid)
Caseinates, sodium, potassium, calcium and ammonium
Cupric sulfate
Edible gelatin
Ethyl maltol
Mineral oil

— 29 —
Oleoresins of paprika
Pure vegetable carbon
Stannous chloride and tin
Tannins (filtration aid)
Carrageenan and furcellaran

Contaminant
Mercury (toxicological evaluation only)

Category 3

Food additives for evaluation of the technological efficacy

Benzonic acid and its salts
Diethylpyrocarbonate
Nitrites and nitrites
p-Hydroxybenzoate esters
Propionic acid and its salts
Sodium diacetate
Sorbic acid and its salts
Sulfurous acid and its salts
Annex 3

IMPURITIES IN SOLVENTS

1. Aromatics

The main aromatic impurity in hydrocarbon solvents is benzene. Food-grade hexane contains less than 0.2% of benzene because it has been hydrogenated in order to convert any benzene it may contain into cyclohexane. In an experiment where a high percentage (3%) of benzene was intentionally added to hexane, the residues in cocoa butter were less than 0.1 ppm, and extracted groundnut meal contained only a few parts per million of benzene.¹ Johnson, Nursten & Self ² have reviewed the literature on the occurrence of aromatic hydrocarbons (including polynuclear ones) in foods at levels substantially below 1 mg/kg.

2. Polynuclear aromatic hydrocarbons

The occurrence of polynuclear aromatic hydrocarbons in foods has been reviewed by Gunther & Buzzetti,³ in crude vegetable oils by Grimmer & Hildebrandt ⁴ and in coconut oil by Biernothen & Rost.⁵

The methods for detecting and estimating polynuclear aromatic hydrocarbons have been reviewed by Haenni.⁶ The method of Howard et al.⁷ was used by Howard, Fazio & White⁸ for the estimation of residues of individual polynuclear compounds in commercial hexane solvents used in edible oil extraction. The hydrocarbons are isolated by partition, column and thin-layer chromatography and measured by ultraviolet and spectro-photofluorometric procedures with recoveries of about 90% when present in the hexane at the 2 µg/kg level. An alternative method is to specify the maximum absorption value at selected wavelengths in the ultraviolet region; although this is a less specific and less sensitive method than that of Howard et al., it has been included in the specifications since it is much simpler.

Alders⁹ has shown on theoretical grounds that, after refining, even raw hexane with an initial content of 3% of aromatic hydrocarbons will not

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¹ Shell Chemical—unpublished report.
⁹ Alders, L., unpublished data.
contain more than 10 μg/kg of residue. A simple estimation of the polynuclear aromatic hydrocarbon levels in the extracted oil can be obtained by calculating these from the amount of "make-up" solvent required in an extraction plant. "Make-up" solvent is necessary to replace solvent losses, which are mainly caused by evaporation through leaks in the equipment and incomplete recovery of solvent from the air. These losses range from 2 to 10 litres (1.4–7 kg) per ton of extracted oil and the detection limit of the polynuclear hydrocarbons in a solvent by the proposed ultraviolet absorption test is 0.5 mg/kg. Consequently, even if these hydrocarbons were present in the solvent up to the detection limit and if they were left entirely in the extracted oil, this would not contain more than 0.7–3.5 μg/kg of polynuclear aromatic hydrocarbons.
Annex 4

RESOLUTION WHA23.50 OF THE
TWENTY-THIRD WORLD HEALTH ASSEMBLY

Health Hazards of Food Additives

The Twenty-third World Health Assembly,
Being concerned about the potential hazards of food additives to the consumer;
Aware of the increasing research done on toxicity of food additives;
Having noted the intensive publicity commonly given by the lay press to questions of safety of food additives and the widespread repercussions which follow action by any country to limit or prohibit the use of a generally used food additive;
Noting that the matter has been raised at the forty-fifth session of the Executive Board; and
Agreeing that there is an urgent need for rapid dissemination of the results of toxicity research of food additives, including the results and consequences of evaluation of such studies,

1. REQUESTS Member States:
   (i) to communicate immediately to WHO any decision to limit or prohibit the use of a food additive; and
   (ii) to supplement as soon as possible such information with the data in support of the decision taken; and

2. REQUESTS the Director-General where such action would be useful:
   (i) to transmit immediately to Member States information received under paragraph (1);
   (ii) to take expeditious steps to evaluate any significant new evidence of toxicity of a specific food additive, including if necessary the convening of a meeting of experts, where appropriate in consultation with FAO;
   (iii) to distribute promptly to Member States any conclusions of such a meeting.

Fifteenth plenary meeting, 21 May 1970.
Annex 5

TOXICOLOGICAL EVALUATIONS:
MISCELLANEOUS FOOD ADDITIVES AND CONTAMINANTS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Acceptable daily intake for man (^3) (mg/kg body-weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brominated vegetable oils (^b)</td>
<td>No ADI</td>
</tr>
<tr>
<td>Carrageenan (^c)</td>
<td>0–50 (^a)</td>
</tr>
<tr>
<td>Furcellaran (^c)</td>
<td>No ADI (^3)</td>
</tr>
<tr>
<td>Cyclamates, calcium and sodium (^d)</td>
<td>No ADI (^4)</td>
</tr>
<tr>
<td>Copper and cupric sulfate (^e)</td>
<td>0–2</td>
</tr>
<tr>
<td>Ethyl maltol (^e)</td>
<td>Use limited by good manufacturing practice</td>
</tr>
<tr>
<td>Food grade mineral oil (^e)</td>
<td></td>
</tr>
<tr>
<td>Mercurial compounds</td>
<td>No ADI</td>
</tr>
<tr>
<td>Monosodium L-glutamate (^e)</td>
<td>0–120 (^5)</td>
</tr>
<tr>
<td>Oleoresins of paprika (^e)</td>
<td>Self limiting as a spice</td>
</tr>
<tr>
<td>Phosphoric acid and phosphates (^f)</td>
<td>0–30 (^6)</td>
</tr>
<tr>
<td>Tin and stannous chloride (^e)</td>
<td>No ADI (^4)</td>
</tr>
</tbody>
</table>

\(^a\) Specifications are also available for gelatin and sodium caseinate (page 12).
\(^b\) Identification test only.
\(^c\) Specifications available (Annex 1, ref. 21).
\(^d\) Specifications available (Annex 1, ref. 16; also Section 5.3.1 (b)).
\(^e\) Specifications available (see p. 2).
\(^f\) Specifications available (see Annex 1, ref. 7).
\(^3\) Unconditional ADIs unless otherwise indicated.
\(^a\) As carrageenan or furcellaran, or the sum of both. (There was a printing error in the thirteenth report (Annex 1, ref. 19) but the monographs (Annex 1, ref. 20) are correct.)
\(^5\) Use in the management of diabetes and gross obesity not considered in this evaluation.
\(^4\) For evaluation see section 5.3.3.
\(^6\) Additional to the amount naturally occurring in the diet. Applicable to the general population except infants under 1 year of age.
\(^7\) Conditional acceptable daily intake 30–70 mg/kg. Both the unconditional and conditional ADIs include the amount occurring in the diet.
Annex 6

TOXICOLOGICAL EVALUATIONS:
FILTRATION AIDS AND RELATED SUBSTANCES

<table>
<thead>
<tr>
<th>Substance</th>
<th>Acceptable daily intake for man (mg/kg body-weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated vegetable carbon*</td>
<td>No limit except for good manufacturing practice</td>
</tr>
<tr>
<td>(food grade)</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td>Decision postponed⁵</td>
</tr>
<tr>
<td>Tannins (food grade)⁺</td>
<td></td>
</tr>
<tr>
<td>Derived from Peruvian tara</td>
<td></td>
</tr>
<tr>
<td>Derived from Turkish aleppo,</td>
<td></td>
</tr>
<tr>
<td>Chinese tara, and Sicilian sumac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–0.3⁴</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Specification available (see p. 2).
⁺ Tentative specifications available for tannins used as a flocculant or clarifying agent (see p. 2).
⁵ See p. 16.
⁴ Temporary ADI.
Annex 7

TOXICOLOGICAL EVALUATIONS:
EXTRACTION SOLVENTS

1. Substances considered
   
<table>
<thead>
<tr>
<th>Substance</th>
<th>Petroleum hydrocarbon fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>hexane and heptane</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>Propan-2-ol</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>1,1,2-Trichloroethylene</td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
</tr>
</tbody>
</table>

2. Evaluations

   (a) The evaluations for these solvents, with the exception of trichloroethylene as a caffeine extractant and ethanol, are tentative, and are subject to re-evaluation when the relevant data become available (see section 4.3.1).

   (b) These solvents should be used only in accordance with good manufacturing practice, in the expectation that this will result in minimal residues.

   (c) With 1,2-dichloroethane and 1,1,2-trichloroethylene, care must be taken to avoid the formation of toxic interaction products with certain treated foods.

3. Specifications are available for all these solvents with the exception of hexane and heptane, for which only tentative specifications were prepared (see p. 2).