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Evaluation of certain food additives

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

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Monographs containing summaries of relevant data and toxicological evaluations are available, upon request, from WHO under the title:

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Geneva, 23 March–1 April 1981

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EVALUATION OF CERTAIN FOOD ADDITIVES

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

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 23 March to 1 April 1981. The meeting was opened by Dr M. Mercier, Manager of the International Programme on Chemical Safety, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Mercier briefly reviewed the achievements of the Committee during its 25 years of activity. In particular, he noted that this Expert Committee was initiated in 1956 as a result of a recommendation of the First Joint FAO/WHO Conference on Food Additives to the Directors-General of FAO and WHO to convene one or more expert committees to be concerned with the technical and administrative aspects of the problem of additives in food. The recommendations made by the Expert Committee have contributed significantly to assist Member States as well as the Joint FAO/WHO Codex Alimentarius Commission and have provided valid instruments for food control programmes.

In addition, in both developing and developed countries, the consumer is demanding firm assurance that food additives be properly and thoroughly tested for safety. A great variety of testing procedures is generally employed. The diverse experimental results must be evaluated in a sound and balanced way by an international, multidisciplinary team, such as that represented in this Expert Committee. Also it is necessary to ensure the identity and purity of chemical additives for technological, nutritional, and public health needs. The deliberations of the Joint FAO/WHO Expert Committee on Food Additives are, therefore, eagerly awaited by the health and food authorities in both developing and developed countries, and by industry. The work of the Committee has substantially increased during the years, reflecting the rise in the number of requests by Member States to evaluate the public health impact of additives used, or proposed for use, in food.

To this end, a recommendation was made by the Programme Advisory Committee of the International Programme on Chemical Safety

that food additives and contaminants should be considered as one of the priority groups of substances for systematic evaluation. The presence at the meeting, as WHO temporary advisers, of a number of scientists on the staff of lead institutions of the International Programme on Chemical Safety—namely, from the International Agency for Research on Cancer, from the Health Protection Branch of Canada, and from the United States Food and Drug Administration—was noted with satisfaction by Dr Mercier. The hope was expressed that such participation will increase in the near future and that other Member States and international organizations will support the activities of the Joint FAO/WHO Expert Committee on Food Additives within the new programme of the International Programme on Chemical Safety.

Later, during the course of the meeting, the Committee was addressed by Dr H. Mahler, Director-General of WHO, on his own behalf and on behalf of Dr E. Saouma, Director-General of the Food and Agriculture Organization of the United Nations. He congratulated the Committee on its silver jubilee and noted that the Joint FAO/WHO Expert Committee on Food Additives was a rather special expert committee, since it dealt with a subject that not only was of high scientific interest but also required continuous updating in view of the rapid developments in toxicology and food technology. The Joint FAO/WHO Expert Committee on Food Additives was a very good example of the way international organizations, such as FAO and WHO, could exert influence on those responsible for promoting public health, whether they were part of a national administration or in the private sector. The Expert Committee had achieved this influence by maintaining a high level of scientific judgement and integrity and addressing itself to practical problems. The Committee has placed increasing emphasis on the evaluation of compounds which were of particular interest to the developing countries and had thus placed its activities in the mainstream of international policy.

On the occasion of the twenty-fifth anniversary of the Joint FAO/WHO Expert Committee on Food Additives, Dr Mahler paid tribute to the work of Professor René Truhaut, who was present at the meeting and, since 1956, had made an outstanding contribution to the achievements of the Expert Committee. He was presented with a medal by the Director-General of WHO bearing the inscription "Health for All by the Year 2000".

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 24 meetings of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1) before the present one, which was convened on a recommendation made at the twenty-fourth meeting (see Annex 1, reference 54). The tasks before the Expert Committee were: (1) to prepare specifications for the identity and purity, and to carry out a toxicological evaluation, of certain food additives; (2) to revise specifications for selected food additives; (3) to undertake a toxicological re-evaluation of certain food additives; (4) to consider the use of hormones in animal production, the use of antibiotics in foodstuffs, and the use of plastic materials in food packaging; (5) to review the work of the Committee during the previous 25 years, and assess its impact and significance for developing countries; and (6) to re-examine the working arrangements between the Committee and the Codex Committee on Food Additives.

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

The Committee agreed to add Fast Green FCF and cinnamyl anthranilate to the list of compounds for toxicological evaluation. Cinnamyl anthranilate and calcium ascorbate were both considered in relation to cinnamaldehyde. Calcium ascorbate was also considered in relation to ascorbic acid and its potassium and sodium salts. Sorbitol was taken off the agenda because further studies were not required until 1982. Sucrose acetate isobutyrate and sucrose octaacetate were removed from the agenda.

2.2 Principles governing the toxicological evaluation of food additives

The Committee reiterated the principles established at its previous meetings (see Annex 1), and by a WHO Scientific Group on Proce-

[1] FAO Nutrition Meeting Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

dures for Investigating Intentional and Unintentional Food Additives[2] and a WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.[3]

2.3 Principles concerning the establishment of specifications

The specifications for the identity and purity of food additives prepared by the Committee are meant to identify and to establish a degree of purity for the substances that is consistent with the material upon which biological testing is to be carried out and to indicate that these substances, when used in food, should reflect these specifications.

The Committee reiterated the importance of the specifications for protecting the consumer, for regulatory purposes, for industry, and in determining safety, which were originally stated in its first and third reports (see Annex 1, references 1 and 3, respectively).

2.4 Relevance of the work of the Committee to developing countries

In reviewing its work over the past 25 years, the Committee noted that extensive information had been made available to Member States of FAO and WHO, including the developing countries. In fact, developing countries rely on the recommendations of the Committee for the toxicological evaluation of food additives and the preparation of specifications of identity and purity, because they are based on independent expert opinions. This dependence is likely to continue owing to the significant technical requirements needed to carry out such evaluations at the national level. Therefore the Committee suggested that the sponsoring organizations, FAO and WHO, should provide governments that are likely to make extensive use of the work of the Committee with additional facilities, such as manpower training, food quality control structures, and rapid information exchange systems.

2.5 International liaison

In considering the food colour Red 2G, the Committee reiterated the comment made in its twenty-second report (see Annex 1, reference 48) on the desirability of international liaison to ensure greater conformity in the evaluations of food additives.

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

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

2.6 Validation of toxicological data

Normally the Committee considers that studies submitted for toxicological evaluations are a true representation of the actual work carried out. However, occasions have arisen (and may recur) when the data submitted to the Committee were unacceptable because of the low standards or unsatisfactory laboratory practices known to exist in the originating laboratory. The Committee considered that in such instances data should be validated[4] prior to their use in evaluation. The Committee agreed not to establish fixed procedures for the validation of data since it considered that a variety of procedures may be acceptable. Each study must be considered individually as the need arises. The Committee considered that when data are of questionable validity and cannot be verified, the results of adequate relevant studies must be made available if they are crucial to the safety evaluation.

2.7 Data required for technological and safety considerations

The twenty-fourth report of the Committee reviewed the importance of technological and nutritional considerations in the safety assessment of food additives. It recorded that methods should be investigated for obtaining more data and for presenting them to the Committee in a readily understandable form.

During the preparations for the present meeting the following information was specifically requested on each food additive to be evaluated:

(1) methods of manufacture;

(2) levels of use of the additives in food;

(3) estimates of intake;

(4) reactions of the additives (with constituents of foods) that might be of toxicological or nutritional significance; and

(5) beneficial effects of the additives on nutrients.

The results of these requests were discussed by the Committee and it was concluded that this information was important and relevant both for the toxicological evaluation and for the preparation of specifications. To assist the process of data collection in future, the Com-

[4] The question of procedures for data validation was discussed by the Joint FAO/WHO Meeting on Pesticide Residues in Food, Rome, 6–15 October 1980—FAO, *Pesticide residues in food, 1980,* Rome, 1981 (FAO Plant Production and Protection Paper, No. 26).

mittee proposed that the type of data required should be more closely identified by the following headings, each of which should be clearly defined:

Description
Raw materials
Method of manufacture
Impurities
Functional use(s)
Estimate of daily intake
Reactions and fate in food
Effects on nutrients
Substitute additives.

Also the source of the information submitted under each heading should be defined.

The Committee recognized the problem of unpublished proprietary data but expressed the hope that manufacturers would do their utmost to supply this information. In the case of certain types of data, especially estimates of daily intake, it was felt that governments might be better placed than industry to supply the information. It was agreed, therefore, that governments should be included in future requests for data, possibly by way of Codex contact points.

2.8 Extraction solvents used in food processing

Three toxicological issues are raised by the use of extraction solvents in food:

(1) the toxicity of the solvent residues themselves;

(2) the toxicity of impurities, degradation products, stabilizers and other additives which may be left behind after removal of the solvent; and

(3) the potential for interaction of the solvent with food constituents to produce a new toxic entity or to decrease the amount of a nutrient.

Where appropriate, data from occupation or inhalation studies have been taken into consideration by the Committee in arriving at its assessments. Where biological or toxicological data provide a more than ample margin of safety, or where considerations of the points listed above raise no concern, limitation of residues to the minimum levels attainable with appropriate technology appears to provide an adequate safeguard for the health of the consumer. Where the toxi-

cological data dictate limitations for reasons of safety, it is appropriate to establish an acceptable daily intake (ADI) or discourage the use of the material.

The Committee reviewed the specifications for a number of solvents. Taking into account the considerations previously outlined by the Codex Committee on Food Additives with respect to the desirability of lowering the limits for impurities, the Committee considered that more information should be obtained on the actual levels of arsenic and heavy metals in solvents.

2.9 Herbs, spices, and natural product food additives

The Committee discussed the problems arising from the presence of potentially toxic substances in foods and beverages as a consequence of the use of herbs and spices in their preparation. The Committee also recognized that potentially toxic components might occur in other foodstuffs. When considering several natural colours, the Committee laid down some general principles for their evaluation (see Annex 1, reference 43, p. 6).

The Committee recognized that some of these substances have been shown to be toxic in animal studies, but their significance for human health as a result of their presence in food is generally obscure. In an effort to resolve the problem so that traditional spices and herbs could continue to be used in the preparation of foods and beverages and yet also reduce the ingestion of the associated toxic substances to a minimum, the following guidelines were laid down to be followed when a potentially toxic substance is present in the herbs or spices in question:

(1) Spices and herbs containing potentially toxic substances should be used at levels consistent with good manufacturing practices.

(2) If there are several varieties or preparations of a particular natural flavouring material and there are significant differences between them with respect to the level of a toxic substance, the varieties or preparations containing the lowest level of the substance in question should be used.

(3) Where it is feasible to reduce the amount of the toxic substance or to remove it completely without destroying the characteristic flavour properties of the herb or spice, this should be done.

(4) In some bases it might be necessary to set specifications to limit the content of potentially toxic substances in spices and herbs, and thereby ensure that ingestion of such substances is kept to a minimum.

The Committee felt that, at this stage, it was difficult to make international recommendations concerning acceptable levels of toxic substances present in herbs and spices, and it laid down the above principles for their use.

2.10 Plastic materials in food packaging

The Committee considered the advancing technology associated with plastic packaging materials for food and discussed the possible hazard to health arising from the ingestion, in the long term, of small amounts of substances migrating from packaging materials into food.

It agreed that the most important factors to be considered in the safety assessment of packaging materials are the chemical nature, the amount, and the toxicological status of the substances actually entering the food. However, for practical reasons it may sometimes be necessary to base the safety assessment on the actual constituents of the packaging material.

2.11 Antibiotics as direct food additives

The Committee reviewed the use of antibiotics as direct food additives in the light of the recommendations and evaluations of such antibiotics made in its twelfth report (see Annex 1, reference 17). It was concluded that the general recommendations of the twelfth report were still applicable, namely:

(1) Only antibiotics that have no important therapeutic use, and that do not give rise to cross-resistance or any other form of interference with the therapeutic use of other antibiotics in human or veterinary medicine, should be considered for use as direct (international) food additives. However, exceptions may be justified in order to solve certain important problems.

(2) An antibiotic that alters the ecological pattern of microbial spoilage of food, resulting in possible danger to the consumer, should not be used as a direct (intentional) food additive.

(3) In considering the use of a given antibiotic as an intentional food additive, information on its effects on the normal body flora of the consumer should be obtained.

(4) No lowering of the usual standards of food hygiene should be permitted because of the use of an antibiotic as a food additive.

The Committee was aware of only two antibiotics being used as intentional food additives—namely, nisin and natamycin (pimaricine).

Both of these antibiotics were evaluated in the twelfth report of the Expert Committee and were allocated ADIs. Specifications for the two substances also exist. In the light of new information, the data on natamycin were reviewed in the twentieth report. The Committee decided that, in view of its present work-load relating to the evaluation of other food additives, it should not consider the use of antibiotics as additives to animal feeds or in other areas of animal husbandry and veterinary medicine, at this time.

2.12 Hormones in animal production

Many studies have established the importance and efficacy of anabolic agents for meat production. Two categories of compounds are used—namely, hormones of natural origin and their derivatives and synthetic compounds with hormonal activity.[5] Examples of anabolic preparations in use are listed in Table 1. When these preparations are properly used, the residue levels of the anabolic agents in meat and other edible tissues of the treated animals have generally varied from a few nanograms down to some hundred picograms per gram of tissue.

The toxicological evaluation of residues of anabolic agents that are present in human food obtained from animals treated with these agents must take into account whether or not the residue is identical to a human endocrine hormone. In the latter case, the possible endocrinological effects and carcinogenic potential of the residue must be closely examined.

With respect to an agent that is identical to a human endocrine hormone, the Committee was provided with evidence that, assuming all meat in the diet was from animals treated with 17β-estradiol, in accordance with good practice the residues would not contribute more than 8% of the intake of estrogenic substances in normal diets (e.g., as estradiol in meat and dairy products, and as plant estrogens) and the endogenous production is at least a thousandfold greater than the intake of residues of 17β-estradiol. Therefore it seems unlikely that there is cause for concern when 17β-estradiol is properly used in animal production. Similar considerations apply to progesterone and testosterone.

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[5] FAO. *Report of the FAO/WHO symposium on the use of anabolic agents in animal production and its public health aspects,* Rome, 1975 (FAO Meeting Reports, AGA, 1975).

Table 1. Hormonally active substances used as anabolic agents in animal production*

Substances	Form	Animals mainly concerned
Estrogens alone		
stilbestrol	feed additive	steers, heifers
stilbestrol	implant	steers
stilbestrol	oil solution	veal calves
hexestrol	implant	steers, sheep, calves, poultry
zeranol	implant	steers, sheep
Progestogens alone		
melengestrol acetate	implant	heifers
Androgens alone		
trenbolone acetate	implant	heifers, culled cows
Combined preparations		
stilbestrol + testosterone	implant	calves
stilbestrol + methyltestosterone	feed additive	swine
hexestrol + trenbolone acetate	implant	steers
zeranol + trenbolone acetate	implant	steers
17β-estradiol + trenbolone acetate	implant	bulls, steers, calves, sheep
estradiol-3β-benzoate + testosterone propionate	implant	heifers, calves
estradiol-3β-benzoate + progesterone	implant	steers

* From unpublished information made available by Professor W. Velle on the use of hormones in animal production.

Chemically modified hormones, hormonally active agents from plants, and synthetic anabolic agents present the following specific problems:

(1) their extreme potency and consequently the need to ensure minimal residues;

(2) their potential tumorogenic activity; and

(3) the presence of their metabolites in animal products that might be of endocrinological or toxicological consequence.

The question of the carcinogenecity of hormonally active agents used in animal husbandry arose as a result of the use of diethylstilbestrol (DES) in large doses in the treatment of women with problems of threatened or habitual abortion. In the offspring of mothers so

treated, a low incidence of vaginal cancer and testicular hypogonadism has been reported. The significance of these observations for the toxicological evaluation of residues of anabolic agents in human food is questionable.

Analytical techniques for use in animal husbandry are available for detecting trace levels of diethylstilbestrol in faeces and urine.

2.13 Enzyme preparations used in food processing

The problems of safety evaluation of enzyme preparations used in food processing were discussed in the fifteenth, eighteenth, and twenty-first reports of the Expert Committee and general considerations, with particular reference to specification requirements, were discussed in the twenty-second report.

At the present meeting, a new general specification for enzymes used in food processing was drafted, which included provisions to take into account the effects of carriers, solvents, preservatives, antioxidants, and other substances deemed necessary for good manufacturing practice in addition to the enzymes themselves. The present Committee reiterated the previously expressed view that these ancillary substances are acceptable only if the Joint FAO/WHO Expert Committee on Food Additives considers them as such, and their presence is declared on the label of the enzyme preparation.

The revised general specifications contain amended criteria for the source materials used for enzyme preparations; revisions in microbiological requirements; and a requirement for fungal enzymes to be free from a number of mycotoxins, including aflatoxin B_1.[6]

It was recognized, in reference to the assay of enzyme preparations, that there are no universally accepted methods which give meaningful results. Products are normally represented as meeting the specifications of the vendor as determined by in-house methods of assay. Typical examples of such methods are noted in the individual specifications.

The Committee recognized the utility of the use of the generic headings "protease" and "carbohydrase", the latter referring to the group of enzymes hydrolysing *O*-glycosyl compounds such as starch. However, in instances where the enzymic action is known to be more specific, for example, α-amylase, the latter term has replaced the generic heading in the individual specifications.

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[6] As determined by the method of Patterson, D. S. & Roberts, B. A. *Journal of the Association of Official Analytical Chemists*, **62**: 1265 (1979).

The twenty-first report of the Expert Committee recognized that the increased potential use of immobilized enzymes called for the evaluation of the immobilizing substrates as well as of the immobilizing techniques. Specifications for immobilized glucose isomerase were published in the twenty-second report of the Expert Committee and were revised by the present Committee to include maximum residue levels for immobilization agents.

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 Food colours

Allura Red AC

This substance was evaluated in the twenty-third and again in the twenty-fourth report of the Expert Committee, which regarded the previously allocated ADI of 0–7 mg/kg of body weight as temporary, since further information from statistical analysis of long-term mouse studies was required. This was available to the present Committee, which considered that the results justified the allocation of an ADI of 0–7 mg/kg of body weight. No new toxicological monograph was prepared. The existing specifications were revised.

Brilliant Black PN

This food colour was allocated a temporary ADI of 0–2.5 mg/kg of body weight in the eighteenth report and this was continued in the twenty-second report pending evaluation of results of additional studies which were to be submitted by 1981. Some of these were available to the Committee: no toxicologically significant effects had been observed in a teratogenicity study and in a reproduction/multigeneration study; also a metabolic study had been carried out; but no

further work was available on the etiology and pathology of intestinal cysts occurring in feeding studies with high levels of Brilliant Black PN in pigs. Therefore the ADI was reallocated on the basis of the no-effect level in the pig to 0–1 mg/kg of body weight. A new toxicological monograph was prepared and the existing specifications were revised.

Brown HT (formerly Chocolate Brown HT)

The Committee was informed that the additional studies requested for 1981 in their twenty-third report were almost complete. The temporary ADI of 0–2.5 mg/kg of body weight was continued, pending submission of the additional studies by 1982. No toxicological monograph was prepared but the existing specifications were revised.

Carmines (formerly cochineal, carmine, and carminic acid)

Cochineal and colouring principles derived from it were considered in the twenty-first report of the Expert Committee but at that time the toxicological data available were considered to be insuficient for an evaluation and the establishment of an ADI. The present Committee understood that the main substances used were ammonium carmine for alcoholic beverages and calcium carmine for foods. Their use was limited because of the small amount of cochineal produced. Recent reproduction studies with ammonium carmine had found no toxicologically significant effects. The Committee was informed that a long-term study had also been completed, but the data had not yet been submitted. The Committee allocated a temporary ADI of 0–2.5 mg/kg of body weight for ammonium carmine, or equivalent amounts of the calcium, potassium, or sodium salts (the lithium salt is not acceptable for food-additive use). This was based on a no-effect level of 500 mg of ammonium carmine per kg of body weight in a multigeneration study. The Committee requested the submission of the results of the long-term study for evaluation at a future meeting. A toxicological monograph and new tentative specifications were prepared.

Fast Green FCF

This colour was allocated an ADI of 0–12.5 mg/kg of body weight in the thirteenth report of the Expert Committee (Annex 1, reference

19). Since then some of the earlier studies have been re-evaluated by the International Agency for Research on Cancer and it was suggested that some of them should have been more extensive. Therefore Fast Green FCF was reviewed by the present Committee and the ADI was converted to a temporary ADI of 12.5 mg/kg of body weight, maintaining the safety factor of 200 which had previously been applied to the no-effect level. The results of further adequate long-term feeding studies and multigeneration/teratology studies are required by 1985. A toxicological monograph was prepared.

Ponceau 4R

Ponceau 4R was last reviewed in the twenty-second report and the temporary ADI of 0–0.125 mg/kg of body weight was extended until 1981 pending evaluation of results of metabolic, long-term, and reproduction studies. The Committee was informed that the laboratory phases of the required studies had been completed but that the data were still being analysed.

The Committee extended the existing temporary ADI to 1982 on the understanding that the results of the required studies would then be available. The existing specifications were revised. No toxicological monograph was prepared.

Red 2G

This food colour was allocated a temporary ADI of 0.006 mg/kg of body weight in the twenty-first report of the Expert Committee. The results of the required additional studies were available for evaluation by the present Committee. The Committee allocated Red 2G an ADI of 0–0.1 mg/kg of body weight, which was based on a no-effect level in long-term animal feeding studies. The existing specifications were revised. A toxicological monograph was prepared.

Riboflavin-5'-phosphate

This substance occurs naturally and has vitaminic activity. The phosphate is rapidly hydrolysed to yield riboflavin after ingestion. Riboflavin and riboflavin-5'-phosphate are in metabolic equilibrium after absorption. Intakes of riboflavin that are many times the nutritionally required levels have no toxic effects in man or experimental

animals. Riboflavin, as a food colour, was evaluated in the thirteenth report of the Expert Committee and allocated an ADI of 0–0.5 mg/kg of body weight. The present Committee allocated a group ADI to riboflavin and riboflavin-5′-phosphate of 0–0.5 mg/kg of body weight expressed as riboflavin, when used as a food-colouring agent—this is an addition to the contents of these substances occurring naturally in food. The Committee did not consider the use of riboflavin in pharmaceutical preparations. New specifications and a toxicological monograph on riboflavin and riboflavin-5′-phosphate were prepared.

3.2 Flavouring agents

β-Asarone

This substance is a constituent of oils of calamus, and occurs in different concentrations in oils from different sources. The Committee was aware of procedures for treating oils of calamus in order to reduce the level of β-asarone. Oils of calamus, and β-asarone, have been shown to be cardiotoxic, hepatotoxic, and to produce intestinal leiomyosarcomas in rats when fed in large doses. A no-effect level has not been established. The Committee decided that it was not appropriate to allocate an ADI for β-asarone and therefore no specifications were prepared. The Committee recommended that oil of calamus when used as a food additive should contain the lowest possible level of β-asarone. A toxicological monograph was prepared. (See also section 2.9.)

(+)-Carvone and (−)-carvone

Carvone isomers were first considered in the eleventh report and additional studies were requested at that time. Some new data were presented for the twenty-third report and a temporary ADI of 0–1 mg/kg of body weight was allocated, pending the submission of further studies in 1981. These were not forthcoming. Since carvone is one of a large number of flavouring substances to be tested and its priority for testing has not yet been established, the Committee extended the temporary ADI until 1983, when the further studies requested should become available for evaluation. The existing specifications were revised. No toxicological monograph was prepared.

Cinnamaldehyde

A temporary ADI of 0–0.7 mg/kg of body weight was allocated in the twenty-third report, since the required 90-day studies were not available. However, some other data were supplied for consideration by the Committee and the temporary ADI was extended to 1984. Additional studies were deemed necessary: a short-term feeding study in a non-rodent species; and long-term feeding studies for evaluating the carcinogenic potential. See also comments on the following compound.) The existing specifications were revised. No toxicological monograph was prepared.

Cinnamyl anthranilate

This is a synthetic flavouring agent that is not known to occur naturally. In long-term feeding experiments with mice, it produced a significant increase in spontaneously occurring hepatomas. The results of a parallel set of experiments with rats were inconclusive. On the available evidence, the Committee considered that cinnamyl anthranilate should not be used as a food additive. The Committee believes that problems posed by substances that enhance the production of spontaneously occurring tumours in a susceptible species but are not otherwise carcinogenic requires evaluation. Additional clarification is needed in this instance because of the structural relationship of this compound to other flavours. A toxicological monograph was prepared.

Coumarin

Coumarin is present in many naturally occurring flavouring agents and widely distributed in nature in low concentrations. Coumarin is hepatotoxic in the rat and the dog but not in the baboon. However, coumarin metabolism in man is different from that in the rat. In one study in rats fed coumarin at 0.5% or more of the diet, bile duct carcinomas were reported, but some doubts have been expressed about the exact nature of the lesions. Therefore adequate life-time feeding studies are required to resolve the question of the carcinogenicity of coumarin for the rat. Until further toxicological studies are available for evaluation, the Committee considered that coumarin should not be used as a food additive; hence no specifications were prepared.

However, it was recognized that natural flavouring substances containing coumarin have been traditionally used in the preparation

of certain foods. The Committee recommended that the use of such coumarin-containing flavouring substances should be limited to these foods and that the level of use should be restricted to the minimum necessary to produce the desired organoleptic effect. (See also section 2.9.) A toxicological monograph was prepared.

Estragole

This flavouring substance occurs in a number of herbs and spices, and is also synthesized for use as a food additive. It was previously reviewed in the twenty-third report of the Expert Committee. Estragole and its metabolites have been shown to be mutagenic in bacterial systems (Ames test) and to produce hepatomas in a susceptible strain of mice. The available toxicological studies were not adequate for evaluation. No ADI was allocated. The Committee requested additional long-term studies for evaluation of carcinogenic potential before an ADI can be established. New tentative specifications were formulated but no toxicological monograph was prepared.

Ethylmethyl ketone

This substance is mainly used as an extraction solvent (see section 3.5). The existing specifications were revised. No toxicological monograph was prepared.

Ethyl 3-phenylglycidate

This compound was last reviewed in the twenty-third report of the Expert Committee. No satisfactory data for toxicological evaluation were available to the Committee, therefore no ADI was allocated. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification. No toxicological monograph was prepared.

Eugenyl methyl ether

This flavour was reviewed in the twenty-third report of the Expert Committee, but there were insufficient data for evaluation and no toxicological monograph was prepared. Results from 90-day studies

or long-term tests were not available to the present Committee; and therefore no ADI could be allocated since this requires results of adequate studies to allow for toxicological evaluation. New tentative specifications and a toxicological monograph were prepared.

Hydrocyanic acid

There are many foods containing cyanogenic substances. Cyanide is produced in intermediary metabolism and is further metabolized to thiocyanate. The main practical problem with chronic ingestion of cyanogenic foods is the goitrogenic effect of thiocyanate, and this is only a serious problem when there is an iodine-deficient diet.[7] The present Committee dealt with cyanide that occurs naturally in certain flavouring agents, particularly those derived from the fruits and other parts of *Prunus* species, and noted that cyanide is an organoleptic constituent. The Committee decided that hydrogen cyanide and its salts should not be used as food additives and hence no specifications were prepared. The Committee considered that the amount of cyanide present in finished foods and beverages as a result of adding cyanide-containing flavouring agents should be kept to the lowest level necessary to achieve the desired organoleptic effect. A toxicological monograph on hydrogen cyanide with reference to its use as a fumigant has been prepared by a joint FAO/WHO meeting on pesticide residues.[8]

Magnesium glutamate

Other glutamates were evaluated on a group basis in the seventeenth report of the Expert Committee and several magnesium salts were accepted on a group basis in the twenty-third report. The present Committee therefore included magnesium glutamate in the group ADI for other glutamates, that is, an ADI of 0–120 mg/kg of body weight (calculated as glutamic acid). New specifications were formulated but no toxicological monograph was prepared.

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[7] Montgomery, R. D. Cyanogens. In: Science, E. I., ed. *Toxic constituents of plant foodstuffs,* 2nd ed., New York, Academic Press, 1980, Chapter 5.

[8] *Evaluation of the hazards to consumers resulting from the use of fumigants in the protection of food.* FAO Meeting Report, No. PL 1965/10/2; WHO/Food Add/28.65.

Maltol

Further studies on maltol required in the twenty-second report were submitted for consideration by the present Committee. In the light of the new information, the "temporary" status was removed and an ADI at the level of 0–1 mg/kg of body weight was allocated. The existing specifications were revised and a new toxicological monograph was prepared.

Methyl β-naphthyl ketone

No toxicological information about this flavouring agent was available to the Committee and therefore no ADI was allocated. The existing specifications were revised and designated as "tentative". No toxicological monograph was prepared.

Octanal

In the twenty-third report of the Expert Committee this substance was reviewed and the previous conditional ADI was converted to a temporary ADI at the same level—namely, 0–0.06 mg/kg of body weight. The requisite results of additional metabolic studies that are needed to confirm the assumption that octanal is metabolically converted to the corresponding acid were not available to the present Committee. If this assumption is correct the small amount of octanal that would be ingested in foods containing this flavouring principle would not pose any toxicological problem. Octanal is present in citrus fruits and their essential oils, and also occurs in lemongrass and some other flavouring agents. The natural occurrence of octanal has been reported for a wide range of meat products, fruits, nuts, vegetables, milk products and beverages. The amounts of octanal added as a flavour range from 0.1 mg/kg to 10 mg/kg in various foods and beverages. The Committee decided to extend the temporary ADI of 0–0.06 mg/kg of body weight and requested that the results of the metabolic studies mentioned above should be available by 1984. The existing specifications were revised. No toxicological monograph was prepared.

p-*Propylanisole*

No toxicological information on this compound was available and therefore no ADI could be allocated. New tentative specifications were formulated, but no toxicological monograph was prepared.

Safrole and isosafrole

Safrole is the main constituent of oil of sassafras and is a minor constituent of many other essential oils. Some important and widely used flavouring agents contain small amounts of safrole and isosafrole. Many toxicological studies have been carried out with safrole and isosafrole, and it has been established that these substances are carcinogenic in rats and mice. The Committee, in reconsidering this substance, endorsed the views expressed in the fifth report of the Committee, namely:

(1) flavouring agents containing safrole or isosafrole as the principal flavour-active ingredient should not be used as food additives;

(2) it is not practicable to advocate the discontinuance of spices containing safrole or isosafrole as minor constituents (e.g., nutmeg, mace, and cinnamon). However, when these spices are used as food additives the amounts of safrole and isosafrole in the finished product should be kept to the absolute minimum as stated in the twenty-second report of the Expert Committee (see Annex 1, reference 48, p. 15). No specifications were formulated but a toxicological monograph was prepared. (See also section 2.9.)

Thujone and isothujone (α- and β-thujone)

These isomers of thujone are widely distributed in herbs and essential oils that are used as flavouring agents. The pharmacological effects of thujone isomers on the central nervous system are well known. No formal toxicological studies relevant to food-additive use were available for evaluation except for acute toxicity. The Committee decided that it was not appropriate to allocate an ADI and considered that the amounts of thujone isomers in foods and beverages resulting from the addition of thujone-containing flavouring agents (e.g., sage) should be reduced to the lowest practicable level. (See also section 2.9.) A toxicological monograph was prepared, but no specifications were formulated.

3.3 Sweetening agents

Acesulfame potassium

This newly developed sweetening agent is chemically related to saccharine. The results of a number of toxicological studies and their

apparent shortcomings were available for evaluation by the present Committee. These included two long-term feeding studies in rats and a long-term mouse study. The most notable deficiencies were the lack of detailed histopathology in a long-term mouse study, and the small proportion of animals given detailed histopathological examinations in the second long-term feeding study in rats. Clarification of the report of an increase in lymphomas restricted to the lung in the first long-term rat study is required. The Committee concluded that the use of acesulfame potassium in food additives could not be properly assessed until these deficiences in the data available for consideration had been remedied. In addition, the results of metabolic studies after multiple exposure to acesulfame potassium are required for the future evaluation of this substance. No ADI was allocated. New tentative specifications and a toxicological monograph were prepared.

Aspartame

Aspartame has been considered in the nineteenth, twentieth, twenty-first, twenty-third, and the twenty-fourth reports of the Expert Committee. The twenty-fourth report allocated an ADI for aspartame of 0–40 mg/kg of body weight and specifications and a toxicological monograph were prepared. The present Committee considered the results of an additional long-term study of aspartame and the diketopiperazine impurity in rats and further biochemical studies of aspartame in humans. The ADI allocated in the twenty-fourth report was confirmed. The existing specifications were revised and an addendum to the previous toxicological monograph was prepared.

Isomaltitol

Complete hydrolysis of isomaltitol yields glucose (50%), sorbitol (25%), and mannitol (25%). In man, hydrolysis by intestinal disaccharidases is incomplete and less than half the glucose units in isomaltitol contribute to metabolic energy production. The Committee allocated isomaltitol a temporary ADI of 0–25 mg/kg of body weight. This was based on the no-effect level in man of 250 mg/kg of body weight with respect to laxation. The Committee regarded this temporary ADI as being applicable to the general use of isomaltitol in foods and considered that higher levels could be taken in dietetic foods. Further results from life-time feeding studies and multigenera-

tion studies in rats are required by 1985. New tentative specifications and a toxicological monograph were prepared.

3.4 Thickening agents

Carob (locust) bean gum

This gum has been considered in the thirteenth, eighteenth, nineteenth, and twenty-fourth reports of the Expert Committee. A temporary ADI "not specified" was allocated in the nineteenth report and this was extended in the twenty-fourth report. The Committee reviewed the considerable body of relevant toxicological data that is now available and removed the temporary status of the ADI. A new toxicological monograph was prepared. The existing specifications were maintained.

Pectins and amidated pectins

Amidated pectins were evaluated in the thirteenth, eighteenth, and twenty-fourth reports of the Expert Committee. The results of the required further studies with amidated pectins were available for evaluation by the present Committee. Long-term feeding studies in rats, as well as a multigeneration reproduction study, showed that there were no toxicological differences between pectins and amidated pectins. A group ADI "not specified" was established for pectins and amidated pectins. The Committee was informed that two distinct classes of products are available as items of commerce. Revised specifications were prepared for pectins and new specifications for amidated pectins. A new toxicological monograph was prepared.

Tara gum

Tara gum was considered in the twenty-fourth report of the Expert Committee and the previously allocated temporary ADI "not specified" was maintained. Further toxicological studies were now available for consideration by the Committee, which also reviewed the toxicological studies that had been evaluated previously, and decided to limit the temporary ADI to 0–12.5 mg/kg of body weight. This decision was based on the no-effect level of 5% in the diet in a long-term feeding study to which a 200-fold safety factor was applied.

A multigeneration reproduction study, with several dose levels of tara gum, and a teratological study are required by 1984. The existing tentative specifications were maintained. A new toxicological monograph was prepared.

3.5 Extraction solvents

The available toxicological information on many of the extraction solvents on the agenda had not changed since the twenty-third report and thus the present Committee had nothing to add to the previous comments (see Annex 7, reference 51). The Committee recommended that the principle set out in section 2.6 should be applied to future considerations of these solvents. The solvents for which the comments of the twenty-third report remain unchanged are: butane, butan-1-ol, butan-2-ol, cyclohexane, 1,1-dichloroethane, diisopropyl ether, furfural, isopropyl acetate, and tetrachloroethylene. However, new tentative specifications have now been prepared for 1,1,2-trichlorotrifluoroethane and ethylmethyl ketone.

The following extraction solvents were considered in more detail.

Light petroleum

This solvent was considered in the twenty-third report of the Expert Committee but the data were inadequate for evaluation. Data available to the present Committee indicated that residues of the solvent occurring in foods when it was used according to good manufacturing practice would not have any significant toxicological effects. The existing specifications were revised and a toxicological monograph was prepared.

2-Nitropropane

The twenty-third report contained tentative specifications for 2-nitropropane, but no toxicological monograph. The present Committee considered the available toxicological information on 2-nitropropane. The evidence indicated that it is mutagenic according to the Ames test and is carcinogenic in inhalation studies in rats. The Committee therefore considered that 2-nitropropane should not be used in food processing. The existing specifications were withdrawn and a toxicological monograph was prepared.

Propan-1-ol (n-Propanol)

This substance was last evaluated in the twenty-third report of the Expert Committee. Specifications were formulated, but no toxicological monograph was prepared, and the substance could not be evaluated on the basis of the data available. Additional toxicological information was available to the present Committee, including a limited study in rats suggesting a carcinogenic potential for propan-1-ol. Lifetime feeding studies in rodents are required to resolve the problem of carcinogenicity. The existing specifications were revised and designated as "tentative". A toxicological monograph was prepared.

Propan-2-ol (isopropanol)

This substance was considered in the fourteenth report of the Expert Committee and accepted for food-processing use on the assumption that only negligible residues would be present in food. The Committee was informed that toxicological studies had been carried out with this solvent, and requested that the results be made available for evaluation by a future Committee. The existing specifications were revised and designated as "tentative". Additional information is required regarding gas-liquid chromatographic methods of assay together with methodology for other volatile impurities, such as aldehydes, ketones, and alcohols. No toxicological monograph was prepared.

Toluene

Specifications for toluene were prepared for the twenty-third report of the Expert Committee but no toxicological data were available and therefore no ADI was established. The Committee took account of the low toxicity of toluene, its rapid hepatic metabolism and clearance, and its lack of carcinogenicity in a life-time inhalation study in the rat; and agreed that residues of toluene occurring in foods, based on good manufacturing practice, would not pose any toxicological problems. The existing specifications were revised and a toxicological monograph was prepared.

1,1,1-Trichloroethane

This solvent was considered in the twenty-third report of the Expert Committee, but the available data were inadequate for evalua-

tion. The present Committee was not aware of any use of 1,1,1-trichloroethane in the food industry. The substance is not mutagenic according to the Ames test, with and without activation, but one limited study, in mice, suggested that it is carcinogenic. However, no other adequate study results were as yet available, but new life-time feeding studies in rodents were in progress. No ADI was allocated. No specifications were formulated. A toxicological monograph was prepared.

3.6 Carrier solvents

The situation in respect of the following carrier solvents on the agenda has not changed since the twenty-third report and its comments are still applicable: diethylene glycol monoethyl ether, diethylene glycol monopropyl ether, dipropylene glycol, and isopropyl myristate.

Diethyl tartrate

No new data were available on diethyl tartrate, but the Committee suggested that information about the hydrolysis of this compound after ingestion might provide a basis for its evaluation in terms of the hydrolytic products. No ADI was allocated. New tentative specifications and a toxicological monograph were prepared.

1,2-Propylene glycol acetate

This compound was reviewed in the twenty-third report of the Expert Committee and no ADI was allocated as insufficient data were available for an evaluation. Since that meeting no further information had become available. However, the Committee noted that a group ADI for propylene glycol esters of fatty acids was established in 1974. It considered that this compound could be placed in the same category, and that it should be included in the group ADI of 0–25 mg/kg of body weight, calculated as propylene glycol. Neither specifications nor a toxicological monograph were prepared.

Triethyl citrate

This compound was allocated a temporary ADI of 0–10 mg/kg of body weight in the twenty-third report of the Expert Committee. The Committee extended this to 1984 and required that evidence be

produced to show that it is hydrolysed to citrate and ethanol in man. The existing specifications were maintained. No toxicological monograph was prepared.

Triglycerides (synthetic)

Information regarding the nature and identity of this class of compounds is required. No specifications were prepared and no toxicological evaluation was possible without them.

3.7 Miscellaneous food additives

Calcium ascorbate

The Committee considered that the evaluation of ascorbic acid and its salts had relevance only with respect to the food-additive use of these substances, and their use as a vitamin C supplement in the usually accepted levels of intake for nutritional purposes. Since oxalate is a major metabolite of ascorbate, the use of the calcium salt in large amounts might increase the risk of crystalluria and the formation of calcium oxalate stones. However, the Committee concluded that in regard to food-additive and nutritional use, the intake of calcium from ascorbate would represent only a small fraction of the total dietary intake of calcium. Therefore it was not envisaged that the use of calcium ascorbate required any special restriction. The Committee concluded that the ADI for ascorbic acid and its potassium and sodium salts should be changed from 0–15 mg/kg of body weight to "not specified" and that the calcium salt should be included in this acceptance. No specifications for calcium ascorbate were formulated. A toxicological monograph was prepared.

Polydextroses

These compounds were evaluated in the twenty-fourth report of the Expert Committee and an ADI of 0–70 mg/kg of body weight was allocated. The Committee regarded this ADI as being applicable to general food uses of polydextroses and considered that higher levels could be taken in dietetic foods. The Committee confirmed the ADI of 0–70 mg/kg of body weight for polydextrose-A and polydextrose-N, singly or in combination. The specifications were revised, to include a limit of 0.05% for 5-hydroxymethylfurfural in poly-

dextroses, and maintained as tentative. A toxicological monograph was prepared.

Polyvidone (poly(vinyl pyrrolidone); PVP)

The tenth report of the Committee allocated an ADI of 0–1 mg/kg of body weight to polyvidone. This ADI was withdrawn in the seventeenth report because of concern about the implications of the accumulation of polyvidone in the reticuloendothelial system. The twenty-fourth report considered the results of some studies with polyvidone, including a long-term feeding study in rats in which there was no evidence of carcinogenicity, but an ADI was not allocated. The present Committee re-evaluated the existing studies on polyvidone. It was noted that the total use of polyvidone in food preparation—average relative molecular mass 40 000—as a filtration aid, colour dispersant, humectant and baking aid, would result in a daily intake of less than 0.5 mg/kg of body weight. The Committee decided to restore the previous ADI of 0–1 mg/kg of body weight to polyvidone. This ADI is considerably less than the figure corresponding to the no-effect level after application of the usual safety factor; this lower figure does not take into account the consumption of polyvidone from non-food sources. The existing specifications were maintained and no new toxicological monograph was prepared.

Sodium sesquicarbonate

The Committee included this substance in the group ADI "not specified" for other carbonates and bicarbonates that had been established in the ninth report of the Expert Committee. New specifications were formulated but no toxicological monograph was prepared.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 57 substances including food colours, emulsifiers, thickening agents, sweetening agents, extraction solvents, carrier solvents, flavouring agents, enzyme preparations and miscellaneous additives (see Annex 2). New specifications were prepared for two sweetening agents, one food colour, two

carrier solvents, three flavouring agents, and three enzyme preparations. In the case of gum arabic (acacia), the Committee was informed of the ongoing research work on analytical methods for this substance and agreed to postpone further consideration until a later date. Specifications were not developed for glucose isomerase (from varieties of *Arthrobacter globiformis*), butane, 1,1-dichloroethane, diethylene glycol, monopropyl ether, diisopropyl ether, fungal rennet (from *Irpex lacteus*), glucose oxidase (from *Penicillium amagasakiense*), 1,2-propylene glycol acetate, glucose isomerase tetrachloroethylene (from varieties of *Streptomyces albus*), and 1,1,1-trichloroethane, because the Committee was uncertain of their use in foods.

Specifications for carbohydrase obtained from varieties of *Aspergillus awamori* were deemed to be unnecessary in view of the existence of specifications for carbohydrase obtained from varieties of *Aspergillus niger*. The Committee was informed that the latter includes strains known under the name *Aspergillus awamori*.

In addition, the existing specifications for microbial rennet, obtained from *Bacillus cereus,* were revised, but maintained as "tentative" pending the receipt of further toxicological information.

The Committee was informed that a number of chemically modified starches are no longer in use. In view of this statement, the Committee concluded that, although revisions of the existing specifications were necessary, they could not be undertaken without additional information on the actual products now used in food. In the case of dipropylene glycol, it was not possible to develop specifications because of the incompleteness of the information available. Information is also required regarding the nature and identity of compounds belonging to the class of triglycerides.

The Committee was requested to prepare specifications for a number of flavouring substances. Four of these substances—β-asarone, coumarin, safrole, and thujones—are active principles in naturally occurring flavouring substances. The thirteenth report of the Codex Committee on Food Additives[9] referred all these substances (with the exception of β-asarone) to the twenty-fourth session of the Expert Committee (see Annex 1, reference 54) for an opinion on the setting of limits in food, noting that these substances were not themselves used as flavouring substances. The present Joint Expert Committee reiterated its previous opinion that it was not appropriate to establish

[9] *Report of the thirteenth session of the Codex Committee on Food Additives,* The Hague, 11–17 September 1979 (Codex Committee Report, Alinorm 79/12-A).

specifications for these substances. It did not establish specifications for hydrocyanic acid.

5. FUTURE WORK

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

2. In reviewing the specifications for a number of colours, the Committee felt that there was a need to review and update the general methods for the identification of dyes and subsidiary dyes to take into account advances in methodology.

3. In reviewing the specifications of a number of alcohols, the Committee reiterated the view, expressed in the twenty-third report, that there was a need to incorporate newer methods of assay and analysis for impurities, such as other alcohols, based on gas-liquid chromatographic methods.

4. The toxicological evaluation of substances migrating from packaging materials into food should be considered by a future meeting.

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. A scientific group should consider the advances made in mutagenicity testing in relation to the toxicological evaluation of food additives and for setting priorities for carcinogenicity testing.

3. Information on the residual levels of solvents (and impurities, additives, etc.) in solvent-processed foods should be collected by such bodies as the Codex. A list of acceptable stabilizers should be established and revised periodically.

4. The multidisciplinary approach to toxicology in recent years has led to significant advances in methodological approaches and procedures for evaluation. Paradoxically, these advances have sometimes made it more difficult to arrive at clear recommendations con-

cerning food additives and contaminants. Examples of problems that have been encountered in the general context of toxicological testing include:

(*a*) the influence of nutritional imbalance on the manifestation of toxic effects including carcinogenic effects;

(*b*) the interpretation of results obtained when excessively high doses are used; and

(*c*) the testing of foods for the presence of small amounts of toxicologically active components.

Examples of problems encountered in testing for carcinogenic potential include:

(*a*) the interpretation of enhancement of some types of spontaneously occurring tumours in susceptible strains of certain animal species;

(*b*) the implications for toxicological evaluations of promoting factors and other modifiers of carcinogenic activity; and

(*c*) the relationship of results of various kinds of mutagenicity tests to the prediction of carcinogenic potential.

In order to resolve these problems, the Committee strongly recommended that a group of experts be convened, as soon as possible, to study the application of advances in methodology to the toxicological evaluation of food additives and contaminants, and also of pesticide residues.

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, text 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.
52. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1979.
53. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.
54. *Evaluation of certain food additives* (Twenty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 653, 1980.
55. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1981.
56. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.

Annex 2

ACCEPTABLE DAILY INTAKE (ADI) AND INFORMATION ON SPECIFICATIONS

	Specifications[1]	*ADI for man (mg/kg of body weight) and other toxicological decisions*
Food colours		
Allura Red	R	0–7
Brilliant Black PN	R	0–1
Brown HT (formerly Chocolate Brown HT)	R	0–2.5[2]
carmines (formerly cochineal, carmine, and carminic acid)	NT	0–2.5[2]
Fast Green FCF	S	0–12.5[2]
Ponceau 4R	R	0–0.125[2]
Red 2G	R	0–0.1
riboflavin-5′-phosphate	N	0–0.5[3]
Flavouring agents		
β-asarone	O	No ADI allocated
(+) carvone and (−) carvone	R	0–1[2]
cinnamaldehyde	R	0–0.7[2]
cinnamyl anthranilate	O	Not to be used[4]
coumarin	O	No ADI allocated
estragole	NT	No ADI allocated
ethylmethyl ketone	R	No ADI allocated
ethyl 3-phenylglycidate	R	No ADI allocated
eugenyl methyl ether	NT	No ADI allocated
hydrocyanic acid	O	Not to be used[5]
magnesium glutamate	N	0–120[6]
maltol	R	0–1
methyl β-naphthyl ketone	RT	No ADI allocated
octanal	R	0–0.06[2]
p-propylanisole	NT	No ADI allocated
safrole and isosafrole	O	No ADI allocated
thujone and isothujone (α- and β-thujone)	O	No ADI allocated
Sweetening agents		
acesulfame potassium	NT	No ADI allocated
aspartame	R	0–40[16]
isomaltitol	NT	0–25[2]

Thickening agents

carob (locust) bean gum	S	ADI not specified[7]
pectins	R	ADI not specified[7, 8]
pectins (amidated)	N	ADI not specified[7]
tara gum	TS	0–12.5[2]

Extraction solvents

light petroleum	R	ADI not specified[7]
2-nitropropane	withdrawn	Not to be used[9]
propan-1-ol (*n*-propanol)	RT	No ADI allocated
propan-2-ol (isopropanol)	RT	No ADI allocated
toluene	R	ADI not specified[7, 10]
1,1,1-trichloroethane	O	No ADI allocated

Carrier solvents

diethyl tartrate	NT	No ADI allocated
1,2-propylene glycol acetate	O	0–25[11]
triethyl citrate	S	0–10[2]
triglycerides (synthetic)	O	No ADI allocated

Miscellaneous food additives

calcium ascorbate	O	ADI not specified [7, 10, 12]
polydextroses	R[13]	0–70[14]
polyvidone (poly(vinyl pyrrolidone) (PVP)	S	0–1
sodium sesquicarbonate	N	ADI not specified[7, 10, 15]

Specifications only

Extraction solvents	*Specifications*[1]
butane	O
butan-1-ol	R
butan-2-ol	O
cyclohexane	R
1,1-dichloroethane	O
diethylene glycol monoethyl ether	R
diisopropyl ether	O
ethylmethyl ketone	R
furfural	S
isopropyl acetate	NT
tetrachloroethylene	O
1,1,2-trichlorotrifluoroethane	NT

Notes to Annex 2

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. Group ADI for riboflavin and riboflavin-5′-phosphate expressed as riboflavin.
4. On the available evidence, this substance should not be used as a food additive.
5. Hydrogen cyanide and its salts should not be used as such as food additives.
6. Group ADI for other glutamate, calculated and expressed as glutamic acid.
7. 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.
8. Group ADI for pectins and amidated pectins, singly or in combination.
9. This solvent should not be used in food processing.
10. Residues of toluene occurring in foods when this solvent is used in accordance with good manufacturing practice would not pose any toxicological problems.
11. Group ADI for propylene glycol esters of fatty acids calculated and expressed as propylene glycol.
12. Group ADI. The Committee concluded that the ADI for ascorbic acid and its potassium and sodium salts should be changed from 0–15 mg/kg of body weight to "not specified", and that the calcium salt should be included in this ADI.
13. The specifications were revised to include a limit for 5-hydroxymethylfurfural of 0.05%.
14. The ADI is for polydextrose A and polydextrose N, singly or in combination.
15. Group ADI for other carbonates and bicarbonates established in the ninth report of the Committee.
16. An ADI for diketopiperazine—an impurity found in aspartame—was established at 0–7.5 mg/kg body weight.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED

Food colours

Brown HT (formerly Chocolate Brown HT)[1]
(1) Multigeneration reproduction/teratology studies.
(2) Metabolic studies in several species, preferably including man.

carmines (formerly cochineal, carmine and carminic acid)[1]
(1) Submission of the results of long-term studies.

Fast Green FCF[4]

(1) Multigeneration reproduction/teratology studies.

(2) Adequate long-term feeding studies.

Ponceau 4R[1]

(1) Metabolic studies in several species, preferably including man.

(2) An adequate long-term feeding study in another animal species.

(3) A reproduction study.

Flavouring agents

(+) carvone and (–) carvone[2]

(1) Further biochemical and metabolic studies in several animal species, preferably including man, using current techniques.

cinnamaldehyde[3]

(1) A short-term feeding study in a non-rodent species.

(2) Long-term feeding studies for evaluating the carcinogenic potential.

octanal[3]

(1) Adequate metabolic studies in several animal species, preferably including man.

Sweetening agents

isomaltitol[4]

(1) Results of life-time feeding studies.

(2) Multigeneration studies in rats.

Thickening agents

tara gum[3]

(1) A multigeneration reproduction/teratology study.

Carrier solvents

triethyl citrate[3]

(1) Additional metabolic studies in several species, preferably including man.

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[1] Information required by 1982.

[2] Information required by 1983.

[3] Information required by 1984.

[4] Information required by 1985.

ADDENDUM

On page 42, at the foot of the page, under "Specifications only", add the following:

	Specifications
Microbial enzyme preparations	
Actinoplanes missouriensis	
glucose isomerase	N
Aspergillus niger varieties	
glucose oxidase and catalase	R
A. oryzae varieties	
amylase and glucoamylase	R
protease	R
Bacillus cereus	
microbial rennet	R
B. coagulans varieties	
glucose isomerase	R
B. licheniformis varieties	
amylase	R
Ficin	R
Klebsiella aerogenes	
pullulanase	R
Micrococcus luteus (lysodeikticus)	
catalase	R
Streptomyces olivaceus	
glucose isomerase	R
S. olivochromogenes	
glucose isomerase	N
S. rubiginosus	
glucose isomerase	N
S. violaceoniger	
glucose isomerase	R

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640	(1979) **WHO Expert Committee on Malaria** Seventeenth report (71 pages)	5.—
641	(1979) **The selection of essential drugs** Second report of the WHO Expert Committee (44 pages)	3.—

642 (1980) **Viral respiratory diseases**
Report of a WHO Scientific Group (63 pages) ..... 4.—

643 (1980) **Epidemiology and control of schistosomiasis**
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647 (1980) **Recommended health-based limits in occupational exposure to heavy metals**
Report of a WHO Study Group (116 pages) ..... 8.—

648 (1980) **Evaluation of certain food additives**
Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives (45 pages) ..... 3.—

649 (1980) **Environmental management for vector control**
Fourth report of the WHO Expert Committee on Vector Biology and Control (75 pages) ..... 5.—

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Report of a WHO Expert Committee (72 pages) ..... 5.—

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Report of an ICMR/WHO Scientific Group (21 pages) ..... 2.—

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658 (1981) **WHO Expert Committee on Biological Standardization**
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660 (1981) **Nongonoccocal urethritis and other selected sexually transmitted diseases of public health importance**
Report of a WHO Scientific Group (142 pages) ..... 9.—

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