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Evaluation of certain food additives

Twenty-fourth Report of the
Joint FAO/WHO Expert Committee on
Food Additives



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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 24 March – 2 April 1980

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EVALUATION OF CERTAIN FOOD ADDITIVES

Twenty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 24 March to 2 April 1980. The session was opened by Dr Z.I. Sabry, Director, Food Policy and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Sabry said that, in order to respond to rapidly evolving scientific and technological knowledge, WHO and FAO were constantly reviewing their activities. One of the principal objects of the proposed WHO International Programme on Chemical Safety was to speed up the current evaluation of food additives and contaminants without jeopardizing its quality. It was hoped to achieve that object by involving international organizations at the planning stage of the work of a few national institutions on food additives. The Joint FAO/WHO Expert Committee on Food Additives would continue to function as in the past, carrying out chemical and toxicological evaluations of food additives through international groups of experts acting in their personal capacity.

1. INTRODUCTION

As a result of the recommendation of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,¹ there have been 23 previous meetings of the Committee (see Annex 1). The present meeting was convened on the recommendation made at the twenty-third meeting (see Annex 1, reference 51). The terms of reference of the Committee were: (1) to prepare specifications and carry out a toxicological evaluation of food additives; (2) to review the findings of toxicological studies of certain food additives; (3) to revise specifications for certain food additives, including antioxidants,

¹FAO Nutrition Meetings Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

emulsifiers, colours, and thickening agents; (4) to undertake a toxicological re-evaluation of certain food additives; (5) to develop specifications for certain artificial flavouring substances, phosphates, and other substances; and (6) to review the importance of technological and nutritional considerations in assessing the safety of food additives.

2. GENERAL CONSIDERATIONS

2.1 Modification of agenda

WHO requested that the Committee should evaluate recent results on the potential carcinogenicity of hydrogen peroxide. The Committee agreed to re-evaluate the status of this substance, which, under special circumstances, may be used to preserve milk, particularly in regions where refrigeration facilities are lacking.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (see Annex 1) and by a WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives,² and a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.³ In addition, it reaffirmed the need to take advantage of recent developments in toxicological techniques, as stated at its seventeenth meeting (see Annex 1, reference 32).

2.3 Noncariogenic substances

At several previous meetings, the Committee had been informed that certain substances being evaluated for use as food additives (e.g., xylitol) were noncariogenic. A claim that hydrogenated glucose syrup was free from cariogenic activity was considered by the Committee, which recommended that data in support of such claims should be evaluated by WHO and reiterated the view that it should deal only with matters pertaining to the safety of substances for use as food additives.

² WHO Technical Report Series, No. 348, 1967.

³ WHO Technical Report Series, No. 546, 1974.

2.4 Support for continuing the work of the Committee

Note was taken of the statement made to the Committee on behalf of WHO during the recent meeting of the Codex Alimentarius Commission to the effect that both the Committee and the Joint FAO/WHO Meeting on Pesticide Residues "would continue to function as in the past to carry out toxicological evaluations by international groups of experts appointed by the Directors-General of the sponsoring agencies and acting in their personal capacity. It was, moreover, planned to increase the support to these Expert Committees with a view to holding two or more meetings in one year".⁴

2.5 Publication of reports

The Committee regretted that it had not been possible to implement the recommendation of the Third Joint FAO/WHO Conference on Food Additives and Contaminants,⁵ to the effect that the Directors-General of FAO and WHO should make available the necessary resources to publish the reports and monographs of the Committee more quickly. The Committee noted the statement, in paragraph 195 of the 12th Report of the Codex Alimentarius Commission (April 1978), that the sponsoring organizations were again requested to ensure timely issue of the Committee's reports and that they had agreed on new procedures to solve this problem.

The Committee noted that the report of its twenty-third meeting (April 1979) had not yet been published (see Annex 1, reference 51) and urged the sponsoring agencies, FAO and WHO, to investigate the best means of accelerating publication of its reports.

2.6 Implications of temporary acceptance of food additives

The Committee expressed the view that FAO and WHO should convey clearly to governments and other interested parties that temporary acceptance of additives is made on the understanding that the recommendations for "further work required" will be actively

⁴ Report of the Thirteenth Session of the Joint FAO/WHO Codex Alimentarius Commission, Rome, 3-14 December 1979. Rome, 1979 (ALINORM 79/38).

⁵ Report of the Third Joint FAO/WHO Conference on Food Additives and Contaminants, Geneva, 22-26 October 1973. Rome and Geneva, 1974 (unpublished document WHO/FOOD ADD/74.43; FAO Miscellaneous Meeting Reports Series - ESN:MMS 74/6).

pursued. The time limits proposed by the Committee to complete further investigations are those which, in its opinion, would create no hazard to public health. Failure to submit data within the specified period may lead to withdrawal of the temporary acceptance. Extension of periods for further work is also possible and the decision may be made by the Committee on the basis of new information or a re-evaluation of existing data, confirming that there are no hazards to public health. The periods proposed by the Committee take into account the availability of testing facilities and are recommended on the understanding that the reports of the Committee will be communicated promptly to interested parties.

2.7 Testing of impurities and transformation products

The need, under certain circumstances, for impurities or transformation products of food additives to be tested separately was pointed out at the nineteenth meeting of the Committee (see Annex 1, reference 37). Diketopiperazine is an impurity and a transformation product of aspartame, and requires separate testing and evaluation. As a guide to food control authorities, a separate ADI for diketopiperazine needs to be established on the basis of existing toxicological studies (see section 3.7).

2.8 Special problems posed by the evaluation of modified food ingredients

The Committee has become increasingly concerned with the development of materials designed as substitutes for normal components of food rather than as food additives. Questions of nutritional adequacy arise in such instances and must not be overlooked. In addition, test procedures for materials ingested in large amounts pose special problems to the toxicologist. The Committee believes that the problems associated with the designing of tests to assess the toxicity of these substances and with their interpretation and extrapolation to man require special consideration.

2.9 Technological and nutritional considerations

The Committee reviewed the importance of technological and nutritional considerations in the safety assessment of food additives. At its thirteenth meeting, in 1969 (see Annex 1, reference 19), the Committee had recommended to FAO and WHO that the efficacy of

food additives should be studied, and that the resulting information should be included in monographs for the benefit of potential users. It had also been suggested that further subjects for study were the possible reactions between additives and nutrients or other food constituents, and the possible occurrence of degradation products.

At its fourteenth and fifteenth meetings (see Annex 1, references 22 and 26), the Committee reviewed the efficacy of a number of antimicrobial agents, antioxidants, and synergists, and monographs were subsequently published. However, these monographs are essentially reviews of the literature.

The Committee felt that any further review of efficacy would produce little other than an extension of the previous literature reviews. The available data on efficacy were best interpreted by individual food manufacturers with a thorough knowledge of their own products and manufacturing-plant capabilities. For these reason, the Committee recommended that it should not extend its previous reviews of efficacy.

The acceptability of food additives depends on the evaluation of toxicological data on the additive itself. However, reactions of the additive with food components, including other additives, may occur during food manufacture, storage, and cooking. In addition, degradation of the additive may occur. These chemical changes may be of toxicological and/or nutritional significance. It was re-emphasized that a better perspective of the safety of food additives would be gained if information on their manufacture and technological uses were more readily available. Such information should cover commercial methods of production, the levels of use of additives in various food commodities in different countries, and any available data on the chemical fate of each additive in those foods and on the effects of additives on nutrients.

Ways and means should be explored of obtaining more data and presenting them to the Committee in a readily understandable form. It may even be necessary sometimes to carry out a study on the technological versus nutritional effects of certain additives and to present this information to the Committee.

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 intake and information on specifications are summarized in Annex 2 and the "further work required" for certain substances is shown in Annex 3.

3.1 Anticaking agents

Talc

Studies available to the Committee demonstrated that talc was nonmutagenic both *in vitro* and *in vivo*. The Committee noted the lack of an adequate long-term study to assess the carcinogenic potential of a well-defined talc when administered by the oral route. The previously established "temporary ADI not specified" was maintained. An adequate long-term feeding study is required by 1983.

No toxicological monograph was prepared. New specifications were prepared.

Magnesium silicate

This substance was evaluated by the Committee in 1976 (see Annex 1, reference 40), at which time a temporary ADI "not specified" was established and specifications were revised which included magnesium trisilicate. Short-term studies to determine whether the renal lesions reported with medicinal magnesium trisilicate may also be caused by the ingestion of food-grade magnesium silicate were requested.

The requested data were not available to the present Committee. The "temporary ADI not specified" was extended until 1982.

No toxicological monograph was prepared. The existing tentative specifications for magnesium silicate, including magnesium trisilicate, were not revised.

3.2 Food antimicrobials

Hydrogen peroxide

This food additive was last evaluated for acceptable daily intake by the Committee in 1973 (see Annex 1, references 32 and 33). No ADI was allocated. At that time the Committee stated that, in view of the limited data available, hydrogen peroxide should be used only where better methods of milk preservation are not available.

The attention of the Committee was drawn to an unpublished Japanese study⁶ submitted to WHO by the Japanese Ministry of Health and Welfare. In this study, C57BL/6J mice were given hydrogen peroxide in their distilled drinking water from 8 weeks to 108 weeks of age. There were three groups, each of approximately 50 male and 50 female mice. One group received 0.4% of hydrogen peroxide, the second received 0.1%, and the third (the control group), 0. A statistically significant increased incidence of gastric and duodenal erosions and adenocarcinoma of the duodenum was reported in the two treated groups. Certain lesions were reported in the control mice that are not usually noted in the literature. Some controls, for example, developed hyperplastic nodules in the glandular stomach and hyperplasia in the duodenum. The duodenal carcinomas reported are unusual in mice. Since no figures were provided on the volume of water drunk, the total exposure levels could not be calculated. In spite of the observed effects, the experimental animals had a greater survival rate than the controls, and all groups manifested a singularly low incidence of tumours other than those in the gastrointestinal tract.

Hydrogen peroxide usually contains stabilizers, and it is important that the contribution of these substances, if any, to tumour induction should be evaluated.

In view of all these facts, the Committee believed that it would be advisable to repeat this type of study, preferably in another strain of mouse given a different feed. The total quantity of hydrogen peroxide administered should be measured.

With respect to the use of hydrogen peroxide for milk preservation, the Committee noted previous recommendations of the FAO/WHO Expert Panel on Milk Quality that had established appropriate guidelines.⁷ The following extract sets out the conditions for the use of hydrogen peroxide for preserving milk.

“When technical and/or economic reasons do not allow the adoption of cooling facilities for maintaining the quality of the raw milk, H₂O₂ may be an acceptable alternative in the early stages of development of an organized dairy industry provided the following conditions are complied with:

⁶ ITO, A. ET AL. (1980) Prevalence of gastric erosions and duodenal tumours with a continuous oral administration of hydrogen peroxide in C57BL/6J mice. Unpublished report from the Department of Cancer Research, Hiroshima University, submitted to WHO by the Japanese Ministry of Health and Welfare.

⁷ Fourth Meeting of the FAO/WHO Expert Panel on Milk Quality. Report. Rome, 23–27 January 1967.

- (a) it has been demonstrated that there is no feasible alternative to the use of H_2O_2 ;
- (b) a food quality H_2O_2 is made available;
- (c) the quantity used is the minimum required to maintain the milk in good condition as determined by the milk plant by means of frequent checks of the raw milk at each stage of transport;
- (d) the addition is not made by the milk producers and is carried out by trained and responsible representatives of the milk plant at the earliest possible opportunity after production;
- (e) milk and milk products distributed to the consumer are free from H_2O_2 .

Special note should be taken of the fact that hydrogen peroxide is recommended only for use as a preservative before the milk is processed by milk-processing plants. If the recommended procedures are followed, then there should be little or no residue of the substance in milk and milk products as consumed.

It appears that: "most of the added H_2O_2 likely to be used for preservation is split into water and oxygen immediately after addition due to the action of catalase. In addition, residual H_2O_2 is likely to disappear during processing or manufacturing as a result of agitation and heating".⁸ Residual hydrogen peroxide may be detected by simple, reliable tests.⁹

Provided that the recommendations of the FAO/WHO Expert Panel on Milk Quality are followed, and in the light of the knowledge available, the Committee considered that the use of hydrogen peroxide for milk preservation prior to further processing did not pose any health hazard. The Committee did not consider risks associated with uses of the substance other than in milk. It recommended that stabilizers used in hydrogen peroxide should be critically evaluated to ensure that they are safe for use in milk preservation. No toxicological monograph was prepared. The existing specifications were revised and designated as tentative.

⁸ TENTONI, R. ET AL. Hydrogen peroxide for milk collection under difficult conditions. *Annali di microbiologia ed enzimologia*, **18**: 85-123 (1968).

⁹ MELLO, F.A. Quick, practical and specific test to detect hydrogen peroxide in milk "in natura" with the use of reagent strips and test-tape. *Revista do Instituto Adolfo Lutz*, **31**: 77-81 (1971).

3.3 Antioxidants

Butylated hydroxyanisole (BHA)

The Committee had before it some new studies with BHA, notably behavioural studies in the newborn rat after exposure to the material *in utero* and through lactation. In contrast to the monkey, the rat showed slight behavioural impairment due to exposure. In addition, at the highest dosage there was increased pup mortality.

The Committee extended the temporary ADI of 0–0.5 mg/kg body weight pending the completion of a multigeneration reproduction study in the Sprague-Dawley rat. These data are required by 1982. The existing tentative specifications were revised and the Committee agreed to delete the “tentative” qualification.

A toxicological monograph was prepared.

Butylated hydroxytoluene (BHT)

Several new studies were available on BHT, including a behavioural study in newborn rats that had been exposed to the material *in utero* and during lactation. Decreased pup survival and slight behavioural effects were noted at levels above 0.1% of the diet. It was noted that behavioural effects were not seen in newborn monkeys whose mothers had been treated with the chemically related BHA.

At its twentieth meeting, the Committee had noted that BHT had been reported to enhance the occurrence of lung adenomas in mice. At that meeting, it had considered that BHT was not likely to be carcinogenic, but had requested additional long-term studies. Recently completed long-term studies in mice and rats have been negative and confirm the view that BHT is not carcinogenic.

Two series of studies with BHT have demonstrated that it enhances the effect of certain chemical carcinogens. In one study, it was shown that mice initially receiving injections of the carcinogen urethane developed more lung adenomas if treated subsequently for some weeks with BHT. In another study, rats treated with low levels of the carcinogen *N*-fluorenyl acetamide and subsequently with BHT developed more hepatomas, more rapidly than with the carcinogen alone.

In these studies, it is implied that BHT is a “promoting” agent. Possible mechanisms of action include enzyme induction and the production of hyperplasia and hypertrophy in both the lung and the liver by BHT.

The phenomenon of "promotion" of carcinogenesis in various systems including the skin and urinary bladder, as well as these examples, are attracting much attention in cancer research. Mechanisms of action, although under intense study, are not yet understood. In addition, since BHT has been shown to inhibit the action of carcinogens under other conditions, it is felt premature to use such information for toxicological evaluation.

The Committee extended the temporary ADI of 0.5 mg/kg body weight. Additional data are required by 1983 to clarify the effects of BHT on pup survival and to assess further the significance of the behavioural effects observed in newborn rats. The existing specifications were revised and the Committee agreed to delete the "tentative" qualification.

A toxicological monograph was prepared.

Propyl gallate (and other gallates)

This substance was evaluated by the Committee in 1976 (see Annex 1, reference 40) and again in 1977 (see Annex 1, reference 43) together with octyl and dodecyl gallates. A temporary ADI of 0.2 mg/kg body weight was established in 1976, pending the results of a study with a mixture of the gallates. This requirement was withdrawn in 1977, but the temporary ADI was continued until the Committee received the results of a study which, it was informed, was in progress in the USSR. The present Committee decided to re-evaluate the previously existing data and agreed on a group ADI for propyl, octyl, and dodecyl gallates of 0.2 mg/kg body weight. This was based on a no-effect level of 50 mg/kg to which a higher-than-normal safety factor was applied.

The existing specifications were revised and the Committee agreed to delete the "tentative" qualification.

No toxicological monograph was prepared.

3.4 Emulsifiers

Esters of glycerol and of thermally oxidized soybean fatty acids

Since the previous evaluation in 1976 (see Annex 1, reference 40), additional data on the metabolic fate of this compound in the rat, mouse, and guinea-pig have become available. Earlier short-term, long-term, and reproduction studies carried out on a product obtained

by a somewhat different manufacturing technique were considered by the Committee to be relevant to the evaluation, but the studies were not found to be fully adequate by present-day standards. The Committee was unable to establish an ADI before it had received the results of a new short-term study, preferably in a nonrodent species, and an additional long-term study in a rodent species. These studies should be carried out on a material with a well-defined composition. Revised specifications were not prepared.

No toxicological monograph was prepared.

Hydroxylated lecithin

Hydroxylated lecithin was considered by the Committee in 1973 (see Annex 1, reference 32). No further data have become available. It was not possible to establish an ADI from the limited data available. The existing specifications for lecithin, including hydroxylated lecithins, were revised and extended to include specifications for bleached lecithins.

No toxicological monograph was prepared.

Sucrose esters of fatty acids and sucroglycerides

Recent metabolic data available to the Committee demonstrated that these materials are hydrolysed in the gut to normal dietary constituents prior to absorption. Previous short- and long-term toxicity studies have not demonstrated any adverse effects related to the administration of this substance. A recent study in dogs likewise did not reveal any noticeable toxic effects when the animals were fed sucrose esters derived from beef-tallow fatty acids or mixed stearic and palmitic acid for 26 weeks. With this substance, the no-effect level was established in the rat at 500 mg/kg body weight. Because this substance is hydrolysed in the gut to normal food constituents a lower safety factor was used to calculate the ADI. The ADI was established at 0–10 mg/kg. The existing specifications were revised.

A toxicological monograph was prepared.

3.5 Flavouring agents

Ethyl lactate

The Committee concluded, at its twenty-third meeting (see Annex 1, reference 51), that this substance was probably hydrolysed *in vivo* to lactic acid and ethyl alcohol. The present Committee had before it new

data on *in vitro* enzymatic hydrolysis of ethyl 1-lactate, but the *in vivo* hydrolysis data requested previously are still lacking. The Committee agreed to extend the temporary allocation of ethyl lactate to the group ADI, nonspecified, for lactic acid, pending the completion of additional studies. *In vivo* hydrolysis studies are required by 1982. The existing tentative specifications were revised but maintained as "tentative".

A toxicological monograph was prepared.

α-ionone

This compound was evaluated by the Committee at its twenty-third meeting (see Annex 1, reference 51), at which time a temporary ADI of 0–0.05 mg/kg body weight was established. The results of the metabolic studies and of the additional short-term toxicity study requested at that meeting were not available. The Committee maintained the temporary ADI, pending the results of the required studies, which are to be completed by 1982. The existing specifications were revised.

No toxicological monograph was prepared.

β-ionone

This compound was evaluated by the Committee at its twenty-third meeting, when a temporary ADI of 0–0.05 mg/kg body weight was established. The results of the additional short-term toxicity study requested at that meeting were not available. The Committee maintained the temporary ADI pending completion of the requested studies. These are required by 1982. The existing specifications were revised.

No toxicological monograph was prepared.

3.6 Food colours

Allura Red AC

After toxicological evaluation of this substance at its twenty-third meeting (see Annex 1, reference 51), the Committee had been advised that further analysis of toxicological data would be forthcoming and that this information might influence the evaluation. The compound had therefore been placed on the agenda of the twenty-fourth meeting. The report of the analysis had not become available

and, as a result, the final evaluation has been postponed to a future session. The Committee considered that the ADI of 0–7 mg/kg established during the twenty-third meeting should be considered as temporary until the statistical analysis of the long-term mouse studies had been carried out. This information is required by 1981. The existing specifications were maintained.

A toxicological monograph was prepared.

Caramel colours (ammonium sulfite process)

The Committee considered at length the problem of specifications for caramel colours in general and for ammonium sulfite caramel colours in particular. It was apparent from the up-to-date information submitted by the International Technical Caramel Association that the existing specifications for ammonium sulfite caramel colours (see Annex 1, reference 45) could be improved.

Intensive efforts are being made by industry to characterize the various caramel products used to colour certain foods and beverages. The Committee wished to give every encouragement to this programme of analytical work, which should provide a better insight into the precise chemical differences not only between caramel colours of different classes (i.e., caustic caramel, ammonia caramel, ammonium sulfite caramel, and caustic sulfite caramel) but also of different caramel colours within each class. Industry has used considerable ingenuity in proposing specifications, based on available information, that will differentiate individual caramel products. However, it should be possible to elaborate even better specifications as soon as the results of the analytical research programmes are available. Specifications preferably should be based on readily analysable chemical, spectrographic, and chromatographic characteristics, and should place less emphasis on the definition of starting materials and processing conditions. On balance, therefore, the Committee decided not to elaborate new specifications for ammonium sulfite caramel colours for the time being but to await the further analytical data.

It was agreed that long-term studies to assess the potential carcinogenicity of ammonium sulfite caramel should be preceded by the establishment of adequate specifications. The temporary ADI for ammonium sulfite caramel colours of 0–100 mg/kg body weight was extended to 1983. The Committee confirmed that caustic sulfite caramel colour has no ADI, since it is not included in the ADI for plain

caramel (caustic caramel) or the temporary ADI for ammonium sulfite caramel. The existing tentative specifications were maintained.

No toxicological monograph was prepared.

Ponceau SX

The multigeneration reproduction/teratology study and the studies in the dog requested by the Committee at its twenty-first meeting (see Annex 1, reference 43) were not available. Therefore no ADI could be established for this substance. Revised specifications were not prepared.

No toxicological monograph was prepared.

Turmeric and curcumin

These additives were last evaluated by the Committee at its twenty-second meeting (see Annex 1, reference 48), when a temporary ADI of 0–2.5 mg/kg body weight was established for turmeric and a temporary ADI of 0–0.1 mg/kg body weight for curcumin.

The Committee evaluated new studies on the metabolism of curcumin and acute, short-term, long-term, reproduction, and mutagenicity studies on turmeric and an alcoholic extract of turmeric.

Concerning curcumin, the Committee considered that an adequate long-term study in a rodent species and teratogenicity studies were required by 1982.

As to turmeric, the Committee considered that an adequate short-term study in a nonrodent species was required by 1982.

The temporary ADIs of 0–2.5 mg/kg (turmeric) and 0–0.1 mg/kg (curcumin) were maintained. The existing specifications for both compounds were revised.

No toxicological monograph was prepared.

3.7 Sweeteners

Aspartame (and its corresponding diketopiperazine)

Aspartame was considered by the Committee at its twentieth, twenty-first, and twenty-third meetings (see Annex 1, references 40, 43, and 51, respectively).

The Committee evaluated additional toxicity animal studies and several human studies. The no-adverse-effect level, based on animal studies, was found to be 4 g/kg. An ADI for aspartame was established at 40 mg/kg.

Aspartame usually contains about 1% of diketopiperazine as an impurity. Furthermore, when aspartame is present in prepared foods, it may be converted to diketopiperazine, the amount being dependent on the moisture content, pH, storage temperature, and time of storage of the food. Extensive toxicological studies have been carried out with diketopiperazine. The level producing no toxicological effect in a two-year feeding study in the rat was 750 mg/kg and an ADI for diketopiperazine was established at 0–7.5 mg/kg. The existing specifications were revised and the Committee agreed to delete the “tentative” qualification.

A toxicological monograph was prepared.

Cyclamates (calcium and sodium)

The Committee noted current studies to assess further the potential effects of cystohexamine on reproduction in the mouse. It was of the view that the current temporary ADI of 4 mg/kg for cyclamates should be maintained pending completion of the reproduction study and studies to establish the extent of conversion of cyclamates to cyclohexylamine in man. The results of current reproduction studies are required by 1982. The existing specifications were revised.

No toxicological monograph was prepared.

Hydrogenated glucose syrup

Although limited data on the use of this substance in man were available for evaluation, the Committee noted the lack of adequate long-term toxicity and reproduction studies. No specifications were prepared.

No ADI was established.

Polydextrose

The Committee considered the extensive studies carried out in animals and human beings on this substance. These studies were conducted on two types of polydextrose: polydextrose-A and polydextrose-N—the latter being neutralized with potassium hydroxide. With regard to animal studies, the Committee evaluated short-term reproduction and teratology studies and long-term studies. The reproduction and teratology studies, of which three were in rats, demonstrated that dietary levels of up to 20% polydextrose-A had no effects on reproductive indices, extent of malformations, or postnatal growth and development. A teratology study in rabbits fed dietary levels corres-

ponding to 1.5–6% demonstrated only slight effects on fetal weight at the highest dose level. Short-term studies in rats, dogs, and monkeys did not reveal any significant effects. Long-term studies in the mouse and rat fed dietary levels of 5% or 10% polydextrose-A revealed no adverse effects with regard to haematology, clinical chemistry, or gross or microscopic pathology. The only effect observed was a slight softening of the stools in rats fed the 10% dietary level. Long-term studies in dogs fed 10%, 20% or 50% polydextrose-N revealed the occurrence of watery diarrhoea in dogs fed the 20% and 50% levels beginning in the third month of administration. These animals subsequently developed hypercalcaemic nephropathy. In an additional study, polydextrose-A was found to produce similar but less marked changes in dogs, and it was concluded that the potassium content of the N-type exacerbated the response. The hypercalcaemic nephropathy was attributed to the severe diarrhoea, which led to marked alterations in the fluid balance and electrolyte status. The no-adverse-effect level for the N-type was estimated to be 10% of the diet in dogs. Separate metabolic studies demonstrated that the feeding of polydextrose to dogs was accompanied by an increased uptake of calcium from the gastrointestinal tract. In a subsequent study in dogs, no adverse effects were noted in dogs fed up to 20% of the diet of polydextrose-A.

Studies in human beings demonstrated that polydextrose-A and polydextrose-N, when administered at very high doses, produced diarrhoea. The N-type, which produces the greatest laxative effect, demonstrated a threshold for this response at 50 g per person per day or about 0.7 g/kg body weight.

The ADI was established at 0–70 mg/kg for polydextrose (both A and N types). Because of the availability of adequate data regarding human beings, a lower safety factor was used in this case. New specifications were prepared. A toxicological monograph was proposed.

Saccharin

In its twenty-first report (see Annex 1, reference 43), the Committee changed the ADI for this substance from 5 mg/kg to a temporary ADI of 2.5 mg/kg and withdrew the conditional ADI of 15 mg/kg for dietetic purposes only. This action was based on studies demonstrating that high doses of saccharin induced bladder tumours in rats. At that time the Committee recommended that several additional studies should be undertaken. The Committee noted that

studies were under way to assess further the carcinogenic potential of saccharin in rodents, to evaluate the physiological effects of saccharin, and to investigate the mechanisms by which saccharin produces tumours at high doses.

The Committee also noted the recent publication of two epidemiological studies in human beings, from which the authors concluded that they found no association between saccharin consumption and the incidence of bladder cancer.¹⁰ The Committee noted that an additional large-scale epidemiological study was under way.

Pending the completion of current investigations, the Committee agreed to extend the temporary ADI of 0–2.5 mg/kg body weight. The additional studies are required by 1982. The existing specifications were revised.

No toxicological monograph was prepared.

Sorbitol

The Committee evaluated only data on the powdered crystalline form of sorbitol. It had evaluated sorbitol in 1973 and in 1978 (see Annex 1, references 32 and 48). In 1978 a “temporary ADI not specified” was allocated.

No new information, apart from a summary of results of an older long-term study, was available for assessment. The “temporary ADI not specified” was maintained.

The Committee still requires the results of an adequate long-term feeding study with sorbitol. These studies are required by 1982. The existing specifications were revised. New specifications were prepared for sorbitol syrup.

No toxicological monograph was prepared.

3.8 Thickening agents

Carob bean gum

This material was last evaluated by the Committee in 1975, when a “temporary ADI not specified”, was set (see Annex 1, reference 37). Since that time, further data have become made available.

¹⁰ MORRISON, A.S. & BURING, J.E. Artificial sweeteners and cancer of the lower urinary tract. *New England journal of medicine*, **302**: 537 (1980); WYNDER, E.L. & STILLMAN, S.D. Artificial sweetener use and bladder cancer: a case-control study. *Science*, **207**: 1214 (1980).

In vitro tests with human enzyme preparations indicate that limited hydrolysis is likely to occur in the gut. Carob bean gum has been shown not to be teratogenic in several mammalian species. The available short-term feeding studies in the rat and dog have shown no evidence of adverse effects at the 5% level. The effects noted in the feeding trials are those to be expected of a nonmetabolized substance acting as a bulking agent. The previously requested long-term feeding and reproduction studies are not yet available.

The Committee decided to extend the previous "temporary ADI not specified" until 1984, and reiterated its previous request for an adequate long-term study in a rodent species and reproduction studies. The existing specifications were revised.

A toxicological monograph was prepared.

Karaya gum

Data available to the Committee included mutagenesis and teratology studies, neither of which demonstrated any adverse effects. On the basis of the limited data available, no ADI could be established. Metabolic, short-term, long-term, and reproduction studies are required for further evaluation of this material. The existing specifications were maintained.

No toxicological monograph was prepared.

Pectin (amidated)

This substance was evaluated by the Committee in 1969 and again in 1974 (see Annex 1, references 19 and 34). Long-term studies in rats, made available to the Committee since then, do not suggest any evidence of carcinogenicity, and teratology studies likewise have demonstrated no adverse effects. The Committee expressed some concern over the quality of the multigeneration reproduction study and the high incidence of pneumonia, which caused all pups of an F₂b litter to die during the test. The temporary ADI of 25 mg/kg body weight was maintained pending the availability of adequate reproduction studies. These are required by 1982. The existing specifications were maintained.

No toxicological monograph was prepared.

Tara gum

The Committee evaluated this substance in 1975 (see Annex 1, reference 37), when it established a "temporary ADI not specified".

Since that time, no new data have become available. However, the Committee was made aware of current studies to assess the toxicity of this substance. The “temporary ADI not specified” was extended until 1984. The existing specifications were maintained.

No toxicological monograph was prepared.

Tragacanth gum

The Committee noted the lack of adequate studies to assess the toxicity of this material. In particular, short-term reproduction and long-term studies are lacking. No ADI could be established. The existing specifications were maintained.

No toxicological monograph was prepared.

3.9 Miscellaneous food additives

Diethylene glycol monoethyl ether

No new data had become available to the Committee on this substance; thus, no ADI could be allocated. The existing specifications were maintained.

Dioctyl sodium sulfosuccinate

The temporary ADI for this material was withdrawn by the Committee at its twenty-second meeting (see Annex 1, reference 48). Since then, additional limited studies in the horse, guinea-pig, and man had become available. These data were not considered adequate to establish an ADI. Teratology and long-term studies—the former including postnatal exposure via the milk—and a study of the effects of the substance on the pulmonary vascular system are required. The existing specifications were revised.

No toxicological monograph was prepared.

Nitrogen

The Committee considered nitrogen to be an inert gas that is not expected to react with components of food. Therefore, provided that the product meets the Committee’s specifications for food grade, there would be no toxicological hazard in its use as a food additive. The existing specifications were revised and the Committee agreed to delete the “tentative” qualification.

No toxicological monograph was prepared.

Polyvinylpyrrolidone

The Committee had given an ADI to this substance in 1966 (see Annex 1, reference 12). However, the ADI was withdrawn in 1973 owing to concern about the potential effects of storage in the body of macromolecules.

The Committee evaluated only data on the soluble form of polyvinylpyrrolidone. Studies in dogs demonstrated that the substance was taken up by the lymphatic system when administered orally. In a long-term feeding study in rats, no evidence of carcinogenicity was noted, and it was reported that the substance did not accumulate in the lymphatic system of the rat. Studies in which it was administered parenterally to rodents demonstrated uptake by the lymphatic system and the induction of reticuloendothelial tumours. The Committee considered it necessary for additional studies to be carried out before any further evaluation could be made.

Other species should be thoroughly investigated for the retention of polyvinylpyrrolidone following feeding, and further long-term studies should be undertaken in an appropriate species manifesting this effect. No ADI was established. The existing specifications were revised.

A toxicological monograph was prepared.

1,1,2-Trichlorethylene

This substance was on the agenda, but no new data pertinent to the evaluation of its carcinogenic potential were available to the Committee. The Committee was aware of current studies, but could not establish an ADI. Revised specifications were not prepared.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 24 substances including antioxidants, colours, emulsifiers, thickening agents, and miscellaneous additives (see Annex 2). New specifications were prepared for 9 inorganic salts, 4 emulsifiers, and 6 miscellaneous substances. New tentative specifications were prepared for 26 artificial flavouring agents and 1 thickening agent. In the case of methoxypyrazine and quillaia, it was not possible to develop specifications because of the incompleteness of the information available. Specifications were not

developed for dipotassium pyrophosphate and monomagnesium orthophosphate because, in the opinion of the Committee, there was uncertainty about their use as food additives.

The Committee was requested to prepare specifications for a number of flavouring substances. Three of these substances—coumarin, safrole, and thujones—were active principles in naturally occurring flavouring substances. The Codex Committee on Food Additives, at its thirteenth meeting (see Annex 1, reference 19), had referred these substances to the Joint Committee for an opinion on the setting of limits in food, noting that these substances were not themselves used as flavouring substances. The Joint Committee decided, therefore, that it was not appropriate to establish specifications for these substances. It did not establish specifications for 7-ethoxy-4-methyl-coumarin, which has been voluntarily withdrawn from use as a food flavouring, or methoxypyrazine, for which no data were available. In the case of quinine, specifications were established only for the derivatives known to be used as food additives, namely the hydrochloric and sulfuric acid salts.

For the remaining flavourings, all of which are artificial, the Committee was able to establish only tentative specifications. Additional data required include, in many cases, clarification of the stereochemistry of commercial products and the identity and concentration of organic impurities. Often there are differences between the values of the physical constants obtained from different sources and the relationship between relative densities determined at 20°C and 25°C. Some of these differences could not be reconciled and are still reflected in the tentative specifications.

5. FUTURE WORK

1. A number of food additives have been allocated temporary ADIs, and should be re-evaluated when the required information becomes available.

2. Sorbitol should be further evaluated. In this connexion, it is of importance to evaluate data pertaining to the acceptability of non-crystallizing solutions of sorbitol—a major item of commerce. The present Committee evaluated data pertaining only to the crystalline form.

3. The following compounds warrant expeditious toxicological evaluation: coumarin, safrole, and thujones.

4. The following compounds warrant toxicological re-evaluation and review of specifications: sucrose acetate isobutyrate and sucrose octa acetate.

5. There is a need for the Committee to evaluate models that can be used to extrapolate *in vitro* biochemical studies to the *in vivo* situation.

6. RECOMMENDATIONS TO FAO AND WHO

1. In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, meetings of the Joint FAO/WHO Expert Committee on Food Additives should continue to be held at least annually, until such time as a quicker procedure for data collection and evaluation has been developed.

2. The Committee noted with concern the recent delays in publishing its reports, and recommended that FAO/WHO should circulate to governments, shortly after the meeting, a summary of acceptable daily intakes of intentional food additives evaluated and details of the further toxicological studies and information required. In addition, governments should be informed of the recommendations concerning the use of hydrogen peroxide in milk preserving.

3. A scientific group should consider the toxicological implications of recent developments in chemical carcinogenesis. In particular the implications of promoting factors and other modifiers of carcinogenic action should be considered. Furthermore, the recent recommendation of the International Agency for Research on Cancer—that evidence for carcinogenesis should be classified into “limited evidence” and “sufficient evidence”—should be considered in the context of food safety evaluation.

4. Concern is often expressed about toxicological results obtained from tests using very high doses of food additives. Attention was drawn to this as early as the second report of the Committee. The Committee believes that, in general, such high-dosage studies are unnecessary. However, it does not believe that arbitrary guidelines to test levels can be recommended. Careful evaluation is the primary safeguard. It is recommended that this matter should be discussed at a future meeting.

5. A number of specifications remain tentative for lack of data on certain chemical-purity criteria, microbiological criteria, or methods of analysis. Steps should be taken to obtain the data necessary to complete these specifications.

6. The Committee recommended that FAO and WHO should reconsider the current procedures for establishing priorities for the evaluation of intentional and unintentional food additives. The selection of the most relevant compounds for future evaluation should be based on existing toxicological knowledge, the extent of use, and the availability of specifications (see Annex 1, reference 48).

7. The Committee, in the report of its twenty-first meeting (page 31), recommended that:

“In view of the rapid progress of the science of toxicology and the increasing refinement of evaluation procedures, the Committee felt strongly that the traditional concepts of setting ADIs, the application of safety factors, and the relationship of these safety factors to the observed toxicological manifestations in animal experiments should be reconsidered. It therefore proposed that these complex problems be a topic of future discussion” (see Annex 1, reference 43).

The Committee wishes to reiterate that recommendation. The need for such discussion continues to be important. Newer uses of statistical methods of extrapolation of experimental data to man further emphasize this need.

8. The toxicological evaluation of modified food ingredients presents special problems in terms of their toxicity testing and evaluation. This requires special attention and should be considered at a future meeting.

Annex 1

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: Division of Environmental Health, 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. 25, 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, diethylpyrocarbonate, 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.
39. *Specifications for the identity and purity of certain food additives.* FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.
40. *Evaluation of certain food additives* (Twentieth report of the Expert Committee). FAO Food and Nutrition Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.
41. *Toxicological evaluation of certain food additives.* FAO Food and Nutrition Series, No. 1A, 1978; WHO Food Additives Series, No. 10, 1978.
42. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Series, No. 1B, 1977.
43. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.
44. *Summary of toxicological data of certain food additives.* WHO Food Additives Series No. 12, 1977.
45. *Specifications for identity and purity of some food additives, including antioxidants, food, colours, thickeners, and others.* FAO Nutrition Meeting Report Series, No. 57, 1977.
46. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers.* FAO Food and Nutrition Paper No. 4, 1978.
47. *Guide to specifications – General notices, general methods, identification tests, test solutions, and other reference materials.* FAO Food and Nutrition Paper No. 5, 1978.
48. *Evaluation of certain food additives* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
49. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series No. 13, 1978.
50. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper No. 7, 1978.
51. *Evaluation of certain food additives* (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980.

Annex 2

ACCEPTABLE DAILY INTAKES AND INFORMATION ON SPECIFICATIONS

<i>Substance</i>	<i>Specifications¹</i>	<i>ADI for man (mg/kg body weight)</i>
Allura Red AC	S	0–7 ²
aspartame	R ¹⁵	0–40 ⁷
butylated hydroxyanisole (BHA)	R	0–0.5 ^{2,6}
butylated hydroxytoluene (BHT)	R	0–0.5 ^{2,6}
caramel colours (ammonium sulfite process)	ST	0–100 ²
carob bean gum	R	ADI not specified ^{2,3}
curcumin	R	0–01 ²
cyclamates (calcium and sodium)	R ¹⁵	0–4 ^{2,13}
diethylene glycol monoethyl ether	S	No ADI allocated ⁴
dioctyl sodium sulfosuccinate	R ¹⁵	No ADI allocated ⁴
esters of glycerol and thermally oxidized soybean fatty acids	S ¹⁴	No ADI allocated
ethyl lactate	RT	ADI not specified ^{2,5}
hydrogen peroxide	RT	No ADI allocated ⁸
hydrogenated glucose syrup	0	No ADI allocated ⁴
hydroxylated lecithins	RT	No ADI allocated ⁴
α -ionone	R	0–0.05 ²
β -ionone	R	0–0.05 ²
karaya gum	S	No ADI allocated ⁴
magnesium silicate	ST	ADI not specified ^{2,10}
nitrogen	R	No ADI necessary
pectin (amidated)	S	0–25 ²
polydextrose	N	0–70
polyvinylpyrrolidone	R	No ADI allocated ⁴
Ponceau SX	S ¹⁴	No ADI allocated ⁴
propyl gallate (and other gallates)	R	0–0.2 ⁹
saccharin (calcium and sodium salts)	R	0–2.5 ^{2,11}
sorbitol	R	ADI not specified ²
sucrose esters of fatty acids and sucroglycerides	R	0–10 ¹²
talc	N	ADI not specified ^{2,10}
tara gum	ST	ADI not specified ^{2,3}
tragacanth gum	ST	ADI not allocated ⁴
1,1,2-trichloroethylene	S ¹⁴	No ADI allocated ⁴
turmeric	R	0–2.5 ²

Specifications only

<i>Substance</i>	<i>Specifications</i>
allyl 3-cyclohexyl propionate	NT
allyl α -ionone	NT
allyl hexanoate	NT
allyl tiglate	NT
α -amyl cinnamic aldehyde	NT
α -amyl cinnamic aldehyde dimethyl acetal	NT
α -amyl cinnamyl alcohol	NT
anisylacetone	NT
benzyl butyl ether	NT
benzyl isobutyl carbinol	NT
benzyl isoeugenyl ether	NT
butyl butyryllactate	NT
coumarin	O
diammonium orthophosphate	N
dibenzyl ether	NT
dibutyl sebacate	NT
dicalcium pyrophosphate	N
2,6-dimethyl-5-heptenal	NT
dipotassium pyrophosphate	O
disodium pyrophosphate	N
7-ethoxy-4-methyl-coumarin	O
ethyl cellulose	N
ethyl methyl phenylglycidate	NT
ethyl phenylglycidate	NT
geranyl acetoacetate	NT
gum ghatti	NT
α -hexyl cinnamic aldehyde	NT
hydroxycitronellal	NT
hydroxycitronellal dimethyl acetal	NT
hydroxycitronellol	NT
isoquinoline	NT
methoxypyrazine	O
α -methyl cinnamic aldehyde	NT
6-methyl coumarin	NT
iso- α -methyl ionone	NT
monoammonium orthophosphate	N
monomagnesium orthophosphate	O
oxidized hydroxypropyl distarch glycerol	NT
pentapotassium triphosphate	N
potassium nitrate	R
potassium polyphosphate	N
quillaia extract	O
quinine hydrochloride	N
quinine sulfate	N
safrole	O
sorbitan monolaurate	N

<i>Substance</i>	<i>Specifications</i>
sorbitan monooleate	N
sorbitol syrup	N
stearoyl monoglyceridyl citrate	N
succinylated monoglycerides	N
tetrapotassium pyrophosphate	N
tetrasodium pyrophosphate	N
thujones	O

1. 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.
2. Temporary acceptance.
3. 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 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.
4. Evaluation not possible on data available.
5. Group ADI: included in the ADI for lactic acid.
6. Group ADI as BHA, BHT, TBHQ singly or in combination.
7. An ADI for diketopiperazine—an impurity found in aspartame—was established at 0–7.5 mg/kg body weight.
8. Hydrogen peroxide may be used only where better methods of milk preservation are not available.
9. Group ADI as dodecyl, octyl, propyl gallates singly or in combination.
10. Group ADI as silicon dioxide and silicates.
11. Group ADI for the calcium and sodium salts singly or in combination.
12. Group ADI for the sucrose esters of fatty acids and sucroglycerides singly or in combination.
13. Expressed as cyclamic acid.
14. The Committee did not find it appropriate to prepare revised specifications for this product.
15. Only editorial changes were considered.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED

Anticaking agents

*Talc*¹

- (1) A long-term feeding study.

*Magnesium silicate*²

- (1) A short-term feeding study.

*Butylated hydroxyanisole (BHA)*²

- (1) A multigeneration reproduction feeding study in Sprague Dawley rats.

*Butylated hydroxytoluene (BHT)*¹

- (1) An adequate study to clarify effects on rat pup survival.
- (2) Elucidation of the significance of the behavioural effects observed in newborn rats.

Flavouring agents

*Ethyl lactate*²

- (1) *In vivo* hydrolysis studies.

*α-ionone*²

- (1) Metabolic studies.
- (2) A short-term feeding study.

*β-ionone*²

- (1) A short-term feeding study.

Food colours

*Allura Red AC*³

- (1) Adequate information on a statistical analysis of the previously submitted long-term study.

*Caramel colours (ammonium sulfite process)*¹

- (1) Efforts should be made to establish adequate specifications.
- (2) A long-term feeding study should be initiated.

*Turmeric and curcumin*²

Turmeric

- (1) Adequate short-term feeding study in a nonrodent species.

Curcumin

- (1) Adequate long-term feeding study in a rodent species.
- (2) A teratogenicity study.

Sweeteners

Cyclamates (calcium and sodium)²

- (1) An adequate reproduction study.
- (2) Elucidation of the extent of conversion of cyclamate to cyclohexylamine in man.

Saccharin (calcium and sodium salts)²

- (1) Studies to determine whether saccharin *per se* produces physiological changes that predispose to, or account for, bladder tumours.
- (2) Chemical studies and short-term *in vitro* studies to isolate and identify potential carcinogenic fractions in saccharin.
- (3) Carcinogenic tests to establish the oncogenic potential of active impurities.
- (4) Studies to determine whether the action of active principles requires exposure *in utero* or exposure through suckling, or both together with long-term feeding exposure. These studies should include an examination of the genesis of the pathological lesion during embryonic development of bladder tissue and of the transplacental pharmacokinetics of saccharin and its impurities.
- (5) Studies to determine whether saccharin promotes the action of impurities or carcinogenic fractions normally found in animal diets.
- (6) The initiation of prospective epidemiology in high-risk populations.

*Sorbitol*²

- (1) A long-term feeding study in rats, with special attention to the effects on the thyroid and adrenal glands.

Thickening agents

A. *Vegetable gums*

*Carob bean gums*⁴

- (1) An adequate long-term feeding study in a rodent species.
- (2) A reproduction study in rodents.

*Tara gum*⁴

- (1) Adequate long-term studies in a rodent species.
- (2) Reproduction and embryotoxicity (including teratogenicity) studies.

B. *Others*

Pectin (amidated)²

- (1) An adequate reproduction study.

¹ Information required by 1983.

² Information required by 1982.

³ Information required by 1981.

⁴ Information required by 1984.

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Committee on Food Additives**

CORRIGENDUM

Page 15, line 1

Delete 0–3.7 mg/kg

Insert 0–3 mg/kg

