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# **EVALUATION OF CERTAIN FOOD ADDITIVES**

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



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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 21-29 April 1976

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# **EVALUATION OF CERTAIN FOOD ADDITIVES**

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

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 21 to 29 April 1976. The meeting was opened by Dr T. Lehti, Assistant to the Assistant Director-General, Economic and Social Policy Department, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Lehti said that, in addition to its normal work on food additives, the Expert Committee was able to make a valuable contribution in the field of contaminants, which was especially relevant to the needs of developing countries. It could have a substantial impact on the health of population groups and on the economies of countries that depend on the export of food and feeding stuffs. He therefore hoped that some of the contaminants still awaiting consideration by the Committee might soon be given attention. As far as food additives were concerned, Dr Lehti noted that some of the additives used in the food industry were substances of a kind that occurred naturally in the traditional foods of developing countries and that the cooperation of scientists from developing countries in connexion with meetings of the Committee could help to overcome a lack of information on such foods, on patterns of consumption and on food habits, and could ensure that the special circumstances in these countries be given due attention.

### **1. INTRODUCTION**

The tasks before the Expert Committee were : (1) to prepare specifications and carry out the toxicological evaluation of certain food additives ; (2) to review recent findings of toxicological studies of certain food additives ; (3) to revise the specifications for certain food additives ; (4) to undertake the toxicological re-evaluation of certain food additives ; (5) to establish criteria that would help in determining priorities for the evaluation of flavouring substances ; and (6) to give further general consideration to the principles and procedures of evaluation of food additives and contaminants.

## 2. GENERAL CONSIDERATIONS

### 2.1 Modification of agenda

The further toxicological information on cyclamates required in the eighteenth report<sup>1</sup> having become available, the Committee agreed to consider cyclamates during its present meeting.

### 2.2 The importance of information on food additives and contaminants to developing and developed countries

Worldwide population growth and improved standards of living call for increased food supply. This can result not only from increased food production but also from better protection and preservation of food supplies and the use of better processing techniques in line with advances in food technology. The use of such techniques implies an increased use of food additives. The progress of industrialization, which may lead to contamination of the environment and hence of food, calls for vigilance to prevent health hazards from such contaminants. In an effort to increase supplies, new food sources are being developed, the safety of which should be given close attention.

The Committee recognized that the growing concern in industrialized countries about carcinogenic, mutagenic and teratogenic contaminants is shared by the health authorities in developing countries, as is the concern about special hazards faced by vulnerable population groups.

It was recalled that the Third Joint FAO/WHO Conference on Food Additives and Contaminants had recommended that the Committee deal with contaminants as a matter of high priority and that FAO and WHO proceed quickly with plans to obtain more information on the intake of contaminants and to develop and operate an internationally coordinated food contamination monitoring system within the framework of the global environment monitoring systems under development by the United Nations Environment Programme. It was agreed that such information, together with toxicological data, would permit the assessment of possible risks of contaminants in food and of the need to reduce contamination.

The Committee agreed that the cooperation of scientists familiar with the circumstances and needs of developing countries would materially assist its work on food contaminants and additives. Such cooperation would reciprocally help those scientists themselves to avoid

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<sup>1</sup> See Annex 1, reference 34.

any pitfalls relating to conditions in their countries and facilitate their utilization of the results of the Committee's work.

### **2.3 General principles for toxicological evaluation**

The Committee reiterated the principles stated in its previous reports (see Annex 1) and in the reports of a WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives<sup>1</sup> and a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.<sup>2</sup> In addition, it reaffirmed the need to take advantage of recent developments in toxicological techniques, as expressed in the seventeenth report of the Committee.<sup>3</sup>

Since toxicology is an evolving multidisciplinary science, the Committee felt it important to emphasize that toxicologists should keep themselves abreast of new developments in the relevant disciplines and endeavour to use them to provide for a better assessment of safety.

Substances with established acceptable daily intakes (ADIs) must be re-evaluated as new information (including specifications) becomes available.

### **2.4 Premature replacement of suspect chemicals by less tested substances**

On occasion the results of a toxicological test on a widely used material are difficult to interpret and there will be some uncertainty about its safety. A general problem will arise in relation to food if a long-used and well tested material is found to have some manifestation of toxicity that is difficult to interpret and if that material is consequently replaced by an untested (or less well tested) substance. The problem may be exemplified by the replacement of trichloroethylene by methylene chloride as a caffeine extractant. Similar examples may be found in the field of industrial chemicals and pesticides. It was decided to defer consideration of this problem until a later meeting.

### **2.5 Supply of information**

The Committee reaffirmed the need for adequate information for its preparation of specifications and toxicological evaluation. It therefore recommended that Member Governments requesting an evaluation of a

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<sup>1</sup> WHO Technical Report Series, No. 348, 1967.

<sup>2</sup> WHO Technical Report Series, No. 546, 1974.

<sup>3</sup> See Annex 1, reference 32.

food additive, either directly or through the Codex Alimentarius Commission, should supply the necessary information, including the function of the substance and the justification for its use.

## **2.6 Short-term screening tests**

Tests are being developed that will enable large numbers of substances, including food additives and contaminants, to be screened rapidly and economically for carcinogenicity and other manifestations of toxicity. However, the interpretation of the results of these rapid tests in terms of likely hazard to man is at present not clearly defined. Such tests might eventually be added to the conventional tests used in screening and setting priorities for complete toxicological evaluations of various compounds.

## **3. COMMENTS ON SPECIFIC FOOD ADDITIVES**

The Committee evaluated a number of food additives for the first time and also re-evaluated some substances that had been considered at previous meetings. Points of interest arising from these evaluations are set out below. The acceptable daily intakes and information on specifications are summarized in Annex 2 and the further data required for certain substances are listed in Annex 3. Additional information about the substances is given in the monographs published separately.<sup>1</sup>

### **3.1 Evaluation and re-evaluation**

#### *Aspartame*

In view of the incompleteness of the information available the Committee decided to defer its consideration of aspartame. Tentative specifications were drawn up but no monograph was prepared.

#### *Avian pepsin*

Specifications were prepared for avian pepsin. These included a number of microbiological criteria. As already noted in the report of the nineteenth meeting, the Committee recognized the need to develop a consistent rationale for such microbiological criteria and the related methodology.

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<sup>1</sup> WHO Food Additives Series, Nos. 10 and 11, 1976 ; FAO Food and Nutrition Series, Nos. 1A and 1B, 1976.

11. The fifteenth meeting of the Committee had laid down guidelines for the evaluation of enzymes. Avian pepsin was considered to meet the definition of an enzyme derived from an edible source. Therefore the Committee considered that avian pepsin prepared under hygienic conditions and according to good manufacturing practice is acceptable. No monograph was prepared. This enzyme was placed in the category "ADI not specified".

#### *Bentonite*

The Committee was unaware of any significant use of bentonite in the food industry, and no data were available on impurities in commercially available products. No specifications were drawn up, no monograph was prepared, and no ADI was allocated.

#### *Butylated hydroxyanisole (BHA)*

Revised specifications were available to the Committee. When this antioxidant had been evaluated at the seventeenth meeting, the Committee had specified the need for further work to study the effect on reproduction of mixtures of BHA, butylated hydroxytoluene, and propyl gallate as well as of BHA alone. A reproduction study using BHA alone was now deemed sufficient. The Committee considered newly submitted data concerning mutagenicity studies on BHA. Although behavioural effects related to BHA were observed in mice, studies of the offspring of BHA-fed monkeys indicated no behavioural changes. The Committee decided that there was no reason to change the temporary ADI. A monograph was prepared.

#### *Butylated hydroxytoluene (BHT)*

Revised specifications were available. The Committee discussed new data for BHT including studies in mice in which an increased incidence of lung adenomas compared with control incidence was observed in some studies but not in others. *In vivo* and *in vitro* mutagenicity studies were negative. In light of this and the negative findings in rats the Committee concluded that BHT was not likely to be carcinogenic. However, an appropriate carcinogenicity study conducted according to present-day standards was required.

The Committee considered the previous evaluation and concluded there were sufficient data to permit the continuation of the temporary ADI. A monograph was prepared.

#### *Calcium hydrogen sulfite*

Specifications were prepared. As this substance is used as a source of sulfur dioxide, the Committee agreed to include it in the group evaluation for sulfur dioxide and sulfites.

#### *Carbon dioxide*

The Committee prepared tentative specifications for this substance, excluding the solid form known as "dry ice". It noted that contamination material from oils and greases could arise as a result of contact during compression or release from pressure containers. The variable origin and nature of such contaminants do not at present permit their inclusion among the criteria of purity.

#### *Cellulose, powdered*

Specifications were prepared. These are distinct from the specifications for microcrystalline cellulose (a purified, partially depolymerized form of cellulose) which was re-evaluated<sup>1</sup> in 1973. The only difference in the two specifications that is relevant to toxicological evaluation is that the average molecular weight in powdered cellulose is much greater than in microcrystalline cellulose. The Committee agreed that the evaluation made for microcrystalline cellulose should apply also to cellulose powder. Therefore no new monograph was written, and the title of the present monograph on microcrystalline cellulose will be changed to "powdered cellulose and microcrystalline cellulose" when a new edition is printed.

#### *Cyclamates, calcium and sodium salts*

The Committee discussed the conversion rate of cyclamate to cyclohexylamine, the recent investigations on cyclohexylamine-induced testicular atrophy, and the question of cyclohexylamine-induced hypertension. The Committee agreed that all the data available for these substances should be reviewed before completing the re-evaluation of cyclamates. No monograph was prepared.

#### *Diethylene glycol monoethyl ether*

Tentative specifications were prepared by the Committee. Much of the earlier work had been carried out on samples of diethylene glycol monoethyl ether contaminated by high concentrations of ethylene glycol.

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<sup>1</sup> See Annex 1, reference 32.

Adequate short-term studies on samples containing less than 4 ml ethylene glycol per litre indicated that the pig was the most sensitive species. However, no studies extending for longer than 3 months were available on this species, while the abnormalities were those that might be expected to become more pronounced with prolongation of treatment. No adequate metabolic, carcinogenicity, reproduction or teratogenicity studies were available, and the Committee did not allocate an ADI. A monograph was prepared.

*Esters of glycerol and of thermally oxidized soybean fatty acids*

The Committee indicated a need to establish precise composition and toxicological data for these esters, which cannot be considered as a simple mixture. The data available on thermally oxidized soybean fatty acids were considered insufficient to prepare specifications. No ADI was allocated and the Committee did not draw up specifications or prepare a monograph.

*Gallates—dodecyl, octyl, propyl*

Revised specifications were available to the Committee. An evaluation was made of a new long-term feeding study in mice, which confirms the lack of carcinogenicity of propyl gallate. Mutagenicity studies on propyl gallate were noted to have given negative results. The previously stated requirement for studies on the effects on reproduction of mixtures of BHA, BHT, and propyl gallate was considered to be no longer necessary. The Committee was informed of studies carried out in the USSR on propyl gallate and concluded that the temporary ADI should be continued pending their review. A monograph was prepared.

*Glycerol*

It was noted that synthetic as well as natural glycerol products exist. A monograph was therefore written to include synthetic glycerol. The known impurities such as butanetriols were considered. Specifications were prepared that limit such impurities in synthetic glycerol. The substance was placed in the category "ADI not specified".

*Glycerol diacetate*

Specifications and a monograph for glycerol diacetate were prepared. The substance was placed in the category "ADI not specified".

#### *Glycerol ester of rosin*

Although additional information had become available since the evaluation made at the eighteenth meeting,<sup>1</sup> the Committee recognized the need to characterize more fully the material from which the glycerol ester is prepared, as well as the mode of preparation of the final product. The specifications apply to the additive produced from unmodified rosin.

Further information is desirable to establish the starting rosin material, for example by specifying ratios of abietic to pimaric acids, in addition to specifying the species of pine trees used. It is suggested that other properties, such as refractive index, might be useful to further specify the final product and to exclude products prepared from modified rosin. The starting material from tall oil may present special problems, since it will have undergone various treatments in the sulfate or kraft paper manufacturing process. More information on the contaminants and treatments would be needed to establish the suitability of this material for use in the preparation of a food grade glycerol ester of rosin. The tentative specification already published<sup>2</sup> should be revised when the further information required is available.

The Committee was informed that the esterification necessary to form the glycerol ester required very severe conditions and resulted in a very stable bond. It was therefore considered that long term and reproduction studies should be done on this specific substance before further evaluation. No monograph was prepared.

#### *Glycerol monoacetate*

The Committee was not aware of any use of glycerol monoacetate as a food additive and did not therefore draw up specifications or prepare a monograph.

#### *Magnesium silicate and talc*

The data available permitted tentative specifications to be prepared for synthetic magnesium silicate, but further information is needed to differentiate it from medicinal "magnesium trisilicate".

No new toxicological data have been made available on these compounds. The Committee considered that separate specifications were needed for talc and magnesium silicate. The latter should differentiate between medicinal magnesium trisilicate, which has been reported<sup>3</sup> to

<sup>1</sup> See Annex 1, reference 34.

<sup>2</sup> See Annex 1, reference 36.

<sup>3</sup> See Annex 1, reference 32.

produce renal lesions in dogs in short-term experiments, and the insoluble magnesium silicate used in food processing. To specify talc, a suitable method for the detection of asbestos is required. The earlier specifications, which covered both magnesium silicate and talc, were revoked. A new monograph was not prepared, but the Committee considered that short-term studies are required to determine whether the renal lesions reported with medicinal magnesium trisilicate may also be caused by ingestion of the food grade material. A long-term study on the toxicity of talc of an acceptable specification will also be required before an ADI can be recommended. Magnesium silicate was placed in the category "ADI not specified".

#### *Mannitol*

Specifications were available to the Committee. An interim report was reviewed on the long-term studies being conducted on three strains of female rats. The data were not sufficient to reassess the toxic effects of mannitol. It is hoped the complete data will be available for evaluation at a future meeting. The temporary ADI was retained.

#### *Menthol*

Specifications and some further toxicological data were available to the Committee, but the previously allocated ADI was not changed. The Committee was aware that much larger doses had been taken by man without ill effect, although one report suggested adverse effects had occurred in man following ingestion of 10 times the acceptable daily intake. It was considered desirable to know the average and the range of intake of menthol from food and other sources. Observations on a group of subjects with a higher than average intake of menthol would be desirable. A monograph was prepared.

#### *Mineral oil, food grade*

Two processes, namely the oleum and hydrogenation procedures, are utilized in the manufacture of mineral oil but, because insufficient information was available on the impurities likely to be present in products obtained by hydrogenation, only the oleum treated products were considered. It was also noted that antioxidants were present in food grade mineral oil and that these substances caused interference in the analytical procedures for polycyclic aromatic hydrocarbons. Because of the lack of a suitable method that would take this fact into account, the existing specifications were made tentative. Additional information is required. A monograph was prepared and the previous categorization "ADI not specified" was confirmed.

*Natamycin (pimaricin)*<sup>1</sup>

The specifications were revised. New information was available on the effects of breakdown products and the development of microbial resistance to the antimycotic if it is used for food preservation. While the Committee expressed general concern about the use of therapeutic agents in food, it agreed that the data on natamycin showed that problems were unlikely to arise from microbial resistance. Annex 4 discusses some of the problems of using therapeutic and antimicrobial substances in food. An ADI was allocated and a monograph was prepared.

*Nitrites, sodium and potassium salts*

Several recent studies on packs of cured meats inoculated with microorganisms indicate that initial nitrite concentrations of the order of 150-200 mg/kg are needed for the effective control of *Clostridium botulinum*. Further data have become available on nitrites and on the formation of nitrosamines *in vivo*. A new monograph was prepared. Examination of reports of a WHO task group and the IARC working group<sup>2</sup> on nitrosamines have not provided sufficient evidence to revise the temporary status of the ADI. The existing specifications remain tentative.

*Nitrogen*

Tentative specifications were prepared.

*Orange RN*

No data had been made available to the Committee since the nineteenth meeting and no evaluation could be made. The Committee did not compile specifications or prepare a monograph.

*Oxidized hydroxypropyl distarch glycerol*

Tentative specifications were drawn up but the Committee did not prepare a monograph because of the need to elucidate principles that would apply to modified starches in general (see section 3.3).

*Sorboyl palmitate*

No new data were made available. The Committee, noting that this substance may not at present be available commercially, decided not to prepare either specifications or a monograph.

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<sup>1</sup> Natamycin is the international nonproprietary name of this substance, hitherto referred to as pimaricin in the reports of the Expert Committee.

<sup>2</sup> *Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents*. Lyons, International Agency for Research on Cancer, 1974 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, volume 4).

### *Sucrose esters of fatty acids and sucroglycerides*

Since these are two distinct products, separate specifications were prepared to replace the previous single specifications, which were revoked. In sucroglycerides dimethyl formamide (DMF) was limited to 10 mg/kg. DMF should not be detectable in sucrose esters of fatty acids. The differences in the specifications were not of toxicological significance, and a combined monograph was prepared. The Committee reviewed a long-term mouse study on mixed palmitic/stearic ester and information on the metabolism of sucrose monopalmitate. The previous temporary ADI was confirmed.

### *Trichloroethylene*

At an earlier meeting the Committee had evaluated this substance as a caffeine extractant and considered this particular use acceptable<sup>1</sup>. It now reviewed a report indicating that trichloroethylene is carcinogenic in mice. However, since the studies as reported were not completely satisfactory, the Committee agreed that well conducted carcinogenicity studies should be carried out. Additional data on the levels and nature of residues present in extracted foods should also be provided. The Committee revoked the previously accepted use and the existing specifications pending a review of the required information. A monograph was prepared.

## **3.2 Review of specifications**

### *Chlorine dioxide*

The specifications previously prepared<sup>2</sup> were not revised. Chlorine dioxide is not known to be available commercially and is normally generated *in situ*. The Committee stressed the need to ensure that only appropriate food grade materials are used to generate chlorine dioxide.

### *Hydrochloric acid*

The specifications were revised. Hydrochloric acid may be prepared in various ways, *inter alia* as a by-product in the manufacture of substances such as organochlorine compounds. Hydrochloric acid from such processes may not be of food grade quality. The need for further information on contaminants and on methods of determining them was stressed.

<sup>1</sup> See Annex 1, reference 22.

<sup>2</sup> See Annex 1, reference 7.

*Lactic acid*

Lactic acid may be prepared by the hydrolysis of cyanohydrins. Residues of CN compounds may be found in lactic acid manufactured by this process. The need for more precise information on the levels of these compounds present in commercial products was stressed as a prerequisite for the selection of a suitable limit test. Revised specifications prepared were designated "tentative".

*Pentasodium triphosphate*

Revised specifications were prepared.

*Polyvinylpyrrolidone (PVP)*

Revised specifications were prepared.

*Propylene glycol*

Revised specifications were prepared.

*Sodium polyphosphate, glassy*

The nomenclature of this substance was changed from "sodium polyphosphate" to "sodium polyphosphate, glassy" and revised specifications were prepared.

*Sorbic acid*

Revised specifications were prepared.

*Sorbitol*

Revised specifications were prepared.

*Sulfuric acid*

Revised specifications were prepared.

*Tartaric acid*

The question whether the specification should exclude the DL isomer was not resolved. The revised specifications were therefore prepared for L-(+)-Tartaric acid and made tentative.

**3.3 Chemically modified starches**

The Committee considered the significance of kidney lesions found in long-term studies in rats fed with diets containing from 5% to 25% of different chemically modified starches. The lesions were characterized

by localized hyperplasia of the pelvic epithelium of the renal medulla associated with focal calcification in the hyperplastic areas. In some cases the hyperplasia was pronounced, and occasionally it was associated with cystic dilatation of distal tubules and slight hydronephrosis. The findings did not seem to be associated with kidney or bladder calculi formation, although the occurrence of very small stones (microlithiasis) was not excluded. The lesion is different from the common finding of mineral deposits in the cortico-medullary junction of kidneys seen in some strains of rats (nephrocalcinosis).

The lesion was found in both control and treated groups. The incidence and severity was highest at the highest dose level but no dose/response relationship was found. Similar lesions have been seen in rats fed diets with high levels of lactose,<sup>1</sup> and alginate,<sup>2</sup> and magnesium<sup>3</sup> and in uninephrectomized rats fed diets containing excess sodium chloride.<sup>4</sup>

Rats fed the modified starches also have caecal enlargement, often associated with diarrhoea, increased microbial fermentation in the large intestine, decreased pH of intestinal contents and urine, alterations of the acid/base balance and other associated changes.

The Committee was informed that experiments designed to elucidate the pathogenesis of the lesion in the rat were in progress.

The Committee recommended that further studies on the kidney lesions should involve examination of physical and chemical changes in urine, including urine volume, pH, and osmolality. The effects of diet composition, especially in relation to minerals, and the effect of the presence of the parasite *Trichosomoides crassicauda* should also be investigated. Moreover it should be determined whether the lesion can be induced in species other than the rat and in the strains of control rats in which the lesion does not occur. However, the Committee did not feel that the kidney lesions found in rats fed chemically modified starches were likely to be relevant to the problem of urinary calculi in humans.

The Committee considered that it would be desirable to have additional data on the metabolism of the modified starches in laboratory animals.

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<sup>1</sup> DE GROOT, A. P. & FERON, V. J. Unpublished report No. R 4812, Central Institute for Nutrition and Food Research TNO, Zeist, Netherlands, 1976.

<sup>2</sup> DE GROOT, A. P. Unpublished report. Copies available on request from Food Additives, World Health Organization, Geneva, Switzerland.

<sup>3</sup> MAGNUSSON, G. & RAMSAY, C. H. *Zeitschrift für Versuchstierkunde*, **17**: 185 (1975).

<sup>4</sup> LALICH, J. J. ET AL. *Archives of pathology*, **97**: 29 (1974).

There is a need for clearly defined specifications and analytical data on the residues of modifying agents and on the potential reaction products (such as chlorhydrins) from chemically treated starches. The Committee was informed of progress in this field and of the further work that is under way.

It was concluded that no new modified starches should be considered pending the resolution of the above questions.

The Committee recommended that chemically modified starches should be re-evaluated at a future meeting when results of the studies in progress and the studies suggested become available and when the chemical aspects have been clarified.

#### 4. PRIORITIES FOR THE EVALUATION OF FLAVOURING SUBSTANCES

At its eleventh meeting<sup>1</sup> the Committee had evaluated a limited number of flavouring substances and at its seventeenth meeting<sup>2</sup> had commented on the procedures adopted by the Council of Europe. The Committee now re-emphasized that flavouring substances should not be exempted from the toxicological evaluation applicable to food additives in general, and that "naturalness" *per se* is no guarantee of safety. Evaluation should be flexible; it may require extensive toxicological testing or may be made simply from available data. In carrying out evaluations, the work of other bodies should be taken into consideration.

Considering the vast number of flavouring substances and materials involved, many of which have a long history of use, the Committee agreed that there was an urgent need to establish some means of deciding in which order they should be evaluated.

The Committee felt that the best approach would be to compile lists of the various flavouring substances and to estimate the likely degree of exposure to each of them. A group of toxicologists and flavour and food technologists should then classify the listed substances in terms of possible health hazard.

Among the factors to be considered in proposing priorities for flavouring substances are:

- the total amount of each substance likely to be consumed by the average person,

<sup>1</sup> See Annex 1, reference 14.

<sup>2</sup> See Annex 1, reference 32.

- the frequency of exposure of individuals to the substance,
- the possibility that a particular age or other group may be highly exposed,
- the similarity of the chemical structure with that of substances of known toxicological and biochemical properties,
- the availability of information sufficient to characterize the substance so that meaningful toxicological evaluation can be made, and
- the nature and source of the substance.

With regard to the last-mentioned point it should be noted that flavouring substances fall into four groups :

- (1) artificial substances unlikely to occur naturally in food ;
- (2) natural materials not normally consumed as food, their derived products, and the equivalent nature-identical flavourings ;
- (3) herbs and spices, their derived products, and the equivalent nature-identical flavourings ; and
- (4) natural flavouring substances obtained from vegetable and animal products and normally consumed as food, whether processed or not, and their synthetic equivalents.

Ideally, this approach should result in a list of flavouring substances in decreasing order of potential hazard. Development of such a priority list could be carried out by an FAO/WHO working group or a group of consultants.

The Committee recommended that, owing to the magnitude of the task and the long time it would take to complete, substances deemed to be of lower priority might be tentatively accepted for use in foods if they are listed as acceptable by organizations such as the Council of Europe or by national regulatory agencies that have carried out detailed evaluation.

## 5. FUTURE WORK

1. The Committee referred to the need to continue with many of the broad areas of work outlined in its seventeenth report<sup>1</sup> and endorsed in its nineteenth report<sup>2</sup>. In particular it noted that the Codex Alimentarius Commission, the principal organ of the Joint FAO/WHO Food Standards Programme, has the function of drawing up international food

<sup>1</sup> See Annex 1, reference 32.

<sup>2</sup> See Annex 1, reference 37.

standards to protect the health of the consumer and facilitate international trade in food. To provide the necessary scientific basis for the work of the Codex Alimentarius Commission, the Committee should continue to evaluate those food additives and consider those contaminants for which it is proposed to include provisions in the Codex standards.

2. In toxicological experimentation attention is nowadays being given more frequently to the investigation of behavioural changes, clinical neurological abnormalities, and adverse effects on special senses, and to the correlation of these factors with electrophysiological monitoring and neuropathology. The Committee thought that this subject should be discussed fully at a future meeting in view of the difficulties in interpreting the results of such toxicity investigations in terms of likely hazard to humans of the substances tested.

3. The Committee should consider the relevance of short-term screening tests to the toxicological evaluation of food additives and contaminants (see section 2.6).

4. The Committee dropped the requirement for teratogenicity and reproduction studies on combinations of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and the gallates. This should also apply to tertiary butyl hydroquinone (TBHQ). In addition, it was noted that in determining combined ADIs, TBHQ should be included together with BHA and BHT. Therefore it was suggested that TBHQ should be re-evaluated.

5. L-(+)-Tartaric acid has been evaluated, but increasing need for use of the DL form was brought to the attention of the Committee for future consideration.

6. A number of food additives have been allocated temporary ADIs. These should be re-evaluated when required information becomes available.

7. At its sixteenth meeting<sup>1</sup> the Committee had recommended that a review should be made of the special problems of the exposure of infants and children to contaminants in food. The Codex Committee on Foods for Special Dietary Uses having referred to the need to act on that recommendation, the Committee suggested early consideration of tolerable intakes by such vulnerable groups of mercury, lead, cadmium, and possibly other contaminants.

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<sup>1</sup> See Annex 1, reference 31.

## 6. RECOMMENDATIONS TO FAO AND WHO

1. The Committee re-emphasized the view of the Third Joint FAO/WHO Conference on Food Additives and Contaminants that many food contaminants pose potential health hazards and recommended that early action be taken to evaluate such important contaminants as mycotoxins, nitroso compounds, certain heavy metals and metalloids, and polychlorinated biphenyls (see section 2.2).

2. FAO/WHO should arrange for a small working group of toxicologists and flavour and food technologists to prepare a list of flavouring substances in order of decreasing potential health hazard based on the criteria discussed in section 4, for eventual evaluation by the Committee. In the meantime action should be taken to gather the necessary data and information.

3. Food from new or unconventional sources may become more important in supplying the needs of the world (see section 2.2). The safety of food from such sources should be properly assessed.

4. Because of the increasing sensitivity of analytical methods, ever more minute amounts of chemical contaminants are being detected in food. Where contamination is unavoidable but represents a real or theoretical hazard to health (as in the case of unavoidable chemical carcinogens) an effort should be made to establish "practical threshold levels". Consideration should be given to the feasibility of establishing these levels, which should be consistent with the need for adequate food supplies and with the best agricultural and manufacturing methods.

5. The Committee reiterated that microbiological criteria are needed for certain food additives, and that a consistent rationale is required in their application and inclusion in specifications. Consideration might be given to having this problem taken up in the near future by an appropriate group of experts in microbiology such as the *ad hoc* FAO/WHO expert consultation on microbiological specifications for foods.

6. Considering the number of food additives in use and the likelihood of the presence of multiple contaminants in food as well as the exposure of man to many environmental chemicals, the Committee stressed the need to explore in depth the influence on toxicity of the interaction between these chemicals.

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

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

Documents marked with an asterisk may be obtained on request from : Food Additives, World Health Organization, 1211 Geneva 27, Switzerland, or from Food Standards and Food Science Service, Food and Agriculture Organization of the United Nations, 00100 Rome, Italy.

1. *General principles governing the use of food additives.* (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957 ; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of intentional food additives to establish their safety for use.* (Second report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 17, 1958 ; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants).* (Third report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. I. *Antimicrobial preservatives and antioxidants*, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. *Specifications for identity and purity of food additives (food colours).* (Fourth report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. II. *Food colours*, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. *Evaluation of the carcinogenic hazards of food additives.* (Fifth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 29, 1961 ; WHO Technical Report Series, No. 220, 1961 (out of print).
6. *Evaluation of the toxicity of a number of antimicrobials and antioxidants.* (Sixth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 31, 1962 ; WHO Technical Report Series, No. 228, 1962.
7. *Specifications for the identity and purity of food additives and their toxicological evaluation : emulsifiers, stabilizers, bleaching and maturing agents.* (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 35, 1964 ; WHO Technical Report Series, No. 281, 1964 (out of print).
8. *Specifications for the identity and purity of food additives and their toxicological evaluation : food colours and some antimicrobials and antioxidants.* (Eighth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 38, 1965 ; WHO Technical Report Series, No. 309, 1965 (out of print).

- \*9. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants.* FAO Nutrition Meetings Report Series, No. 38A, 1965 ; WHO/Food Add/24.65.
- \*10. *Specifications for identity and purity and toxicological evaluation of food colours.* FAO Nutrition Meetings Report Series, No. 38B, 1966 ; WHO/Food Add/66.25.
- 11. *Specifications for the identity and purity of food additives and their toxicological evaluation : some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases.* (Ninth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 40, 1966 ; WHO Technical Report Series, No. 339, 1966.
- 12. *Specifications for the identity and purity of food additives and their toxicological evaluation : some emulsifiers and stabilizers and certain other substances.* (Tenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 43, 1967 ; WHO Technical Report Series, No. 373, 1967.
- \*13 *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases.* FAO Nutrition Meetings Report Series, No. 40A, B, C ; WHO/Food Add/67.29.
- 14. *Specifications for the identity and purity of food additives and their toxicological evaluation : some flavouring substances and non-nutritive sweetening agents.* (Eleventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 44, 1968 ; WHO Technical Report Series, No. 383, 1968.
- \*15. *Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968 ; WHO/Food Add/68.33.
- \*16. *Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44B, 1969 ; WHO/Food Add/69.31.
- 17. *Specifications for the identity and purity of food additives and their toxicological evaluation : some antibiotics.* (Twelfth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 45, 1969 ; WHO Technical Report Series, No. 430, 1969.
- \*18. *Specifications for the identity and purity of some antibiotics.* FAO Nutrition Meetings Report Series, No. 43A, 1969 ; WHO/Food Add/69.34.
- 19. *Specifications for the identity and purity of food additives and their toxicological evaluation : some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances.* (Thirteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 46, 1970 ; WHO Technical Report Series, No. 445, 1970.
- \*20. *Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents and certain other substances.* FAO Nutrition Meetings Report Series, No. 46A ; WHO/Food Add/70.36.
- \*21. *Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents and certain other food additives.* FAO Nutrition Meetings Report Series, No. 46B ; WHO/Food Add/70.37.

22. *Evaluation of food additives : specifications for the identity and purity of food additives and their toxicological evaluation : some extraction solvents and certain other substances ; and a review of the technological efficacy of some antimicrobial agents.* (Fourteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 48, 1971 ; WHO Technical Report Series, No. 462, 1971.
- \*23. *Toxicological evaluation of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48A, 1971 ; WHO/Food Add/70.39.
- \*24. *Specifications for the identity and purity of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48B, 1971 ; WHO/Food Add/70.40.
- \*25. *A review of the technological efficacy of some antimicrobial agents.* FAO Nutrition Meetings Report Series, No. 48C, 1971 ; WHO/Food Add/70.41.
26. *Evaluation of food additives : some enzymes, modified starches, and certain other substances : toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants.* (Fifteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 50, 1972 ; WHO Technical Report Series, No. 488, 1972.
27. *Toxicological evaluation of some enzymes, modified starches and certain other substances.* FAO Nutrition Meetings Report Series, No. 50A, 1972 ; WHO Food Additives Series, No. 1, 1972.
28. *Specifications for the identity and purity of some enzymes and certain other substances.* FAO Nutrition Meetings Report Series, No. 50B, 1972 ; WHO Food Additives Series, No. 2, 1972.
29. *A review of the technological efficacy of some antioxidants and synergists.* FAO Nutrition Meetings Report Series, No. 50C, 1972 ; WHO Food Additives Series, No. 3, 1972.
30. *Evaluation of certain food additives and the contaminants mercury, lead and cadmium.* (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972 ; WHO Technical Report Series, No. 505, 1972, and corrigendum.
31. *Evaluation of mercury, lead, cadmium and the food additives amaranth, diethyl-pyrocyanate and octyl gallate.* FAO Nutrition Meetings Report Series, No. 51A, 1972 ; WHO Food Additives Series, No. 4, 1972.
32. *Toxicological evaluation of certain food additives with a review of general principles and of specifications.* (Seventeenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 53, 1974 ; WHO Technical Report Series, No. 539, 1974, and corrigendum.
33. *Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents.* FAO Nutrition Meetings Report Series, No. 53A ; WHO Food Additives Series, No. 5, 1974.
34. *Evaluation of certain food additives.* (Eighteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 54, 1974 ; WHO Technical Report Series, No. 557, 1974, and corrigendum.
35. *Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 54A, 1975 ; WHO Food Additives Series, No. 6, 1975.

36. *Specifications for the identity and purity of some food colours, flavour enhancers, thickening agents and certain food additives.* FAO Nutrition Meetings Report Series, No. 54B, 1975 ; WHO Food Additives Series, No. 7, 1975.
37. *Evaluation of certain food additives : some food colours, thickening agents, smoke condensates, and certain other substances.* (Nineteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 55, 1975 ; WHO Technical Report Series, No. 576, 1975.
38. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series No. 55A. WHO Food Additives Series, No. 8, 1975.

Annex 2

ACCEPTABLE DAILY INTAKES AND INFORMATION  
ON SPECIFICATIONS

<i>Substance</i>	<i>Specifications</i> <sup>1</sup>	<i>ADI</i> (mg/kg body weight)
aspartame	NT	Decision postponed
avian pepsin	N	ADI not specified <sup>2</sup>
bentonite	O	No ADI allocated
butylated hydroxyanisole	RT	0-0.5 <sup>3,4</sup>
butylated hydroxytoluene	RT	0-0.5 <sup>3,4</sup>
calcium hydrogen sulfite	N	0-0.7 <sup>5</sup>
cellulose, powdered	N	ADI not specified <sup>2</sup>
cyclamates, sodium and calcium salts	T	No ADI allocated
diethylene glycol monoethyl ether	NT	No ADI allocated
esters of glycerol and thermally oxidized soybean fatty acids	O	No ADI allocated
gallates, dodecyl, octyl, propyl	RT	0-0.2 <sup>3,6</sup>
glycerol	N	ADI not specified <sup>2</sup>
glycerol diacetate	N	ADI not specified <sup>2</sup>
glycerol ester of rosin	T	No ADI allocated
magnesium silicate	RT <sup>7</sup>	ADI not specified <sup>2,3</sup>
mannitol	T	0-50 <sup>8</sup>
menthol	S	0-0.2
mineral oil, food grade	T	ADI not specified <sup>2</sup>
nitrites, sodium and potassium salts	T	0-0.2 <sup>3,8</sup>
orange RN	O	No ADI allocated
oxidized hydroxypropyl distarch glycerol	NT	Decision postponed
pimaricin	R	0-0.3
sorboyl palmitate	O	No ADI allocated
sucrose esters of fatty acids	RT	0-2.5 <sup>9</sup>
sucroglycerides	RT	0-2.5 <sup>9</sup>
trichloroethylene	O <sup>10</sup>	No ADI allocated <sup>10</sup>

Specifications only

<i>Substance</i>	<i>Specifications</i> <sup>1</sup>
carbon dioxide (except "dry ice")	NT
hydrochloric acid	R
lactic acid	RT
nitrogen	NT
pentasodium triphosphate	R
polyvinylpyrrolidone	R
propylene glycol	R
sodium polyphosphate, glassy	R
sorbic acid	R
sorbitol	R
sulfuric acid	R
L-(+)-tartaric acid	R

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

<sup>2</sup> The statement "ADI not specified" means that, on the basis of the available data (chemical, biochemical, toxicological and other), the total daily intake of the substance, arising from its use or uses at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, and for the reasons stated in the individual evaluations, the establishment of an acceptable daily intake (ADI) is not deemed necessary.

<sup>3</sup> Temporary.

<sup>4</sup> As BHA, BHT, or the sum of the two chemicals.

<sup>5</sup> Included in the group evaluation of sulfur dioxide and sulfites.

<sup>6</sup> Applicable to individual gallates or their sum. (Notes : *n*-octyl gallate should not be used in beverages).

<sup>7</sup> Previous specifications for "magnesium silicate and talc" are revoked.

<sup>8</sup> Food for babies less than 6 months old should not contain added nitrites.

<sup>9</sup> As sucrose esters of fatty acids, sucroglycerides, or the sum of both ; previous specifications for sucrose esters of fatty acids and sucroglycerides are revoked.

<sup>10</sup> The permitted use as an extractant is withdrawn, and the previous specifications are revoked.

### Annex 3

#### FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED

*Butylated hydroxyanisole*<sup>1</sup>

A multigeneration reproduction study.

*Butylated hydroxytoluene*<sup>1</sup>

An adequate carcinogenicity study meeting currently accepted standards.

*Diethylene glycol monoethyl ether*<sup>2</sup>

Studies on absorption, distribution, excretion and metabolism; an adequate carcinogenicity study in the rat; a 6-month study in the pig; studies of the effects on reproduction and possibly of teratogenicity.

*Magnesium silicate*<sup>1</sup>

Short-term studies to determine whether the renal lesions reported with medicinal magnesium trisilicate may also be caused by ingestion of the food grade material.

*Menthol*<sup>3</sup>

Long-term toxicity and carcinogenicity study in rats; information on the average and maximum likely intakes of menthol; clinical observations on subjects with a higher than average intake of menthol; metabolism studies.

*Propyl gallate*<sup>1</sup>

Submission of the results of studies in progress in the USSR.

*Nitrite, potassium and sodium salts*

These compounds should be kept under regular review at future meetings.

*Sucrose esters of fatty acids and sucroglycerides*<sup>1</sup>

Studies on individual sucrose esters to demonstrate their likely sites and degree of hydrolysis; a 6-month toxicological study in a non-rodent species on a sucrose ester other than sucrose palmitate.

*Talc*<sup>2</sup>

A long-term study on the toxicity of talc of an acceptable specification.

*Trichloroethylene*<sup>2</sup>

Two long-term studies by the oral route; levels and nature of residues.

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<sup>1</sup> Information required by 1980.

<sup>2</sup> Further work required before an acceptable daily intake can be allocated.

<sup>3</sup> Information desirable.

NOTES ON THE USE OF THERAPEUTIC AND  
ANTIMICROBIAL SUBSTANCES IN FOOD

The Committee re-evaluated natamycin<sup>1</sup> (see section 3.1) and considered in this connexion certain problems and principles.

Natamycin is widely used in medicine as an antimycotic mainly for external application. There are rare oral applications (against intestinal candidiasis), but, because it is inactive against bacteria, it produces no significant effect on the normal intestinal flora. It is insoluble in water and is not absorbed from the intestine. No allergic reactions have been reported.

Objections to the use of therapeutic antibiotics in food are based on the following factors.

(1) There is a rapid appearance of high levels of acquired resistance in intestinal bacteria when antibiotics (especially tetracyclines or streptomycin) are ingested. The levels may become so high, indeed, that the greater concentrations used therapeutically cease to be effective.

(2) Resistance to one antibiotic of a group (e.g., tetracyclines) is accompanied by "cross-resistance" to others of that group.

(3) There is a simultaneous transfer of resistance to antibiotics and drugs unrelated to the one used to induce the resistance.

(4) There is a ready transfer of resistance from harmless to pathogenic Gram-negative bacteria, diminishing the therapeutic value of the antibiotic.

These phenomena occur slightly or not at all with natamycin, which has virtually no effect on bacteria and is not used to control them. Natamycin produces unusually little resistance among fungi and yeasts, and then only by selection and not by induction and only to levels corresponding to those applied. The same is true of related polyene antimycotics.

Cross-resistance between antifungal polyenes is relatively infrequent. In particular, resistance to natamycin seldom implies resistance to related polyenes. Although cross-resistance with nystatin and amphotericin has been observed, selection of natamycin-resistant strains *in vitro* has never been accompanied by such cross-resistance.<sup>2,3</sup>

Transferable resistance between bacterial cells depends on the transfer of DNA and does not occur with yeasts and fungi, which have a different cell-wall barrier.

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<sup>1</sup> Natamycin is the international nonproprietary name for the antibiotic referred to as pimaricin in previous reports of the Expert Committee.

<sup>2</sup> RAAB, W. P., *Natamycin*. Stuttgart, Georg Thieme, 1972.

<sup>3</sup> KHOUDOKORMOFF, B. & PETRU, M. On the possible development of antibiotic resistance amongst fungi, with special reference to the use of pimaricin as a preservative in the food industry. Unpublished report submitted to WHO by Gist-Brocades N.V., 1976. Copies are available on request from Food Additives, World Health Organization, Geneva, Switzerland.

It appears therefore that the usual objections to the use of therapeutic antibiotics in foods have little relevance to natamycin.

Natamycin is used as a food additive to prevent the surface growth of moulds, which could in principle produce mycotoxins. This is an important advantage and one regarded by some experts as sufficient to offset any misgivings about the use of therapeutic antibiotics in food.<sup>1</sup>

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<sup>1</sup> EEK, T. VAN. Mycotoxins and the feasibility of the control of their occurrence by means of pimaricin. Unpublished report from the Ministry of Public Health and Environmental Hygiene, Netherlands, submitted to WHO by Gist-Brocades N.V., 1975. Copies are available on request from Food Additives, World Health Organization, Geneva, Switzerland.