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Evaluation of certain food additives and contaminants

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

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Rome, 19–28 March 1984

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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 19 to 28 March 1984. The meeting was opened by Mr G.O. Kermode, Chief, Food Quality and Standards Service, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Mr Kermode recalled the Expert Committee's world-wide reputation for sound and independent judgement in regard to the toxicological evaluation of food additives and contaminants and the elaboration of specifications for the identity and purity of food additives.

He referred to the general task before the Expert Committee of reviewing the methodology for testing and assessing the safety of chemicals in food, which he hoped would lead to clarified and simplified test criteria.

The publications emanating from the work of the Committee—reports, monographs, and specifications—were highly appreciated by the Members of the two organizations, and by the manufacturers and users of food additives. A revision of the *Guide to specifications* had recently been published[1] and the published information contained in the computerized FAO/WHO food additives data system[2] was also being revised. A complete up-to-date set of the specifications for food additives prepared by the Committee over the years was being compiled.

1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,[3] there

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[1] FAO Food and Nutrition Paper, No. 5 Rev. 1, 1983 (*Guide to specifications—General notices, general methods, identification tests, test solutions, and other reference materials*).

[2] FAO Food and Nutrition Paper, No. 30, 1984 (*FAO/WHO food additives data system*).

[3] FAO Nutrition Meetings Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

have been 27 previous meetings of the Committee (Annex 1). The present meeting was convened on the recommendation made at the twenty-seventh meeting (Annex 1, reference *62*). The tasks before the Committee were: (*a*) to prepare specifications for the identity and purity of certain food additives and to carry out toxicological evaluations of them; (*b*) to review specifications for selected food additives; (*c*) to undertake toxicological evaluations and re-evaluations of certain food additives; and (*d*) to consider the methodology for testing and assessing chemicals in food.

During the meeting the Committee members invited by WHO were primarily responsible for reviewing the toxicological and related data and estimating, where possible, Acceptable Daily Intakes (ADIs), and for formulating other toxicological recommendations for compounds on the agenda. The members invited by FAO were primarily responsible for reviewing the specifications for identity and purity.

2. GENERAL CONSIDERATIONS

2.1 Modification of the agenda

Ethyl methylphenyl glycidate was added to the agenda, to consider the information, provided by FAO, on impurities in the samples used in the toxicity studies discussed by the Committee in 1983.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee reiterated the principles established at its previous meetings (Annex 1) and by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives[1] and the WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals.[2] In addition, the Committee reaffirmed the need to take into consideration recent developments in toxicological techniques, as stated in its seventeenth report (Annex 1, reference *32*). The Committee also had the benefit

[1] WHO Technical Report Series, No. 348, 1967.
[2] WHO Technical Report Series, No. 546, 1974.

of the consolidated guidelines for the evaluation of various groups of food additives and contaminants which are appended, as Annex 6, to the twenty-sixth report (Annex 1, reference *59*).

2.2.1 *Aluminium lakes of food colours*

The Committee considered the status of aluminium lakes of food colours within the context of its overall revision of the specifications for food colours. It was agreed that the ADIs allocated to food colours should encompass the aluminium lakes of colours. The Committee reaffirmed that aluminium (metal) used as a silvering decoration for certain items of confectionery is not considered to present a hazard, since its use is very limited (Annex 1, reference *44*).

2.2.2 *Substances migrating into food from food-contact materials*

Plastic materials in food packaging and the possible hazard to health of ingesting small amounts migrating into the food were considered at the twenty-fifth meeting of the Committee in 1981 (Annex 1, reference *56*) when general guidelines for evaluating food-contact materials were stated.

The Committee considered four specific substances referred for safety evaluation by the Codex Committee on Food Additives at its sixteenth session.[1]

On the basis of the information available it was not considered appropriate to allocate ADIs for the four substances. Although the toxicological data for one enabled a provisional maximum tolerable intake to be laid down, the Committee recommended that, for all four, the levels in food should be kept to the lowest technologically attainable, i.e., both the level of the potential migrant in the food-contact material and the extent of its migration into the food. While recognizing that the request for evaluation implied a wide use of such food-contact materials, the Committee recommended that the use of any food-contact materials containing potentially hazardous migrants should be limited to situations where no satisfactory alternative existed; it noted that certain types of material would not be suitable for all types of foodstuff.

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[1] *Report of the sixteenth session of the Codex Committee on Food Additives*, Rome, FAO, 1983 (FAO document, ALINORM 83/12A).

2.3 Principles governing the establishment and revision of specifications

2.3.1 *The need for sufficient data*

The Committee had on the agenda of its present meeting substances that the Codex Committee on Food Additives at its sixteenth session had requested should be reviewed.[1] It had endeavoured to consider expeditiously substances not previously reviewed, in the order of priority listed in the Codex Committee's report. It could not, however, review ferrous manganocyanide, magnesium ferrocyanides, manganese ferrocyanides, or potassium alumino silicate, because no data were available on their use in food, their manufacture, or their chemical composition. The Committee reiterated that such data should be presented in the format recommended in its twenty-fifth report (Annex 1, reference *56*). It emphasized that the review of substances could not proceed until sufficient data were provided.

2.3.2 *Review of specifications for food colours*

The twenty-seventh report of the Committee (Annex 1, reference *62*) provided for its future work to include the revision of specifications for food colours as a group, to reflect current methodology and to provide for a consistent format. In the review at the present meeting the Committee took into account the recommendations of the Codex Committee on Food Additives at its sixteenth session with respect to the modernization of test methods, provision for lakes of food colours, tests for specific impurities, the uniformity of trace metal limits, and consideration of the total composition of the material.[1]

The Committee decided that more informative definitions of food colours and, in some cases, their methods of manufacture, should be introduced generally. The term "total colouring matters" is used to include all the coloured components present in a food colour. Reference is made, where appropriate, to the presence of inorganic salts resulting from the manufacturing process. The Committee concluded that a general heading "organic compounds other than colouring matters", followed by a list of the specific chemicals found

[1] *Report of the sixteenth session of the Codex Committee on Food Additives*, The Hague, Rome, FAO, 1983 (FAO document, ALINORM 83/12A).

in an individual food colour prepared by good manufacturing practice, will avoid the misunderstandings that result from using the term "intermediates".

The Committee considered whether individual subsidiary colouring matters should be named in each specification. The term "subsidiary colouring matters" is intended to apply solely to the minor coloured components that arise during the manufacture of the food colour and contribute to the overall colouring effect of the product. The term is not intended to apply to foreign colouring matters added to the product that, unlike the true subsidiary colouring matters, are not present in the product when it is toxicologically tested. The Committee concluded that it is not necessary to name the individual subsidiary colouring matters in a specification except in certain instances (e.g., fluorescein in erythrosine) when there is a need to apply a separate limit.

Food colours may contain metallic contaminants from environmental sources and from sources related to the manufacture of specific colouring matter. Although the common environmental contaminants, such as arsenic and lead, are not a particular problem in food colours, the Committee felt that the basic criteria for food additives should continue to apply to food colours. Uniform limits for arsenic, lead, and other heavy metals were included in the revised food colour specifications. Limits for chromium, mercury, and zinc were included for those colours that have a specific source of such contamination.

In considering the methodology for determining the individual organic compounds other than colouring matters, the Committee recognized that some analytical reference standards were not readily obtainable commercially. To facilitate the use of the specifications the Committee encouraged the producers to make these standards available commercially.

In regard to specifications for lakes of food colours, the Committee noted that their manufacture involves the use of colours that conform to food-grade criteria. A general specification for lakes of food colours was prepared which requires the colour to conform to the Committee's specifications.

Food colours from natural sources, or food colours synthesized to simulate colours naturally present in food, are often supplied in a diluted form. The Committee agreed that such products should be manufactured with adjuvants (e.g., carrier solvents or emulsifiers) which comply with its specifications.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS

The Committee evaluated a number of food additives and contaminants for the first time and re-evaluated some substances considered at previous meetings. Information on the evaluation and on specifications is summarized in Annex 2. The further toxicological studies and information required or desired for certain substances are shown in Annex 3.

3.1 Specific food additives

3.1.1 *Antioxidants*

Anoxomer

Anoxomer was evaluated and a monograph prepared in 1982 (Annex 1, references *59* and *60*). At that time a temporary ADI of 0–8 mg/kg of body weight, using a safety factor of 100, was allocated. More information was requested about the occurrence of senile cataract in rats exposed to high levels of anoxomer in the diet. Senile cataract is frequently observed in rats. Its occurrence may be influenced by diet and exposure to light and it has been produced by the administration of a high level of certain sugars normally consumed by man, e.g., galactose. The Committee considered the results of a re-evaluation of the histopathological data from the long-term study and concluded that the development of cataract was not related to treatment. An ADI of 0–8 mg/kg of body weight was allocated. An addendum to the existing toxicological monograph was prepared. The existing tentative specifications were maintained.

3.1.2 *Enzyme preparations*

Glucose isomerase (isolated from Streptomyces violaceoniger)

Streptomyces violaceoniger glucose isomerase was evaluated in 1982 (Annex 1, references *59* and *60*) when the Committee allocated a temporary ADI "not specified" and prepared a toxicological monograph. Further information was requested on the occurrence of the microorganism in nature. The Committee was informed that the microorganism was naturally present in soil. The results of multigeneration reproduction and long-term studies were also

submitted. An ADI "not specified" was allocated. A new toxicological monograph was prepared and the existing specifications revised.

Protease (isolated from Streptomyces fradiae)

When *Streptomyces fradiae* protease was evaluated in 1982 (Annex 1, references *59* and *60*) a temporary ADI "not specified" was allocated, and histopathological observations from the feeding studies and information on the occurrence of the microorganism in nature were requested. Since further information was not made available, it was assumed there was no commerical interest in this enzyme preparation. The temporary ADI was withdrawn. The existing specifications were maintained.

3.1.3 *Flavouring agents*

Trans-*anethole*

Trans-anethole was evaluated in 1967, 1979 (when a toxicological monograph was prepared), and 1983 (Annex 1, references *14, 50, 51,* and *62*). The Committee was informed that the results of the long-term feeding study required for re-evaluation would not be available until 1986. It was, however, reassured by the fact that *trans*-anethole had been shown to be inactive in a mouse hepatocarcinogenicity model,[1] and extended the temporary ADI of 0–2.5 mg/kg of body weight until 1987. No new toxicological monograph was prepared but the existing specifications were revised.

Cinnamaldehyde

Cinnamaldehyde was evaluated in 1967, 1979, and 1981 (Annex 1, references *14, 50,* and *56*). A toxicological monograph was prepared in 1979 (Annex 1, reference *51*). The Committee was informed that the further data requested, from a short-term feeding study in a non-rodent species and a long-term carcinogenicity study, were not available. The structure of cinnamaldehyde is clearly related to the cinnamyl moiety of cinnamyl anthranilate which has

[1] MILLER, E.C. ET AL. *Cancer Research,* **43**: 1124 (1983).

"limited evidence" of carcinogenicity,[1] since in a study in mice it enhanced the incidence of hepatoma but, in a concurrent study, was without carcinogenic activity in rats. It was assumed that the carcinogenicity in mice was associated with the cinnamyl moiety of the molecule. Both cinnamyl anthranilate and cinnamaldehyde are inactive in mutagenicity tests.

Many cinnamyl compounds occur as natural flavours and the use of cinnamaldehyde as a food flavouring additive must be evaluated in that context. The Committee extended the temporary ADI of 0–0.7 mg/kg of body weight until 1989. It was understood that a long-term study is to be carried out, and the Committee suggested that, as well as investigating the potential carcinogenicity of cinnamaldehyde, it would be of value to re-test cinnamyl anthranilate in order to confirm the limited response in the previous study in mice. The Committee also suggested that the metabolic and pharmacokinetic data on the cinnamyl compounds be reviewed. No new toxicological monograph was prepared but the existing specifications were revised.

Ethyl methylphenyl glycidate

Ethyl methylphenyl glycidate was last considered in 1983, when a toxicological monograph was prepared (Annex 1, references *62* and *63*). The Committee had been satisfied with the results of short- and long-term studies in rats and had defined 50 mg/kg of body weight as the no-effect level. An ADI had not been allocated because questions remained to be answered on impurities in the samples used in the toxicity studies. The Committee was informed that 99% of the flavouring agent consists of *cis*- and *trans*-isomers of ethyl methylphenyl glycidate and the impurities identified are: 2-phenyl-2-ethoxypropanal, ethyl 3-phenyl-2-butenoate, ethyl 3-phenyl-2-hydroxy-3-butenoate, acetophenone, cinnamyl butenoate, methyl cinnamate, methyl phenyl glycidate, and ethyl phenyl glycidate.

The Committee noted that two of the impurities contain the cinnamyl moiety. It was considered that the comments made in

[1] For an explanation of this International Agency for Research on Cancer (IARC) classification see: *Some food additives, feed additives and naturally occurring substances*. Lyons, International Agency for Research on Cancer, 1983, p. 18 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, volume 31).

evaluating cinnamaldehyde would apply. Nevertheless, the levels of all impurities arising in food from the use of ethyl methylphenyl glycidate as a flavouring agent were considered unlikely to be of toxicological significance.

An ADI of 0–0.5 mg/kg of body weight was allocated for ethyl methylphenyl glycidate. No new toxicological monograph was prepared. However, the Committee had received sufficient information to revise the existing specifications and delete the tentative designation.

α- and β-Ionone

α-Ionone and β-ionone were last evaluated in 1979, when temporary ADIs of 0–0.05 mg/kg of body weight were allocated for each and monographs prepared (Annex 1, references *50* and *51*). A short-term toxicity study of both substances and data on the metabolism of α-ionone were requested. The temporary ADIs were extended in 1982. Satisfactory results from the short-term study were now available. The Committee considered that the metabolism of α-ionone ressembles that of β-ionone. ADIs of 0–0.1 mg/kg of body weight were allocated for α-ionone and β-ionone in single or combined use. A new toxicological monograph covering the two substances was prepared. The existing specifications for α-ionone were maintained with editorial changes. The existing specifications for β-ionone were revised.

Nonanal

Refer to the text for octanal below.

Octanal

Octanal was last considered in 1981 (Annex 1, references *56* and *57*). The results of adequate metabolic studies were requested by 1984. The Committee noted that octanal probably undergoes *in vivo* oxidation to yield the corresponding acid, that it is used at a very low level in food, and that it occurs naturally in many foods. It considered that a similar approach could be adopted in evaluating nonanal (Annex 1, references *50* and *51*). ADIs of 0–0.1 mg/kg of body weight were allocated for octanal and nonanal in single or combined use. No new toxicological monograph was prepared but the existing specifications for octanal were revised.

Amaranth

When amaranth was last reviewed in 1982 (Annex 1, reference *59*) new metabolic and mutagenicity data were considered, but the long-term feeding studies requested by the Committee at its 1978 meeting were not available (Annex 1, reference *47*). The previously established temporary ADI of 0–0.75 mg/kg of body weight was, therefore, extended. The Committee considered the results of a long-term feeding study in rats, with an *in utero* exposure phase, which revealed no evidence of carcinogenicity but demonstrated a dose-related increase in pelvic nephrocalcinosis. Caecal enlargement was seen in the two highest dose groups (250 and 1250 mg/kg of body weight) and may have influenced the development of nephrocalcinosis by altering the mineral absorption rate. Although long-term studies in two species had been requested, the Committee noted that the results of several previous feeding studies in mice were available. It was considered that the collective data from all those studies, together with that from the long-term study in rats, enabled the evaluation of amaranth to be completed. On the basis of a no-effect level of 50 mg/kg of body weight in the long-term study in rats, an ADI of 0–0.5 mg/kg of body weight was allocated. A revised toxicological monograph was prepared and the existing specifications revised.

Brown HT (formerly Chocolate Brown HT)

Brown HT was evaluated in 1977 (when a toxicological monograph was prepared) (Annex 1, references *44* and *45*), 1979, 1981, and 1982 (Annex 1, references *50, 56, 57, 59,* and *60*). A temporary ADI of 0–0.25 mg/kg of body weight was allocated until the results of multigeneration reproduction, teratological, and metabolic studies became available. Those results, and results from a special study on pigment deposition in the kidney and mesenteric lymph nodes, were considered by the Committee. An ADI of 0–1.5 mg/kg of body weight was established, on the basis of a no-effect level of 0.1% (equivalent to 150 mg/kg of body weight) in the long-term feeding study in mice. The Committee was informed that Brown HT is manufactured with a higher salt content (sodium chloride and/or sodium sulfate) than most other colouring matters

in order to reduce the organic impurity content. In the specific case of Brown HT a change in the purification process to effect a threefold reduction in the naphthionic acid content is accompanied by a 10% increase in the salt content. An addendum to the existing toxicological monograph was prepared and the specifications were revised accordingly.

Erythrosine

Erythrosine was evaluated in 1964, 1969, and 1974 (Annex 1, references *8, 19,* and *35*). Toxicological monographs were prepared in 1969 and 1974 when an ADI of 0–2.5 mg/kg of body weight was allocated (Annex 1, references *20* and *36*).

The Committee considered information obtained since 1974 which included: measurements of thyroid function in human subjects ingesting erythrosine; data on mutagenicity; data on reproduction and behavioural toxicity; the results of long-term feeding studies in mice and rats; and the results of 90-day and 6-month studies in rats, in which effects on the thyroid function were demonstrated. In the latter studies it was shown that the effects on the thyroid function were not due to sodium iodide, which is normally present in the commercial product. The results of tests for mutagenicity were negative. The Committee considered that the development of thyroid tumours in the long-term studies on rats might be mediated by a hormonal effect, although the mechanism for this was not demonstrated. One way of determining the no-effect level would have been by assessing the extent of diffuse hyperplasia in the thyroid glands of erythrosine-treated rats, as this was likely to have accompanied the observed increase in thyroid weight and would indicate an effect on thyroid function. However, the data for this purpose were not available to the Committee. Because insufficient data were available to determine a no-effect level, the existing ADI was reduced to 0–1.25 mg/kg of body weight and made temporary. The Committee requested that information on the following topics be assembled before the re-evaluation of erythrosine in 1986:

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

2. The mechanism of the effects of erythrosine on the thyroid gland, in terms of the biochemical and histopathological parameters;

and the existence of a threshold level of these effects and their reversibility.

It was also considered desirable for the Committee to have information on the pharmacokinetics of erythrosine and its effect on the thyroid functions of human subjects. An addendum to the previous toxicological monograph was prepared and the existing specifications revised.

Quinoline Yellow

Quinoline yellow was evaluated at several meetings of the Committee between 1959 and 1982 (Annex 1, references *4, 8, 13, 19, 35, 36, 38, 39, 46, 47, 48, 59,* and *60*). At the last evaluation the temporary ADI of 0–0.5 mg/kg of body weight was extended until the results of metabolic and chronic toxicity/carcinogenicity studies were available. Those data were available to the Committee at its present meeting.

At previous meetings the Committee had noted that there were two types of quinoline yellow. One is prepared by sulfonating 2-(2-quinolyl)indan-1,3-dione and the other by sulfonating a mixture containing about two-thirds 2-(2-quinolyl)indan-1,3-dione and about one-third 2-[2-(6-methylquinolyl)]indan-1,3-dione. The former is usually known as the unmethylated variety and the latter as the methylated variety. The latter has normally been used for toxicity testing. At present the quinoline yellow available for use as a food colour is of the unmethylated variety. The Committee considered that the toxicological data could be used to evaluate both types. On the basis of a no-effect level at 1% in the diet (equal to 1500 mg/kg of body weight) in the long-term study in mice, ADIs of 0–10 mg/kg of body weight were allocated for both the methylated and the unmethylated varieties. A revised toxicological monograph was prepared and the existing specifications were revised but maintained as tentative.

3.1.5 *Solvents*

2-Nitropropane

2-Nitropropane was evaluated in 1979 and 1981 (Annex 1, references *50* and *56*). A toxicological monograph was prepared in 1981, but no ADI was allocated (Annex 1, reference *57*). The

Committee had considered that, because of the toxic and carcinogenic effects of inhaled 2-nitropropane on the liver in rats, it should not be used as a solvent in food processing. Its use was being reviewed by the Joint Expert Committee at its present meeting at the request of the Codex Committee on Food Additives. The Committee was aware that 2-nitropropane is used in both food contact material applications and as a fractionating solvent for certain fats and oils; at its present meeting it considered only the latter use. Additional data were made available concerning metabolism, pharmacokinetics, and mutagenicity, as well as further histopathological data from the previous long-term inhalation study in rats. The Committee considered that 2-nitropropane was mutagenic according to the Ames test, but the results from the mutagenicity tests in mammalian systems were inconclusive, and that the liver was the target organ for its toxic and carcinogenic effects.

The Committee was informed that the residue of 2-nitropropane in fats and oils is less than 10 μg/kg (the limit of detection). On the assumption that a residue of 10 μg/kg remains in all fats and oils fractionated with 2-nitropropane, the estimated maximum daily intake by a regular consumer of products containing them would be 10 *n*g. The Committee noted that the carcinogenic effect demonstrated in rats was associated with exposure to relatively high concentrations (100–800 mg/m^3) of inhaled 2-nitropropane, and that residue levels in fats and oils are very low. 2-Nitropropane was therefore considered to be temporarily acceptable for use as a fractionating solvent in the production of fats and oils, as long as its use continues to be limited and residue levels are kept to the lowest technologically attainable (understood to be below the current limits of detection). The results from a long-term carcinogenicity study, using *per os* dosing, are required by 1989. A revised toxicological monograph was prepared and the tentative specifications, withdrawn in 1981, were reinstated.

Triethyl citrate

Triethyl citrate was evaluated in 1979 and 1981 (Annex 1, references *50* and *56*). A toxicological monograph was prepared in 1979 (Annex 1, reference *51*) and a temporary ADI of 0–10 mg/kg of body weight was allocated. Evidence was requested of hydrolysis to citrate and ethanol in man. Data demonstrating that such hydrolysis would occur was presented to the Committee. An ADI

of 0–20 mg/kg of body weight was allocated. An addendum to the existing toxicological monograph was prepared and the existing specifications were revised.

3.1.6 *Sweetening agents*

Saccharin, and its calcium, potassium, and sodium salts

Saccharin was last evaluated in 1982 (Annex 1, reference *59*). A temporary ADI of 0–2.5 mg/kg of body weight had been allocated in 1977. A revised toxicological monograph was prepared in 1982 (Annex 1, reference *60*).

New information presented to the Committee included biochemical, pharmacokinetic, mutagenicity, and epidemiological data; the results of special studies on urine volume and composition and the effect of saccharin on the bladder epithelium; the results of studies on saccharin as a promoter or co-carcinogen; and the results of a carcinogenicity study in rats designed to investigate the dose–response relationship in the development of bladder tumours and the outcome of *in utero* exposure.

In the Committee's opinion the available evidence indicated that saccharin is not mutagenic. An *in utero* phase of exposure is not essential for a carcinogenic response to saccharin in the bladder of the male rat. There was a definite carcinogenic effect at levels of dietary inclusion of 3% and above in the long-term study with *in utero* exposure. There was also a carcinogenic effect at a level of 5%, the only level tested, in the 1-generation study with exposure from birth, which included pups suckled by dames receiving saccharin in their diets. The Committee considered that a 1% dietary inclusion level could be taken as a no-effect level. Further data on the bladder histopathology in the carcinogenicity study mentioned above were received too late to be reviewed by the Committee. Within the statistical limitations of the studies, the epidemiological data do not show any evidence that saccharin is a bladder carcinogen.

The Committee decided that, on the basis of a no-effect level of 1% in the diet (equivalent to 500 mg/kg of body weight), a temporary group ADI of 0–2.5 mg/kg of body weight could be allocated for saccharin, including its calcium, potassium, and sodium salts. The Committee recommended that saccharin be kept under continuous review and that information be provided to elucidate the mechanism by which it produces bladder tumours,

including the possible significance of exposure through lactation, the influence of gastrointestinal tract microorganisms, the effect of osmolar changes in the urine, and species specificity in the development of urothelial changes.

An addendum to the existing toxicological monograph was prepared. New specifications for potassium saccharin were prepared and the existing specifications for saccharin, calcium saccharin, and sodium saccharin maintained.

3.1.7 *Thickening agents*

Carrageenan and furcellaran

Carrageenan and furcellaran were last evaluated in 1973 and an ADI of 0–75 mg/kg of body weight allocated (Annex 1, references *32* and *33*). New data made available included that obtained from short- and long-term studies in rats, hamsters, and monkeys. The Committee considered that the laxative effect seen with 15% carrageenan in feeding studies is the result of a high proportion of this non-absorbed hydrocolloid having been incorporated in the diet. The Committee affirmed that the ADI applies to refined non-degraded carrageenan hydrocolloid. It was aware of the toxic effects associated with degraded carrageenan. The distinguishing feature of refined non-degraded carrageenan is that it is manufactured by dissolving the polysaccharide from washed seaweed, removing the insoluble matter, and isolating the dissolved hydrocolloid. Some other seaweed materials, referred to as "semi-refined carrageenan" are regarded as food in some countries. Neither degraded carrageenan nor "semi-refined carrageenan" are included in the specifications for food-grade carrageenan. The existing specifications for carrageenan include furcellaran. The Committee maintained furcellaran within the specifications for carrageenan. An ADI "not specified" was allocated for refined non-degraded carrageenan. A new toxicological monograph was prepared and the existing specifications were revised and designated as tentative.

Tara gum

Tara gum was last evaluated in 1981 when a temporary ADI of 0–12.5 mg/kg of body weight was allocated and a new toxicological monograph prepared (Annex 1, references *56* and *57*). A multigeneration reproduction study, using several dose levels, and

a teratological study were requested, since a previous reproduction study using a 5% dietary exposure level had produced equivocal results. The Committee was informed that ways of meeting its request are being explored. It was decided to extend the temporary ADI of 0–12.5 mg/kg of body weight until 1986 when the results of the required studies are expected to be available.

The existing specifications were originally classified as tentative because of the need for information on microbiological criteria. The Committee was informed that experience had shown that microbial growth on tara gum is unlikely. No new toxicological monograph was prepared. The previous tentative specifications were revised and the tentative designation was deleted.

3.2 Contaminants

3.2.1 *Substances migrating into food*

Some substances may become food contaminants as a result of the use of food-contact materials. The Committee considered that the general principles governing the use of food additives established by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives,[1] and the WHO Scientific Group on the Assessment of the Carcinogenicity and Mutagenicity of Chemicals,[2] should be applied in the overall evaluation of substances migrating into food from food-contact materials (see section 2.2).

Many such materials are made of polymer systems and the polymers *per se* are usually inert, non-toxic, and do not migrate into food. However, monomers, which are inevitably present in the polymeric materials, residual reactants, intermediates, manufacturing aids, solvents, and plastic additives, as well as the products of side reactions and chemical degradation, may be present. These substances may migrate into food and may be toxic. The Committee was informed that migration from food-contact materials may arise during processing and preparation operations such as heating, microwave cooking, or treatment with ionizing radiation. For evaluation purposes information on the following is required: (1) the chemical identity and toxicological status of the

[1] WHO Technical Report Series, No. 348, 1967.
[2] WHO Technical Report Series, No. 546, 1974.

moieties that enter food; (2) the possible exposure, details of which can be derived from migration studies using suitable extraction procedures, and/or the analysis of food samples; and (3) the nature and amount of food in contact with the packing materials, and the intake of such food (Annex 1, reference *56*). As recommended by the Committee for the four substances considered at the present meeting (see section 2.2) it is necessary, in many instances, to recommend that human exposure to migrants from food-contact materials be restricted to the lowest levels technologically attainable. One way to achieve this is to draw up strict specifications limiting the quantities in the materials. It is also necessary to determine whether food processing has an effect in generating the potentially toxic substances in food-contact materials.

The Committee considered that for the further evaluation of the four substances on the agenda of the present meeting information on the following is required: (1) the lowest levels of potential migrants from within the polymeric system(s) that are technologically attainable with improved manufacturing processes for food-contact materials; (2) the resulting levels of the migrants in the foods; (3) the intake of the foods; and (4) the most appropriate statistical design that will enable the implications for health to be interpreted from adequate and relevant toxicological data. The Committee recommended that a monitoring programme be established, with a view to supplementing the existing data on human exposure and providing a means of demonstrating a reduction in such exposure as techniques improve. Priority in the programme should be given to the substances with the greatest potential for adversely effecting human health.

Acrylonitrile

Acrylonitrile had not previously been considered by the Committee. The information evaluated included data on the pharmacokinetics of the substance, and on metabolism, reproduction, teratogenicity, mutagenicity, short- and long-term toxicity, and carcinogenicity, as well as epidemiological data. Acrylonitrile is considered to be teratogenic in hamsters and rats, and carcinogenic in rats when administered orally and when inhaled. The results of epidemiological studies of workers exposed to acrylonitrile suggest that it may also be a human carcinogen. The Committee recommended that human exposure to acrylonitrile as

a result of its migration into food from food-contact materials be reduced to the lowest level technologically attainable. It provisionally accepted the use of food-contact materials that contain acrylonitrile as a potential migrant into food subject to the conditions outlined in section 2.2 and the first paragraph of section 3.2. It asked that the justification for the use of such food-contact materials be examined and recommended that acrylonitrile be kept under continuous review. A toxicological monograph was prepared.

Bis(2-ethylhexyl) phthalate

Bis(2-ethylhexyl) phthalate had not previously been considered by the Committee. The information evaluated included data on the pharmacokinetics of the substance, and on metabolism, reproduction, teratogenicity, mutagenicity, short- and long-term toxicity, and carcinogenicity, as well as the results of special studies on the substance in relation to liver peroxisome proliferation and testicular atrophy. It was considered to be a liver carcinogen in rats and mice. Although it appeared not to be mutagenic, its principal metabolite, monoethylhexylphthalate, was mutagenic in a number of systems. The Committee recommended that human exposure to bis(2-ethylhexyl) phthalate in food as a result of its migration from food-contact materials be reduced to the lowest level technologically attainable. The Committee understood that the substance is an environmental contaminant. It provisionally accepted the use of food-contact materials that contain bis(2-ethylhexyl) phthalate as a potential migrant into food subject to the conditions outlined in section 2.2 and the first paragraph of section 3.2. A toxicological monograph was prepared.

Styrene

Styrene had not previously been considered by the Committee. The information evaluated consisted of data on the pharmacokinetics of the substance and on metabolism, reproduction, teratogenicity, mutagenicity, and carcinogenicity, as well as epidemiological data. The evidence from tests that styrene itself might be mutagenic was equivocal, although chromosomal effects were produced. However, its intermediate metabolite, styrene oxide (epoxide), was strongly mutagenic. Styrene has not been demonstrated to have carcinogenic properties in rats. One of three

studies in mice provided "limited evidence" of carcinogenicity.[1] Epidemiological studies have failed to demonstrate a link between occupational exposure to styrene and cancer in man. The Committee considered it possible to allocate a provisional maximum tolerable daily intake for styrene. On the basis of the no-effect level (related to decreased body weight) of 125 mg/litre in drinking water (equivalent to 7.7 mg/kg of body weight) in a long-term study in rats, this would be 0.04 mg/kg of body weight per day. However, the Committee was aware that the likely human intake of styrene migrating from food-contact materials is 4 µg a day. It was also informed that there had been a more recent study on the carcinogenicity of styrene oxide. Therefore, as a matter of prudence, and until it had evaluated the data from the recent study, it recommended that the intake of styrene migrating from food-contact materials be restricted to the lowest level technologically attainable. Subject to the considerations outlined in section 2.2 and the first paragraph of section 3.2 the Committee provisionally accepted the use of food-contact materials that are potential sources of styrene contamination of food. A toxicological monograph was prepared.

Vinyl chloride

Vinyl chloride had not previously been considered by the Committee. The information evaluated consisted of data on the pharmacokinetics of the substance and on metabolism, reproduction, teratogenicity, mutagenicity, and carcinogenicity, and included observations in man. Vinyl chloride is known to be a carcinogen in mice, rats, and hamsters. Epidemiological studies have demonstrated that it is a human carcinogen. It was noted that the likely human dietary intake resulting from the migration of vinyl chloride from food-contact materials is 0.1 µg a day. The Committee recommended that human exposure to vinyl chloride in food as a result of its migration from food-contact materials be reduced to the lowest levels technologically attainable. It provisionally accepted the use of food-contact materials that contain vinyl chloride as a

[1] For an explanation of this International Agency for Research on Cancer (IARC) classification see: *Some food additives, feed additives and naturally occurring substances*. Lyons, International Agency for Research on Cancer, 1983, p. 18 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, volume 31).

potential migrant into food, subject to the conditions outlined in section 2.2 and the first paragraph of section 3.2. It asked that the justification for the use of such food-contact materials be examined and recommended that vinyl chloride be kept under continuous review. A toxicological monograph was prepared.

4. ESTABLISHMENT, REVISION, AND WITHDRAWAL OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 70 substances and prepared new specifications for 26 substances. It reviewed 87 food colours as a group with the intention of improving the specifications for food colours in a uniform manner.

4.1 Anticaking agents

Calcium aluminosilicate

Aluminium calcium silicate was on the agenda; it was observed, however, that this substance had already been evaluated under its synonym, calcium aluminosilicate, at the seventeenth meeting of the Committee (Annex 1, reference *32*).

Ferric ammonium citrate

The Committee referred to the two forms of ferric ammonium citrate, which differ in iron content, and are distinguishable by their colours—brown or green. It prepared new specifications for ferric ammonium citrate which include requirements for both forms.

Salts of fatty acids

The Committee considered 20 salts of fatty acids—the aluminium, calcium, magnesium, potassium, and sodium salts of capric, caprylic, lauric, and oleic acid. It had already prepared specifications for the ammonium, aluminium, magnesium, potassium, and sodium salts of myristic, palmitic, and stearic acid. In view of the large number of possible commercial products involved, all of which have the same general specification criteria,

the Committee prepared specifications for the aluminium, ammonium, magnesium, potassium, and sodium salts of all seven acids—capric, caprylic, lauric, myristic, palmitic, stearic, and oleic.

Because the new specifications relate to a large number of substances, some having had their specifications revised and some having new specifications, they are designated as tentative. The Committee requested information on the commercial usage of these salts of fatty acids in food and the capacity of manufacturers to comply with the specifications.

4.2 Emulsifiers

Calcium and sodium stearoyl lactates

The Committee referred to recent advances in techniques for the analysis of mixtures of salts of esters of fatty acids and lactic acid, which permit a more comprehensive determination of the structure and amount of each individual component of a commercially available product. In view of the limited information available, it was not possible for the Committee to consider all the revisions to the specifications for calcium and sodium stearoyl lactates requested. Nevertheless, the existing specifications were revised and designated as tentative. The Committee requested additional information on nomenclature, including the adequacy of the principal names and synonyms, the structural formulae, and the chemical composition of the commercial items.

4.3 Food colours

4.3.1 *Specifications withdrawn*

In reviewing the specifications for food colours the Committee noted that certain of them were prepared many years ago and since that time no new information had been received. It was concluded that 31 were apparently not used commercially for colouring food. Two of the 31 substances and 3 additional substances either had no existing specifications or no ADI; a further substance was little used and, it was understood, its use would be discontinued. Specifications were therefore withdrawn or not prepared.

In order to prepare new specifications for these substances the Committee requires information on methods of manufacture, chemical composition, and their usage in food.

4.3.2 *Comments on specific colours*

Anthocyanins

The Committee prepared specifications for anthocyanins in grape-skin extract at its twenty-sixth meeting (Annex 1, references *59* and *60*). It was aware that there are other potential sources of anthocyanins that may be used as food colours. The Committee maintained the existing specifications for anthocyanins (grape-skin extract) but withdrew the specifications for anthocyanins and anthocyanin colour from grape skin because it had no knowledge of their continuing use in food and had received no information in regard to the specifications over a long period of time. It requested information on the source, manufacture, and chemical composition of anthocyanin-type colouring matter other than grape-skin extract.

Carbon Blacks

The Committee prepared specifications for carbon blacks made from vegetable matter. It was aware that carbon blacks from other source materials may also be used in food and asked for information on those materials with a view to preparing specifications.

Carotenes (natural)

The existing specifications for carotenes (natural) were revised but were designated as tentative because of insufficient information on the definition of the source material and the method of extraction of the colouring principal.

Curcumin

The Committee was apprised of the fact that, since this substance was last considered at the twenty-sixth meeting and the specifications revised (Annex 1, references *59* and *60*), chemically synthesized curcumin had become available. The Committee requested information on the range of products marketed as curcumin and whether they comply with the revised specifications.

Gold and silver

The Committee was unable to prepare specifications for gold and silver because the data on their purity were inadequate.

Iron oxide black, iron oxide red, and iron oxide yellow

In view of the chemical similarity of the iron oxide colours, the three separate existing specifications were combined into one, which was designated as tentative.

4.4 Stabilizers and thickeners

Dammar gum

In considering specifications for dammar gum, the Committee was informed that it is produced from the seeds of a wide variety of trees. The Committee found it difficult to prepare specifications for commercial products such as this, which are obtained from many sources in so many grades. It prepared new tentative specifications, however, while requesting information on the sources and on the purity requirements for different grades of dammar gum.

Pectin and amidated pectins

At its twenty-fifth meeting the Committee concluded that there were no toxicological differences between pectins and amidated pectins and a group ADI "not specified" was allocated (see Annex 1, references *56* and *57*). The Committee decided, therefore, to combine the separate specifications for pectins and amidated pectins into one for pectin, in view of their chemical and toxicological similarity.

5. METHODOLOGY FOR TESTING AND ASSESSING CHEMICALS IN FOOD

In response to the Committee's repeated recommendations (Annex 1, references *56*, *59*, and *62*) a meeting of a group of experts to study the application of advances in methodology to the toxicological evaluation of food additives and contaminants, and also of pesticide residues, was convened in September 1983.[1] The objectives of the meeting were defined as the formulation of specific recommendations in order to bring the following up to date:

(*a*) the principles set out in earlier reports of the Joint FAO/WHO Expert Committee on Food Additives concerning safety evaluation

[1] *Updating principles of methodology for testing and assessing chemicals in food: report of a strategy meeting* (unpublished WHO document ICS (Food)/83.3).

in relation to specific toxicological problems or specific chemical entities or groups;

(*b*) the test methods used in the toxicological evaluation of chemicals in food; and

(*c*) the assessment procedures adopted by the Joint FAO/WHO Expert Committee on Food Additives in determining quantitative endpoints.

The Committee considered the report and working papers on specific issues of the meeting. A historical review of concepts concerning endpoints of assessment and relevant recommendations of the Committee formed the basis of discussion. Because of the magnitude of the task, the discussion was restricted to selected specific issues. It was recommended that the task of bringing the methodology up to date be completed at the earliest opportunity, and a detailed consolidated document prepared for the use of the Committee at future meetings.

The specific issues discussed by the Committee are reviewed in the following paragraphs.

1. *Factors influencing test requirements and the interpretation of data*

The factors considered were:

(*a*) structure/activity relationships;
(*b*) usage and exposure;
(*c*) natural occurrence;
(*d*) metabolism into natural body constituents.

Each factor was considered to be of importance in planning and interpreting toxicity tests. However, data have been of variable quality and availability. The Committee considered that greater efforts for improvement should be made.

2. *The role of short-term tests for genetic damage in the safety evaluation of food additives*

The Committee recognized the usefulness of such tests in setting priorities for long-term testing, resolving debatable issues arising from the results of long-term tests, and assisting in clarifying the possible mechanisms by which carcinogens act. However, data from

short-term tests alone do not provide an adequate basis for the safety assessment of food additives.

3. *The role of pharmacokinetic and metabolism studies*

Such investigations, involving both experimental animals and man, are vital parts of safety assessment; the Committee reiterated the need for them. In some cases, *in vitro* systems can provide valuable data in this context.

4. *The role of the gut microflora in safety assessment*

The gut microflora can play an important role in metabolizing chemicals under investigation. Furthermore, they may be changed, qualitatively or quantitatively, as a result of exposure to the chemicals, and this may lead to nutritional or physiological changes, with pathological consequences. These factors are important in any analysis of toxic effects.

5. *The use of human data in safety assessment*

That data from human studies are of value in safety evaluation and that it is desirable to have such data are widely recognized. Both the scientific and the ethical aspects need to be taken into account.

6. *The influence of age and nutrition in toxicological studies*

The outcome of exposure to toxic chemicals may differ with extremes of age. Thus, in the evaluation of chronic effects in animal studies, the neonate may be particularly susceptible to certain toxic effects, and the pathological complications of senility may constitute a problem.

Nutritional status and modifications in feeding patterns as complicating factors in interpreting the results of toxicity tests were realized to be of importance.

7. *The criteria for the inclusion of* in utero *exposure in long-term feeding studies*

The Committee considered it would be prudent to include *in utero* exposure as a test in long-term feeding studies during investigations of food additives in widespread use at high levels.

8. *Problems in the determination of no-effect levels and safety factors*

The Committee considered that, in deciding what constitutes a no-effect level and applying a safety factor, it would be desirable for it to adopt a more consistent approach to manifestations of toxicity, both acute and chronic. This approach should as far as possible reflect patterns of disease seen in the human population.

9. *The distinction between toxicological and physiological responses*

The Committee recognized that a reversible effect could represent a physiological response to chemical stress and that this poses problems of interpretation. The value of studies involving excessive dosing, in evaluating additives used at low levels in foods, was questioned.

10. *Questions remaining to be considered*

The Committee pointed to the following as requiring more detailed consideration:

(*a*) special problems associated with bulking agents and novel foods;
(*b*) food contaminants;
(*c*) animal feed additives and veterinary drug residues;
(*d*) test methods and principles (including alternative methods of testing);
(*e*) testing for allergenicity;
(*f*) problematic lesions in bioassays (e.g., some murine tumours, tumours of the forestomach, caecal enlargement, and renal calcinosis);
(*g*) assessment procedures; extrapolation and quantitative assessment.

The Committee considered it to be important that the task of bringing the methodology up to date should continue to a satisfactory conclusion.

6. FUTURE WORK

1. The principles involved in the safety assessment of substances with physical properties that prevent them from being fed to animals

at a high enough level to produce a toxic effect should be re-examined.

2. The work in connection with bringing the methodology for testing and assessing chemicals in food up to date, as outlined in section 5 and begun by the Committee at its twenty-eighth meeting, should be continued in 1985.

3. The specifications for chemically modified celluloses should be reviewed as a group for consistency in format.

4. Guiding principles for the evaluation of food contact materials should be formulated.

7. RECOMMENDATIONS TO FAO AND WHO

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

2. WHO should consider convening a meeting of a group of experts to prepare a unified document, for consideration by the Joint Expert Committee at a future meeting, on the issues discussed in the context of bringing the methodology for testing and assessing chemicals in food up to date.

3. Considering that the report of the Joint Expert Committee is vital to the work of the Joint FAO/WHO Food Standards Programme, and in order to expedite the dissemination of the information it contains to Member States, FAO and WHO should take the necessary steps to ensure the distribution of a summary report as soon as possible after each meeting.

4. The Committee reaffirmed its recommendation, made at the twenty-seventh meeting, that specific problems identified by the Codex Committee on Food Additives be regularly brought to its attention, taking into account the availability of data.

Annex 1

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

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 (out of print).
7. *Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents* (Seventh report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. *Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants* (Eighth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants.* FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).
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 (out of print).

12. *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, 1967.
13. *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.
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. 45A, 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, 1970; 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, 1970; 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 (out of print).
33. *Toxicological evaluation of certain food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents*. FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.
34. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers*. FAO Food and Nutrition Paper, No. 4, 1978.
35. *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.
36. *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.
37. *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.
38. *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.
39. *Toxicological evaluation of some food colours, thickening agents, and certain other substances*. FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.
40. *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.

41. *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.
42. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 10, 1976.
43. *Specifications for the identity and purity of some food additives.* FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additive Series, No. 11, 1977.
44. *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.
45. *Summary of toxicological data of certain food additives.* WHO Food Additives Series, No. 12, 1977.
46. *Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.
47. *Evaluation of certain food additives and contaminants* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
48. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series, No. 13, 1978.
49. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 7, 1978.
50. *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, and corrigenda.
51. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1980.
52. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.
53. *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.
54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.
55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.
56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.
57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1982.
58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.
59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.
60. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 17, 1982.

61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.
62. *Evaluation of certain food additives and contaminants.* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.
63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.
64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.
65. *Guide to specifications—General notices, general methods, identification tests, test solutions, and other reference materials.* FAO Food and Nutrition Paper No. 5 Rev. 1, 1983.

Annex 2

ACCEPTABLE DAILY INTAKES, OTHER TOXICOLOGICAL RECOMMENDATIONS, AND INFORMATION ON SPECIFICATIONS

	Specifications[1]	*ADI for man (mg/kg of body weight) [and other toxicological recommendations]*
A. Specific food additives		
Antioxidants		
Anoxomer	ST	0–8
Enzyme preparations		
Glucose isomerase (isolated from *Streptomyces violaceoniger*)	R	ADI not specified[2]
Protease (isolated from *Streptomyces fradiae*)	S	ADI withdrawn[3]
Flavouring agents		
Trans-anethole	R	0–2.5[4]
Cinnamaldehyde	R	0–0.7[4]
Ethyl methylphenyl glycidate	R	0–0.5
α-Ionone	S	0–0.1[5]
β-Ionone	R	0–0.1[5]
Nonanal	O	0–0.1[6]
Octanal	R	0–0.1[6]
Food colours		
Amaranth	R	0–0.5
Brown HT	R	0–1.5
Erythrosine	R	0–1.25[4]
Quinoline Yellow	RT	0–10
Food solvents		
2-Nitropropane	ST	Temporary acceptance[7]
Triethyl citrate	R	0–20
Sweetening agents		
Saccharin	S	0–2.5[4, 8]
Saccharin, calcium	S	0–2.5[4, 8]
Saccharin, potassium	N	0–2.5[4, 8]
Saccharin, sodium	S	0–2.5[4, 8]
Thickening agents		
Carrageenan and furcellaran	RT	ADI not specified[2]
Tara gum	R	0–12.5[4]

	Specifications[1]	*ADI for man (mg/kg of body weight) [and other toxicological recommendations]*
B. Contaminants		
Potential migrants from food-contact materials		
Acrylonitrile	–	Provisional acceptance[9]
Bis(2-ethylhexyl) phthalate	–	Provisional acceptance[9]
Styrene	–	[0.04][10]
Vinyl chloride	–	Provisional acceptance[9]

	Specifications only[1]		
Anticaking agents		*Extraction solvents*	
Ferrous manganocyanide	O	Butan-1-ol	R
Magnesium ferrocyanides	O	Ethyl methyl ketone	R
Manganese ferrocyanides	O	Isobutanol	R
Potassium alumino silicate	O	Methanol	R
Salts of fatty acids (aluminium, calcium, magnesium, potassium, and sodium salts of capric, caprylic, lauric, myristic, oleic, palmitic, and stearic acids)	NT[11]	Propan-1-ol	R
		Flavouring agents	
		Methyl β-naphthyl ketone	R
		Para-propylanisole	T
Buffering agents		*Flour treatment agents*	
Sodium sesquicarbonate	R	Chlorine	R
		Food colours	
Carrier solvents		Allura Red AC	R
Propan-2-ol	R	Aluminium powder	RT
		Annatto extracts	S
Colour adjuncts		Anthocyanins (grape skin extract)	S
Ferrous gluconate	R	Azorubine	R
		Beet Red	T
Emulsifiers		β-apo-8′-carotenal	R
Calcium stearoyl lactate	RT	β-apo-carotenal	R
Sodium stearoyl lactate	RT	β-carotene (natural)	R
		β-apo-8′-carotenoic acid, ethyl or methyl ester	R
Enzyme preparations			
Glucose isomerase (isolated from *Actinoplanes missouriensis*)	R	Brilliant Black BN	R
		Brilliant Blue FCF	R
Glucose isomerase (isolated from *Bacillus coagulans var.*)	R	Canthaxanthin	R
		Caramel colour (ammonia process)	T
Glucose isomerase (isolated from *Streptomyces olivaceous*)	R	Caramel colour (ammonia-sulfite process)	T
Glucose isomerase (isolated from *Streptomyces olivochromogenes*)	R	Caramel colour (plain)	T
		Carbon Blacks	R
Protease (isolated from *Bacillus cereus*)	R	Carmines	S

Specifications only[1]

Carotenes (natural)	RT	Riboflavin	R
Carthamus Red	RT	Riboflavin 5′-phosphate sodium	R
Carthamus Yellow	RT	Saffron	T
Chlorophyll	RT	Silver	O
Chlorophyll copper complex	RT	Sunset Yellow FCF	R
Chlorophyllin copper complex,		Tartrazine	R
sodium and potassium salts	T	Titanium dioxide	R
Citranoxanthin	T	Turmeric	S
Citrus Red No. 2	NT	Xanthophylls	RT
Cochineal and carminic acid	NT		
Crystal Violet	NT[12]	*Propellants*	
Curcumin	R	Nitrous oxide	R
Fast Green FCF	RT	*Thickening agents*	
Fast Red E	R	Dammar gum	NT
Food Green S	R	Ethyl hydroxyethyl cellulose	T
Gold (metallic)	O	Hydroxypropyl cellulose	RT
Indigotine	R	Hydroxypropyl methyl cellulose	RT
Iron oxides (black, red, yellow)	RT[13]	Methyl cellulose	R
Lithol rubine BK	R	Pectin and amidated pectin	R[13]
Paprika, oleoresins	R	Sodium carboxymethyl cellulose	R
Patent Blue V	R		
Ponceau 4R	R	*Miscellaneous*	
Red 2G	R	Ferric ammonium citrate	N
		Sodium thiocyanate	N

Food colours—specifications were withdrawn

Acid fuchsine FB[14]	Orange GGN[14]
Alkanet and alkannin[15, 17]	Orange I[14]
Anthocyanin colour from grape skin[14]	Orange RN[16]
Anthocyanins[14]	Orchil and orcein[14, 15, 17]
Benzyl Violet 4B[14]	Ponceau 2R[14]
Black 7984[14]	Ponceau 6R[14]
Blue VRS[14]	Ponceau SX[15]
Brown FK[15]	Quercitin and quercitron[14, 15]
Chocolate Brown FB[14]	Red 10B[14]
Chrysoine[14]	Rhodamine B[14]
Eosine[14]	Scarlet GN[14]
Fast Yellow AB[14]	Sudan G[14]
Guinea Green B[14]	Sudan Red G[14]
Indanthrene Blue RS[14]	Ultramarines[14]
Light Green SF Yellowish[14]	Violet 5 BN[14]
Methyl Violet[14]	Yellow 2G[14]
Naphthol Yellow S[14]	Yellow 27175 N[14]
Orange G[14]	

[1] N, new specifications prepared; O, specifications not prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; T, the existing, new, or revised specifications are tentative and comments are invited.

[2] 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 that reason, and for the reasons stated in the individual evaluations, the establishment of an acceptable daily intake (ADI) is not deemed necessary.

[3] Insufficient toxicological data available.

[4] Temporary acceptance.

[5] Group ADI for α-ionone and β-ionone, singly or in combination.

[6] Group ADI for octanal and nonanal, singly or in combination.

[7] The previous recommendation that 2-nitropropane should not be used as a solvent in food processing changed to temporary acceptance for use as a fractionating solvent for edible fats and oils only, with the stipulation that residue levels are kept to the lowest technologically attainable, which is understood to be lower than the detection limit by current analytical methods.

[8] Group ADI for saccharin, saccharin calcium, saccharin sodium, and saccharin potassium, singly or in combination.

[9] The use of food-contact materials from which the substance may migrate is provisionally accepted, on condition that the amount of the substance migrating into the food is reduced to the lowest level technologically attainable.

[10] This figure represents the provisional maximum tolerable daily intake (PMTDI) of styrene. It is not an ADI. The MTDI for styrene is provisionally accepted under the same conditions as those set out in Note 9.

[11] The existing specifications for some salts of fatty acids are incorporated in the new specifications.

[12] Replaces the specification for methyl violet, of which the colour crystal violet is a purified component.

[13] The existing specifications incorporated into a single specification covering a series of related substances.

[14] No knowledge of the continuing use of the colour in food and no information received in regard to the specifications over a long period of time.

[15] No ADI allocated because of insufficient data.

[16] The colour is little used and it is understood its use will be discontinued.

[17] Specifications withdrawn at previous meetings.

Annex 3

FURTHER TOXICOLOGICAL STUDIES AND INFORMATION REQUIRED OR DESIRED

A. Specific food additives

Flavouring agents

Trans-*anethole*[1]

Adequate data from a long-term feeding study.

Cinnamaldehyde[2]

1. A short-term feeding study in a non-rodent species.
2. A long-term feeding study to evaluate the carcinogenic potential.
3. A re-test of cinnamyl anthranilate so as to clarify the limited response obtained in the previous study in mice as well as to investigate the potential carcinogenicity of cinnamaldehyde.
4. Metabolic and pharmacokinetic data on the cinnamyl compounds.

Food colours

Erythrosine[3]

Information on the following topics:

1. The histopathology (including the assessment of diffuse hyperplasia) of all thyroid glands from the recent long-term studies in rats.
2. The mechanism of the effects of erythrosine on the thyroid gland, in terms of the biochemical and histopathological parameters; and the existence of a threshold level of these effects and their reversibility.
3. The pharmacokinetics of erythrosine in human subjects and its effect on the thyroid function.

Food solvents

2-Nitropropane[2]

A long-term carcinogenicity study using *per os* dosing.

Food sweeteners

Saccharin and its calcium, potassium, and sodium salts[4]

1. Data on the bladder histopathology.
2. Information to elucidate the mechanism by which the compounds produce bladder tumours, including the possible significance of exposure through lactation, the influence of gastrointestinal tract microorganisms, the effect of osmolar changes in the urine, and species specificity in the development of urothelial changes.

Thickening agents

Tara gum[3]

A multigeneration reproduction/teratological study.

B. Contaminants

Acrylonitrile,[4] *bis(2-ethylhexyl) phthalate,*[4] *styrene,*[4] *and vinyl chloride.*[4]

1. Data on the lowest technologically attainable level of each of these potential migrants in food.
2. Information on how each substance is used in food-contact material in order to verify that no satisfactory alternative exists.
3. Estimates of the intake of each substance after it has migrated into food (together with information on the procedures used to estimate the intake).
4. Estimates of the lowest level of each substance in the food contact material and in the food that can be achieved with improved manufacturing processes.
5. An appropriate statistical design that will enable the toxicological data amassed to be evaluated.

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[1] Information required by 1987.
[2] Information required by 1989.
[3] Information required by 1986.
[4] Information to be submitted when it becomes available.