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# **Evaluation of certain food additives and contaminants**

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Thirty-third Report of the  
Joint FAO/WHO Expert Committee on  
Food Additives



World Health Organization  
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Monographs containing summaries of relevant data and toxicological evaluations are available under the title:

*Toxicological evaluation of certain food additives and contaminants.* Cambridge, Cambridge University Press, 1988 (WHO Food Additives Series, No. 24).

Specifications are issued separately by FAO under the title:

*Specifications for the identity and purity of certain food additives.*  
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#### INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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Geneva, 21–30 March 1988

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# EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

## Thirty-third Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 21 to 30 March 1988. The meeting was opened by Dr M. Mercier, Manager, International Programme on Chemical Safety, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Dr Mercier pointed out that the Joint FAO/WHO Expert Committee on Food Additives had probably contributed more to the development of sound national legislation regarding food safety and to the modelling of food safety assessment than any other international body aimed at harmonizing the often-divergent national approaches to problems of food safety, food technology, and food control. He noted that many chemicals on the agenda for the present meeting were contaminants, which reflected the changing emphasis of the Codex Committee on Food Additives and Contaminants.<sup>1</sup> Dr Mercier also noted that the Expert Committee would consider a scheme for setting priorities for the testing and evaluation of flavouring substances during the meeting.

### 1. INTRODUCTION

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been 32 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the thirty-first meeting (Annex 1, reference 77).

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 of

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<sup>1</sup> In July 1987 the name of this Committee was changed from the Codex Committee on Food Additives to the Codex Committee on Food Additives and Contaminants.

certain food additives and contaminants; (d) to assess a method for setting priorities for the safety review of food flavouring substances; and (e) to discuss and advise on matters arising from the nineteenth (2) and twentieth (3) sessions of the Codex Committee on Food Additives (and Contaminants).

## **2. GENERAL CONSIDERATIONS**

### **2.1 Modification of the agenda**

Hydrogenated glucose syrups and maltitol were added to the agenda for safety consideration. Sucralose, which was on the agenda, was evaluated under the name trichlorogalactosucrose. Inorganic mercury was not evaluated because new data were not available.

### **2.2 Principles governing the toxicological evaluation of compounds on the agenda**

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76). This publication, developed in response to repeated recommendations by the Committee, embraces the major observations, comments, and recommendations on the safety assessment of food additives and contaminants contained in the previous reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate, and points out the problems associated with those that are no longer valid in the light of modern technical advances.

#### *2.2.1 The basis for the provisional tolerable weekly intake*

At this meeting, the Committee established provisional tolerable weekly intakes (PTWIs) for several metal contaminants. Limits formerly given as provisional maximum tolerable daily intakes were changed to PTWIs.

At its sixteenth meeting (Annex 1, reference 30) the Committee established the concept of the PTWI for heavy metals. The rationale

for establishing a weekly intake was that such contaminants “are able to accumulate within the body at a rate and to an extent determined by the level of intake and by the chemical form of the heavy metal present in food. Consequently, the basis on which intake is expressed should be more than the amount corresponding to a single day. Moreover, individual foods may contain above-average levels of a heavy metal contaminant, so that consumption of such foods on any particular day greatly enhances that day’s intake.”

At its present meeting, the Committee concluded that it is appropriate to establish weekly rather than daily tolerable intakes, even for metal contaminants that are not known to accumulate in the body, in order to emphasize that it is often impracticable and unnecessary to remain within the established limits on a daily basis. From the toxicological point of view, it is important that these limits are adhered to on a longer-term basis (see section 2.2.2).

### *2.2.2 Short-term intakes in excess of recommended limits*

In setting PTWIs for various contaminants at this meeting and at others, the Committee recognized that, as a result of seasonal variations and other factors, some individuals are likely to exceed the PTWI established for a contaminant for short periods of time. However, the Committee concluded that short-term exposure to levels exceeding the PTWI is not a cause for concern, provided the individual’s intake averaged over longer periods of time does not exceed the level set.

It is impossible to make generalizations concerning the length of time during which intakes in excess of the PTWI would be toxicologically detrimental. Any detrimental effect would depend upon the nature of the toxicity and the biological half-life of the chemical concerned. Thus, for cadmium, which accumulates throughout the lifetime, the critical factor appears to be the total intake during a period of many years (see section 3.2). In this case, intakes in excess of the PTWI for an extended period of time would be of less concern than would be the case for a contaminant with a shorter biological half-life. Evidence of acute toxicity as well as chronic toxicity, as obtained for tin (see section 3.2), should also be taken into account when evaluating the consequences of acute exposure above the PTWI.

Intakes of food additives in excess of the acceptable daily intake (ADI) are less likely to occur and are easier to control than is the case

for contaminants. The ADI is not intended to address acute toxicity caused by short-term excesses. It is intended to provide an indicator of safety for a lifetime of use. The large safety factors used in establishing ADIs provide assurance that intake above the ADI for short periods of time will not pose a safety problem, provided the average intake taken over a longer period of time does not exceed the ADI (Annex 1, reference 76, page 79).

### 2.2.3 *Average body weights*

The ADI for humans is expressed in terms of mg per kg of body weight. When calculating an ADI for an additive based on animal experiments, the Committee uses the data expressed in terms of mg per kg of body weight per day. Thus, a direct comparison between animals and human beings is made on a "per kg of body weight" basis. Users of the ADI can then convert this figure to mg per person per day using a value for average body weight that is appropriate for the particular case in question.

When an ADI or PTWI is calculated from human data, an average body weight value of 60 kg is used by the Committee to convert the figure obtained in terms of mg per person to a per kg of body weight value. The Committee believes that 60 kg represents a good average adult body weight for both men and women around the world.

## 2.3 **Principles governing the establishment and revision of specifications**

### 2.3.1 *General*

The specifications for the identity and purity of food additives developed by the Committee have three purposes:

- (a) to identify the substance that has been subject to biological testing;
- (b) to ensure that the substance is of the quality required for safe use in food; and
- (c) to reflect and encourage good manufacturing practice.

The Committee affirmed the principle that its specifications should be periodically reviewed in the light of changes in patterns of additive use, in raw materials, and in methods of manufacture. For

example, at this meeting the Committee re-evaluated specifications for “bulk” sweetening agents (i.e., polyols, such as sorbitol) intended for use as sugar replacements, thus improving the consistency between specifications for related substances and lowering the concentration limits for metallic impurities to levels consistent with those established for sugars in the standards set by the Codex Alimentarius Commission. The Committee will continue to update its specifications using a process of periodic review.

### *2.3.2 The need for adequate chemical and physical data*

For one of the compounds on the agenda at the present meeting, the Committee was again confronted with the problem of not having the necessary chemical and physical data to identify the substance that was actually used in the biological studies. Therefore, the Committee reiterated that it is important that detailed information is available on the chemical composition of materials used in toxicological testing, as laid down in section 4.1 of *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference 76). Without this information the Committee is unable to evaluate toxicological studies. For example, see the discussion on mineral oil in section 3.1.7.

### *2.3.3 Evaluation of specifications for complex substances*

For certain complex substances, e.g., mineral oil, the Committee did not receive detailed information on chemical composition. The review of biological studies on different batches of a substance, where each has been designated “food grade”, is difficult in the absence of such detailed information. In such cases, the Committee prepares specifications based on the worldwide consensus of the “food grade” for the substance. In identifying such a consensus, the Committee evaluates specifications adopted by governmental bodies and scientific associations, manufacturers’ criteria for the release of food-grade substances, and food processors’ criteria for the acceptance of food-grade substances. Nevertheless, the Committee stressed that detailed information on chemical composition is necessary for a full evaluation of any substance (see section 2.3.2). When specifications are developed in the absence of detailed information, it may be necessary to designate them as “tentative” pending receipt of the necessary information.

#### 2.3.4 *Guidelines for designating titles for specifications monographs*

The Committee had been asked to evaluate sucralose as an item on the agenda; no name had been previously established for this substance by any governmental or international body. During the Committee's deliberations on a title for the specifications monograph, it was recognized that there was no single common or trivial name established through common usage. In view of difficulties on this matter, the Committee developed the following guidelines for designating titles for specifications monographs:

1. Names established by international bodies whose terms of reference include the designation of nonproprietary names will be used for the titles of specifications monographs. If a given substance has more than one such established nonproprietary name, the monograph title will be a name established by an international body operating under the auspices of FAO or WHO.
2. If there is no established nonproprietary name, but there is a name established by governmental legislation that is not a scientifically inappropriate registered tradename, this name may be used as the title.
3. If there is neither an established nonproprietary name nor an acceptable governmentally established name, but a common or trivial name has been established by common usage, this name will be used as the monograph title, provided that it is not a proprietary name.
4. If none of the conditions above apply, then the monograph title will be selected from the available scientific, common, and trivial names. The name chosen:
  - must be nonproprietary;
  - should be a scientifically accurate description of the substance;  
and
  - should communicate to consumers an accurate description of the substance, within the scope of existing names for food additives.

#### 2.3.5 *Revision of the general methods section of the Guide to specifications*

The Committee noted that the general methods section of the *Guide to specifications* (Annex 1, reference 65) had not been revised since 1983, and recommended that attention be given to reviewing

and updating the methods of analysis to take account of changes in specifications, methodology, and analytical techniques. The Committee at its thirtieth meeting recommended that the separate Annex of Methods of Analysis for Colours (Annex 1, reference 68) be incorporated into the general methods section along with certain other new methods adopted at that meeting. Additional general methods of analysis were prepared at the thirty-first meeting (Annex 1, reference 79) and at the present meeting.<sup>1</sup> The Committee stressed that the need for an updated revision of the *Guide to specifications* becomes greater with the passage of time.

In considering new general methods of analysis, the Committee noted that improvements in analytical methodology have led to the common use of instrumental techniques that were previously considered too sophisticated for specifications testing. There are advantages to the use of such instrumental techniques for specifications testing, for example the increased specificity of techniques such as capillary-column gas chromatography applied to flavouring agents. The Committee concluded that improved methods of this type should be included in new and revised specifications drawn up by the Joint FAO/WHO Expert Committee on Food Additives.

The Committee recognized that, although improved methods may be commonly used in developed industrialized countries, methods using simpler instrumentation are needed in developing countries. The Committee was of the opinion that such simpler methods could be established as alternatives to the existing test methods published in its specifications.

The Committee concluded that, before new general methods and alternative methods can be established, data are required concerning the analytical performance of the proposed new methods in terms of precision, accuracy, and interlaboratory variability. As a mechanism for encouraging the submission of data, the Committee agreed that these methods should continue to be published as "tentative" in an annex to its specifications, with a request for information on analytical performance. If the proposed methods are intended as replacements for existing specifications tests, comparative data on analytical performance of both the proposed and the existing methods should be submitted.

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<sup>1</sup> For details see *Specifications for the identity and purity of certain food additives*. FAO Food and Nutrition Paper, No. 38, in press.

### 3. COMMENTS ON SPECIFIC FOOD ADDITIVES AND CONTAMINANTS<sup>1</sup>

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 evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and of other information required or desired for certain substances are given in Annex 3.

#### 3.1 Specific food additives

##### 3.1.1 *Antioxidant*

##### *Butylated hydroxyanisole*

Butylated hydroxyanisole was last evaluated at the thirtieth meeting of the Committee (Annex 1, reference 73). A temporary ADI of 0–0.3 mg per kg of body weight was established pending the outcome of studies to explore the potential of butylated hydroxyanisole to cause oesophageal hyperplasia in pigs and monkeys. A multigeneration reproduction study was also requested and the Committee considered that it would be desirable to carry out additional studies to determine the mechanism of action of butylated hydroxyanisole on the forestomach.

No new studies have been carried out on the effect of butylated hydroxyanisole on the stomach and oesophagus of species that do not have a forestomach, for example pigs or monkeys. However, studies carried out have provided additional information on the proliferative changes observed in the forestomach of rats fed butylated hydroxyanisole. The data show that continuous exposure of the rat forestomach to butylated hydroxyanisole at 20 g per kg in the diet for 6–12 months is necessary to produce squamous-cell carcinoma. The data also show that the induction of mild hyperplasia can occur at butylated hydroxyanisole levels of 1.25 g per kg in the diet, but not at 1.0 g per kg.

After re-evaluating the data from studies in pigs, the Committee concluded that the evidence that butylated hydroxyanisole produces

<sup>1</sup> Bibliographical references to toxicological studies are included in this section only for substances for which toxicological monographs (which would normally list such references) have not been prepared.

hyperplasia in the oesophagus of the pig is questionable. Moreover, these presumptive effects in pigs were reported to occur at levels that are significantly higher than those that produced the observed effects in the rat forestomach.

Considering the absence of any significant adverse effects in two dog studies, the Committee concluded that further investigations in animals without forestomachs were not required. The Committee believed that the relevance to human beings of the rat studies, while inherently questionable because the target tissue in the rat has no human counterpart, could not readily be ignored. The Committee concluded that an ADI could be established on the basis of the dose-dependence and reversibility of the lesions produced in the rat, which had been discussed previously in 1986 (Annex 1, reference 74) and since confirmed by more recent studies.

The Committee also reviewed both its earlier request for a multigeneration reproduction study (Annex 1, reference 73) and the currently available data on reproduction, which are limited to the results of a 1962 single-dose study of butylated hydroxyanisole in rats (Annex 1, reference 33). The Committee was made aware of an ongoing reproduction-related study and stated its desire to evaluate the study when completed.

The Committee based its evaluation of butylated hydroxyanisole on the no-observed-effect level found in long-term toxicity studies in rats, in which it was shown that butylated hydroxyanisole at 1.0 g per kg in the diet, equivalent to a daily intake of approximately 50 mg per kg of body weight, produced no significant effects. An ADI of 0–0.5 mg per kg of body weight was established.

An addendum to the toxicological monograph was prepared. The existing specifications for butylated hydroxyanisole were revised.

### 3.1.2 *Flavouring agents*

#### *trans-Anethole*

*trans*-Anethole was first evaluated at the eleventh meeting of the Committee when a conditional ADI of 0–1.25 mg per kg of body weight was allocated (Annex 1, reference 14). After re-evaluation at the twenty-third meeting (when a toxicological monograph was prepared) a temporary ADI of 0–2.5 mg per kg of body weight was allocated pending submission of the results of an adequate long-term study (Annex 1, reference 50). At the thirty-first meeting, the

Committee considered preliminary data on a long-term study in rats, but did not have an adequate opportunity to review the toxicological significance of an increase in the incidence of hepatomas in female rats reported in that study (Annex 1, reference 77). The existing temporary ADI was therefore extended to 1988 pending a full review of the new data.

At the present meeting, the Committee reviewed the available data from the long-term rat study (4, 5) and data on the metabolism of *trans*-anethole, including several recent studies (6-9). The Committee stated that it required additional information to make a definitive evaluation of the long-term rat study. In particular, information was needed on the survival times and the pathological findings in individual animals. Since the data clearly raised the possibility that carcinogenic effects occur in the liver of female animals, the Committee decided to extend the temporary ADI, but reduced it to 0-1.2 mg per kg of body weight.

Preliminary metabolic data from rats, mice, and human subjects show dose-, sex-, and species-dependent variations. Further work is needed to complete these studies, which may be relevant to the safety evaluation.

The following additional information is required by 1990: (a) further details of the long-term rat study, and (b) a review of the detailed study records and of the histopathological material, which should be undertaken by an independent institute in collaboration with WHO. In addition, studies are known to be in progress that may clarify the significance of interspecies, intersex, and dose-dependent differences in metabolism for the induction of hepatic tumours; these studies should be reviewed as soon as the results become available.

When the results of the above-mentioned reviews are available, the Committee will consider the need for further studies such as a long-term dietary study in the mouse and a reproduction/teratogenicity study.

The Committee felt that it would also be desirable to consider the feasibility of conducting an epidemiological study of consumers of food or beverages containing high levels of *trans*-anethole.

No toxicological monograph was prepared. The existing specifications for *trans*-anethole were revised.

#### *d-Carvone and l-carvone*

*d*-Carvone and *l*-carvone were evaluated at the twenty-third, twenty-fifth, and thirtieth meetings of the Committee (Annex 1, references 50, 56, 73). The temporary ADI of 0–1.0 mg per kg of body weight was extended at the thirtieth meeting to 1988 pending submission of the results of two long-term and/or carcinogenicity studies in mice and rats. The Committee noted that, although the studies on *d*-carvone were completed in 1984, the results would not be available before 1989. The Committee therefore extended the temporary ADI to 1990 pending submission of the results of these studies.

No toxicological monograph was prepared.

The existing specifications for *d*-carvone and for *l*-carvone were revised.

#### 3.1.3 *Flour-treatment agent*

##### *Potassium bromate*

Potassium bromate is used mainly as an agent for the treatment of flour and was considered in this respect in the seventh and twenty-seventh reports of the Committee (Annex 1, references 7 and 62). At its present meeting, the Committee endorsed the recommendation made in the previous reports that, as a general principle, bromate should not be present in foods *as consumed*, and reiterated that potassium bromate could be approved for use only if this principle was upheld.

The Committee considered new data on the carcinogenicity of potassium bromate and new studies on the fate of bromate in bread flour for which more sensitive methodology had been used than for earlier studies. In the new studies at levels of flour treatment of up to 62.5 mg of bromide per kg of flour, no bromate residues were detected in the resulting bread and the principal breakdown product was identified as bromide; at levels of treatment of 75 mg per kg of flour or higher, detectable residues of bromate were found in the bread. In the light of the previously established ADI for bromide (10), the Committee was of the opinion that the bromide arising from flour treatment with bromate within the acceptable levels of treatment did not present a toxicological hazard. However, as levels of treatment of 75 mg per kg of flour resulted in detectable residues of bromate in the bread, the Committee reduced the previous

acceptable level of treatment for flour for bread-making to 0–60 mg of potassium bromate per kg of flour. In arriving at this conclusion, the Committee took cognizance of earlier long-term studies in mice and rats which showed that products made from flour treated with bromate produced no adverse effects.

The Committee had no toxicological data on other food products treated with bromate but was aware that some applications could result in significant residues being present in food. Accordingly, no acceptable level of treatment could be established for foods other than flour intended for baking.

A toxicological monograph was prepared.

The existing specifications for potassium bromate were maintained.

#### 3.1.4 Food colour

##### *Erythrosine*

At the thirtieth meeting (Annex 1, reference 73), the Committee allocated a temporary ADI to erythrosine of 0–0.6 mg per kg of body weight, based on the biochemical effects of this food colour on thyroid hormone metabolism and regulation.

At its present meeting, the Committee considered additional human studies which confirmed that erythrosine is poorly absorbed from the gut. The data did not indicate the mechanism by which erythrosine exerted its effect on the thyroid; however, it appeared that inorganic iodine *per se* was not the causative agent. The no-observed-effect level with respect to thyroid function in human beings was 60 mg per person per day (equivalent to 1 mg per kg of body weight per day). At the higher dose level of 200 mg per person per day, an effect on thyroid function was detected with a small change in the responsiveness of the pituitary to thyrotropin-releasing hormone (in terms of thyrotropin release).

The results of the pharmacokinetic studies requested by the Committee at its thirtieth meeting were not available; therefore it was decided to adopt a temporary ADI pending the results of such studies.

On the basis of the no-observed-effect level of erythrosine with respect to thyroid hormone regulation in human beings, to which a safety factor of 20 was applied, the Committee allocated a temporary ADI of 0–0.05 mg per kg of body weight for erythrosine.

The results of pharmacokinetic studies that relate the level of absorption of erythrosine to the amount ingested are required by 1990. These studies would permit a correlation to be made between blood/tissue levels of erythrosine and the effects on the thyroid and may help elucidate the mechanism of thyroid effects.

An addendum to the toxicological monograph was prepared. The existing specifications for erythrosine were revised.

### 3.1.5 *Sweetening agents*

#### *Maltitol syrup (hydrogenated glucose syrups) and maltitol*

The present specifications for hydrogenated glucose syrups relate to products consisting of mixtures of glycitols and hydrogenated oligomers of glucose. Although the major component of such mixtures is maltitol, the maltitol content ranges from 50% to 90%. The Committee had before it a request to evaluate a product containing at a minimum 98% maltitol with a correspondingly low content of other polyhydric alcohols. The Committee was satisfied that this product has a separate commercial and technological identity from the hydrogenated glucose syrups evaluated previously and agreed to treat it separately for the purpose of specifications. As a consequence of this decision, the Committee had cause to reconsider the nomenclature of hydrogenated glucose syrups. Commercial glucose syrups range in composition from relatively low to high dextrose equivalent and the term hydrogenated glucose syrups is therefore a generic term that encompasses products of widely varying composition. Indeed, sorbitol syrup could be considered to fall within the category. The Committee concluded that the products covered by the present specifications for hydrogenated glucose syrups should more properly be called maltitol syrup and the title of the specifications monograph was changed accordingly.

The Committee noted that much of the available metabolic and toxicological information on maltitol syrup (previously hydrogenated glucose syrups) was derived from materials containing up to 90% maltitol. The Committee considered new metabolic studies on maltitol *per se* in which maltitol was administered to rats and dogs at doses of 150–300 mg per kg of body weight; at these doses the maltitol was extensively hydrolysed and metabolized in both species (11).

On the basis of the evaluation of hydrogenated glucose syrups (now maltitol syrup) containing high proportions of maltitol (Annex 1, reference 72) and the new metabolic data, the Committee allocated an ADI "not specified" to maltitol and confirmed that the ADI "not specified" previously allocated to hydrogenated glucose syrups applies to maltitol syrup meeting the revised specifications.

The fact that high doses of maltitol syrup and other polyols exert a laxative effect in human beings should be taken into account when appropriate levels for their use, alone or in combination, are being considered.

No toxicological monograph was prepared. New specifications were prepared for maltitol of minimum 98% purity and the existing specifications for hydrogenated glucose syrups were revised and retitled "maltitol syrup".

#### *Trichlorogalactosucrose*

Trichlorogalactosucrose has not previously been evaluated by the Committee. The title trichlorogalactosucrose was selected from the available scientific and other names for this sweetening agent in line with the guidelines formulated in section 2.3.4, because there is no officially recognized name for this substance, nor any single established common name.

The Committee considered the extensive studies carried out in animals and humans with trichlorogalactosucrose and with an equimolar mixture of its hydrolysis products, 4-chlorogalactose and 1,6-dichlorofructose. The animal studies evaluated included pharmacokinetic, metabolic, mutagenicity, teratogenicity, reproduction, neurotoxicity, short-term, long-term, and carcinogenicity studies.

Trichlorogalactosucrose is poorly absorbed after oral administration in mice, rats, dogs, and human subjects, and is excreted essentially unchanged in human urine. Its half-life in human beings is approximately 13 hours.

The available *in vitro* and *in vivo* studies indicate that trichlorogalactosucrose is not mutagenic.

Trichlorogalactosucrose is not embryotoxic or teratogenic in rats or rabbits. However, toxic effects were observed in pregnant rabbits with some deaths, associated with severe disturbances in gastrointestinal function, although only at the highest dose tested

(700 mg per kg of body weight). These toxic effects appear to be nonspecific and to be caused by the sensitivity of the rabbit to high doses of compounds producing osmotic effects in the large bowel. In a two-generation study in rats, trichlorogalactosucrose levels of up to 30 g per kg of the diet produced no evidence of any adverse effects on reproductive indices.

There was no increase in tumour incidence in the two-year studies in the mouse and the rat, or in a one-year study in the dog at doses of up to 30 g per kg of the diet. The depressed growth rate observed in the rat studies was shown to be due to the unpalatability of diets containing trichlorogalactosucrose. However, a depressed growth rate was also seen in the mouse study, and the mechanism for this effect in that species is not clear.

No neurological effects were observed in mice and marmoset monkeys receiving trichlorogalactosucrose or its hydrolysis products by gavage.

Trichlorogalactosucrose at 10 mg per kg of body weight did not stimulate the secretion of insulin or influence the absorption of sucrose in human beings and no effects of clinical significance were observed in a study in normal subjects (500 mg per day for 13 weeks).

Although very little trichlorogalactosucrose is hydrolysed *in vivo* in any of the species studied, when present in food and drink it will slowly hydrolyse in acidic conditions to produce 4-chlorogalactose and 1,6-dichlorofructose. These hydrolysis products are readily absorbed. In rats, 4-chlorogalactose is excreted mainly unchanged in the urine, but 1,6-dichlorofructose is either reduced in the liver to 1,6-dichloromannitol or conjugated with glutathione to produce an extensive displacement of the chlorine atom at position 1 (60% of the dose).

There was no evidence of mutagenic activity of 4-chlorogalactose in the available *in vitro* and *in vivo* studies. In some *in vitro* tests in bacterial and mammalian cell systems, 1,6-dichlorofructose was found to be weakly mutagenic. However, there was no evidence of mutagenic activity in three *in vivo* tests (micronucleus test, rat bone marrow test for chromosomal aberrations, and sex-linked recessive lethal test in *Drosophila melanogaster*).

The hydrolysis products of trichlorogalactosucrose produced some developmental toxicity in the rat, although this was only observed at doses that also produced maternal toxicity. A no-observed-effect level may be established for maternal and

developmental toxicity of 90 mg of hydrolysis products per kg of body weight.

There were no adverse effects on reproductive performance at levels of hydrolysis products of up to 2 g per kg of the diet in a two-generation study in rats. A 26-week study in dogs also revealed no adverse effects. There was no increase in tumour incidence in a carcinogenicity study in rats with hydrolysis products at up to 2 g per kg in the diet.

Changes were observed in organ weights (thymus, kidney, liver), biochemical variables (activities of alanine aminotransferase and aspartate aminotransferase, and magnesium concentration), lymphocyte counts, and histological parameters in rats, and to a lesser extent in mice and dogs, given trichlorogalactosucrose or the hydrolysis products. However, these changes were not considered toxicologically significant because they were generally minimal, sporadic, not reproducible, and not dose-related.

On the basis of the one-year study of trichlorogalactosucrose in the dog the Committee allocated a temporary ADI of 0–3.5 mg per kg of body weight. The following information and results of toxicological studies are required by 1990:

1. Information on the absorption and metabolism of trichlorogalactosucrose in humans after prolonged oral dosing.
2. Results of studies to ensure that trichlorogalactosucrose produces no adverse effects in people with insulin-dependent and maturity-onset diabetes.
3. Results of further studies in rats on the elimination of trichlorogalactosucrose from pregnant animals and from the fetus, to exclude the possibility of bioaccumulation.
4. Results of a short-term rat study on 6-chlorofructose.

A toxicological monograph and new tentative specifications were prepared.

#### 3.1.6 *Thickening agent*

##### *Karaya gum*

This substance was last evaluated at the thirtieth meeting of the Committee when the existing temporary ADI of 0–20 mg per kg of body weight was extended pending the submission of the results of

a feeding study in monkeys known to be in progress (Annex 1, reference 73).

The results of this study have now been published. The Committee considered that a more detailed description of the study would have been desirable; nevertheless the report of the study contained sufficient information to reinforce the Committee's conclusions that the use of karaya gum would be safe. The Committee considered that the data provided additional information on the lack of toxicity of karaya gum when fed at high dietary levels.

The Committee noted that the analysis of the gum revealed that there are no unusual amino acids present. Karaya gum is not degraded by strains of bacteria found in the human colon and does not undergo any metabolic modification in the intestinal tract of rats and dogs. Studies in both rats and human subjects failed to detect rhamnose in the urine of either species, suggesting that the gum is neither digested nor degraded by enteric bacteria.

A short-term study in rats showed no evidence of adverse effects of karaya gum at a level of 50 g per kg of the diet. Dietary studies in human subjects indicate that karaya gum is tolerated for 21 days at a dose level of 10.5 g per day, without any adverse effect.

The Committee, in keeping with the principles stated in section 3.5.2 of the thirtieth report regarding allocation of an ADI when no toxicity has been observed at high feeding levels (Annex 1, reference 73), established an ADI "not specified" for this compound. Further detailed histopathological information on the monkey studies is desired.

A toxicological monograph was prepared. The existing specifications for karaya gum were maintained.

### *3.1.7 Miscellaneous food additives*

#### *Glycerol ester of wood rosin*

Glycerol ester of wood rosin was evaluated at the eighteenth and twentieth meetings of the Committee (Annex 1, references 35 and 41). On both occasions, the Committee stressed the need to develop adequate specifications for this compound. At the present meeting, the Committee was informed that sufficiently detailed specifications were available to characterize the compound adequately. The existing tentative specifications were revised to provide identity criteria for

distinguishing glycerol ester of wood rosin from glycerol ester of gum rosin and glycerol ester of tall oil rosin. The revised specifications were designated "tentative", with a request for information on improvements in analytical methodology for two purity tests.

The Committee agreed to reconsider available toxicological data in the light of these specifications at a future meeting. The Committee's evaluation of glycerol ester of wood rosin would be facilitated by the submission of data on related substances, such as unesterified rosins and other ester derivatives of wood, gum, and tall oil rosins.

*Mineral oil, paraffin wax, and petroleum jelly*

At its thirtieth meeting (Annex 1, reference 73) the Committee discussed mineral oil, hydrocarbon waxes, and petroleum jelly and concluded that there was a need to review available toxicological data and to consider updating and revising specifications for these compounds. This latter requirement was considered particularly important in the light of new manufacturing technologies.

*Mineral oil.* At its present meeting the Committee reviewed two recently completed 90-day dietary studies with mineral oil in rats. In these studies haematological changes were found, as was mineral oil deposition in the liver, spleen, and portal tract lymph-nodes with an associated inflammatory and granulomatous macrophage response. In an additional skin-painting study, one mineral oil produced malignant skin neoplasms in rats. In interpreting these studies, the Committee was hampered by the fact that the chemical composition of the materials tested was not adequately specified (see section 2.3.2), so that the significance of the findings for the safety of food-grade mineral oil was unclear.

The existing tentative specifications for mineral oil were revised and the Committee agreed to delete the "tentative" qualification. However, the Committee was unable to determine whether mineral oils currently in use are chemically identical to the oils used in the past studies and conform to these specifications.

Before it can evaluate the new mineral oils tested toxicologically, the Committee requires the completion of further studies to characterize these materials adequately. The Committee extended the current temporary ADI "not specified" for mineral oils currently in use as releasing agents and lubricants until the results of such studies are available, which should be not later than 1990.

No toxicological monograph on mineral oil was prepared.

*Paraffin wax and petroleum jelly.* The Committee had before it for re-evaluation earlier studies on paraffin wax and petroleum jelly, the chemical compositions of which were representative of the compounds in use at the time the studies were performed. The Committee reiterated its concern about whether or not the chemical compositions of paraffin wax and petroleum jelly in current use meet the specifications for these compounds. The Committee decided that, for newer formulations of paraffin wax and petroleum jelly, new specifications are required and adequate long-term, mutagenicity, and reproduction/teratology studies should be completed. Until these studies are completed, no ADI can be allocated by the Committee for these new materials.

No toxicological monograph was prepared for paraffin wax or petroleum jelly.

The existing specifications for paraffin wax were revised but maintained as "tentative".

The existing "tentative" specifications for petroleum jelly were maintained and the Committee agreed to reprint the specifications to encourage submission of the required data.

#### *Sodium, potassium, and calcium salts of oleic acid*

At the twenty-ninth meeting, the Committee considered a list of salts used as food additives and concluded that ADIs for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions (Annex 1, reference 70). At the same meeting, the Committee extended the previous list of fatty acids for which ADIs "not specified" had been allocated to include oleic acid, based on its occurrence in edible oils and fats with a long history of use as foods or food components. However, the Committee did not allocate an ADI for the sodium, potassium, and calcium salts of oleic acid because no information was available on the food use of these salts.

At its present meeting, the Committee was informed that the sodium, potassium, and calcium salts of oleic acid have technical applications, and are employed as food additives in some Member countries. In addition, suitable specifications were available. Therefore the Committee concluded that these salts could be used according to the guidelines established at the twenty-ninth meeting, with ADIs "not specified".

No toxicological monograph was prepared.

The existing specifications for salts of fatty acids were revised to include salts of oleic acid.

### 3.2 Contaminants

#### *Aluminium*

Aluminium intake from foods, particularly those containing aluminium compounds used as food additives, represents the major route of aluminium exposure for all except those who regularly ingest aluminium-containing drugs.

Sodium aluminium phosphate, a primary source of dietary aluminium intake, was first evaluated by the Committee in 1982, when a temporary ADI of 0–6 mg per kg of body weight was allocated (Annex 1, reference 59). Concern was expressed by the Committee at that time that there was: (a) insufficient information available on the aluminium content of the diet, and (b) a need for additional safety data, including the results of absorption and metabolic studies in humans and of short-term studies and a multigeneration reproduction study in animals. At the twenty-ninth meeting of the Committee (Annex 1, reference 70), limited new data from absorption studies, including a study in human subjects, were considered. The Committee noted that: (a) the accumulation of aluminium ions was increased in individuals with chronic renal disease; (b) aluminium had been implicated in the etiology of certain neurological disorders, but definitive studies relating diet to these conditions were lacking; and (c) other dietary factors affected the absorption of aluminium. The Committee concluded that the temporary ADI of 0–6 mg per kg of body weight for sodium aluminium phosphate (equivalent to 0–0.6 mg per kg of body weight as aluminium) should be applied to all aluminium salts added to food.

At the thirtieth meeting (Annex 1, reference 73), the Committee reviewed additional studies on sodium aluminium phosphate and other selected aluminium compounds indicating that aluminium is poorly absorbed and, in the short term, does not accumulate significantly in the body. At that meeting, the Committee extended the temporary ADI of 0–0.6 mg per kg of body weight for aluminium, to be applied to all aluminium salts added to food.

At the present meeting, the Committee reviewed estimates of human exposure to aluminium from food, absorption and distribution of dietary aluminium, and the possible but unproved association between aluminium intake and disorders such as Alzheimer's disease. Recent estimates of aluminium intake from food using newer methods of analysis and improved quality control are considerably lower than previous estimates; they range from about 2 to 6 mg/day for children and from 6 to 14 mg/day for teenagers and adults. Low total body burdens of aluminium, coupled with information on urinary excretion, suggest that, even at high levels of consumption, only a small amount of aluminium is absorbed. The aluminium that is absorbed is located primarily in the heart, spleen, and bone but its presence in these organs has not been found to be accompanied by any histopathological lesions.

The Committee considered the completed studies to be adequate to be used to set a PTWI for aluminium of 7 mg per kg of body weight. The Committee concluded that there was no need to set a separate ADI for sodium aluminium phosphate, basic or acidic, since the PTWI included aluminium intake resulting from food additive uses.

A toxicological monograph was prepared.

### *Arsenic*

In the twenty-seventh report of the Committee (Annex 1, reference 62) a provisional maximum tolerable daily intake of 0.002 mg per kg of body weight was assigned for ingested inorganic arsenic, but no figure was set for organic arsenicals in food.

At its present meeting the Committee decided to confirm the previous evaluation by assigning a PTWI of 0.015 mg per kg of body weight for inorganic arsenic, but stressed that there is a narrow margin between this PTWI and intakes reported to have toxic effects in epidemiological studies. The Committee recognized the practical necessity of recommending tolerable intakes that took into consideration the natural occurrence of high levels of inorganic arsenic in water supplies in certain areas of the world. Nevertheless, the continuation of the provisional status of the maximum weekly intake was meant to convey the desirability of seeking ways of reducing the arsenic intake of populations exposed to naturally elevated levels of inorganic arsenic in drinking-water. Furthermore, the Committee recommended that further epidemiological studies be

undertaken in such populations to define more clearly the levels of inorganic arsenic that may result in adverse effects.

The Committee recognized that the organic forms of arsenic present in seafoods need different consideration from the inorganic arsenic in water. There are many regional and ethnic populations whose consumption of large quantities of fish results in organoarsenical intakes of about 0.05 mg per kg of body weight per day. There have been no reports of ill-effects among these groups, but further investigation of these populations would be desirable to assess the implications for human health of exposure to naturally occurring organoarsenic compounds in marine products.

The Committee had before it the results of a short-term rat study in which diets containing enough fish to produce intakes of naturally occurring organoarsenicals of up to 3 mg per kg of body weight per day did not elicit toxic effects. Additional information indicated that the organoarsenicals present in fish are excreted very rapidly by both laboratory animals and humans.

On the basis of the available data, and recognizing that fish is a nutritious food, the Committee did not recommend a change in dietary habits because of the presence of organoarsenicals in fish. However, further studies are desirable to investigate the type and levels of organoarsenic compounds naturally occurring in marine products, as are further animal studies of these compounds.

A toxicological monograph was prepared.

### *Cadmium*

Cadmium was last reviewed at the sixteenth meeting of the Committee (Annex 1, reference 30) when a PTWI of 400–500 µg per capita (6.7–8.3 µg per kg of body weight per week) was allocated.

Since the previous evaluation, a large number of reviews have become available and these were considered by the Committee at its present meeting.

Cadmium is a pollutant that affects many different areas of the environment. Food is normally the major source of cadmium exposure in the general population and available data indicate that the current intake of cadmium from the diet is most commonly 10–35 µg/day. Although water is not a major contributor to cadmium intake for most individuals, naturally elevated levels of cadmium can occur in water and the resultant cadmium intake can

be as large as the dietary intake. Cadmium may also be ingested from non-food sources, for example smoking 20 cigarettes per day may contribute a further 1–4 µg of cadmium per day.

Cadmium has an extremely long biological half-life in humans. Even low exposure levels may, in time, cause considerable accumulation, especially in the kidneys.

The kidney, in particular the renal cortex, has been identified as the critical organ in relation to the toxic effects of chronic exposure to relatively low levels of cadmium (12). The critical tissue concentration of cadmium at which renal injury occurs varies between individuals and can be specified in terms of the “population critical concentration” (PCC) for a given response rate (e.g.,  $PCC_{50}$  = the concentration of cadmium in the renal cortex at which 50% of the human population studied have reached their individual critical concentration). The first adverse functional change following chronic exposure to cadmium is usually low-molecular-weight proteinuria; intakes in the range of 140–255 µg/day have been associated with low-molecular-weight proteinuria in the elderly. Low-molecular-weight proteinuria is not accompanied by any specific histological changes and its pathological significance is unclear. However, it can be used as an indicator of the threshold of possible toxic effects and it is appropriate to set the PTWI on the basis of the dose–response data for this end-point.

There are limited data on population critical concentrations on which to base an evaluation, particularly since the concentrations of cadmium in the renal cortex may fall when proteinuria occurs. Generally, there has been evidence of renal dysfunction in animals at cadmium concentrations in the renal cortex of 200–400 mg/kg, but there is also some evidence of effects at even lower concentrations. In humans studied with no, or only slight, changes in renal tubular function, cadmium levels in the renal cortex have varied, with few exceptions, between 100 and 450 mg of cadmium per kg and studies aimed at determining critical concentrations in the renal cortex have yielded estimates of about 200 mg of cadmium per kg for the  $PCC_{10}$ . The  $PCC_{10}$ , of course, does not represent a no-effect level.

From dose–response analysis of individual critical concentrations, it can be estimated that a 10% prevalence rate for low-molecular-weight proteinuria would occur after 45 years of dietary intake of 200 µg of cadmium per day for people weighing 70 kg. Essentially similar estimates result from regression analysis of

cadmium intake and mean kidney cadmium concentration in various countries, i.e., the  $PCC_{10}$  of 200 mg of cadmium per kg of renal cortex would be attained after a dietary intake of 175  $\mu$ g of cadmium per day for 50 years. The fact that low-molecular-weight proteinuria can be demonstrated in individuals over 50 years of age with a daily intake of cadmium of 140–255  $\mu$ g per day confirms that these estimates are reasonable. Since dietary intake is usually 10–35  $\mu$ g/day, there is only a relatively small safety margin between exposure in the normal diet and exposure that produces deleterious effects.

In view of estimates that a daily intake of 100  $\mu$ g of cadmium would lead to about 2% of the population exceeding their individual critical concentration, levels of cadmium in foods and total diet should continue to be monitored and should not increase further. The Committee reiterated that the use of cadmium-plated utensils in food processing and preparation should be discouraged and galvanized equipment should be avoided where possible. Leachable cadmium in enamel and pottery glazes may be a source of contamination and cadmium-based pigments or stabilizers should not be used in food-contact plastics. Phosphate fertilizers and sewage sludge used on agricultural land may be significant sources of cadmium and in some circumstances could lead to elevated levels in crops; attempts should be made to minimize such accumulation in agricultural produce.

Assuming an absorption rate for dietary cadmium of 5% and a daily excretion rate of 0.005% of body burden, the Committee concluded that total intake should not exceed about 1  $\mu$ g per kg of body weight per day continuously for 50 years, if levels of cadmium are not to exceed 50 mg/kg in the renal cortex. The PTWI for cadmium was therefore set at 7  $\mu$ g/kg of body weight.

Since the PTWI is derived from estimated cadmium accumulation over a period of 50 years at an exposure rate equivalent to 1  $\mu$ g per kg of body weight per day for adults, excursions above this figure may be tolerated provided that they are not sustained for long periods of time and do not produce a significant increase in the integrated lifetime dose. In particular, it is recognized that exposure to cadmium will vary according to age. The Committee noted that the recommended PTWI does, in fact, take into account the higher cadmium intake on a body weight basis by infants and children.

It is recommended that biological monitoring of groups exposed to relatively high levels of cadmium should be carried out to provide

information to supplement that obtained from estimates of dietary intake.

A toxicological monograph was prepared.

#### *Bis(2-ethylhexyl) phthalate*

This substance was evaluated previously by the Committee at its twenty-eighth meeting (Annex 1, reference 66), when it considered results of pharmacokinetic, metabolic, reproductive, teratogenicity, mutagenicity, short- and long-term toxicity, and carcinogenicity studies, as well as special studies related to testicular atrophy and hepatocellular peroxisome proliferation. The Committee concluded that bis(2-ethylhexyl) phthalate was a hepatocarcinogen in both rats and mice and recommended that human exposure to this compound as a result of its migration from food-contact materials be reduced to the lowest level that is technologically feasible.

Since the Committee last considered bis(2-ethylhexyl) phthalate, additional data have become available regarding the probable mechanism of its hepatocarcinogenic effects and induction of testicular atrophy. The testicular atrophy induced by the compound in rats is an age-dependent response, with younger rats being more susceptible. Although zinc-deficient rats showed enhanced susceptibility to the gonadotoxic effects of bis(2-ethylhexyl) phthalate, testicular atrophy still occurred when zinc was given together with the phthalate ester. However, the co-administration of testosterone and bis(2-ethylhexyl) phthalate to adult male rats appears to prevent the testicular injury that would otherwise be induced by the ester alone. Mono-2-ethylhexyl phthalate is probably the active metabolite of bis(2-ethylhexyl) phthalate that affects rat testes both *in vivo* and *in vitro*. There is a partial reversal of testicular atrophy in rats following cessation of exposure to bis(2-ethylhexyl) phthalate.

The hepatocarcinogenesis in rats and mice attributed to bis(2-ethylhexyl) phthalate and other phthalate esters is preceded by hepatocellular peroxisome proliferation. Suggestions as to the probable mechanism of peroxisome proliferation have been advanced, but remain unproved.

The Committee was informed of current food-contact uses of materials containing bis(2-ethylhexyl) phthalate in various countries. It was noted that the lowest level of the ester in food-contact materials is a function of its effectiveness in plasticizing

(softening) plastic materials. Technically, the optimum levels range from 20 to 50% of the weight of the plastic material. Migration levels of bis(2-ethylhexyl) phthalate into food are influenced by its level in the packaging material and by factors such as the composition of food and the time and temperature of processing and storage of packaged food. As a consequence of the marked solubility of bis(2-ethylhexyl) phthalate in lipid materials, the use of materials containing this compound is limited in some countries to foods of high water content (non-fatty foods).

After reviewing all the information available, the Committee reiterated its recommendation that human exposure to bis(2-ethylhexyl) phthalate in food be reduced to the lowest level attainable. The Committee considered that this might be achieved by using alternative toxicologically acceptable plasticizers or alternatives to plastic materials containing the phthalate ester.

An addendum to the toxicological monograph was prepared.

### *Iodine*

The Committee had not previously considered iodine. In reviewing the safety of iodine in order to set a maximum tolerable daily intake for humans, the Committee considered information concerning dietary iodine exposure and noted that iodine and compounds containing iodine are used in a variety of food-related applications including nutrient fortification, food additives, agricultural chemicals, veterinary drugs, and sanitizing solutions. The Committee recognized that iodine is an essential micronutrient. It also noted that various therapeutic uses of iodine may result in significant intakes.

The Committee was informed that dietary iodine intakes have been estimated in various countries and are highly correlated with dietary habits. An iodine intake of 1 mg per day or less is probably safe for most people, but may cause adverse effects in some individuals, e.g., those with thyroid disorders or those who are particularly sensitive to iodine. WHO has recommended a dietary iodine intake of 0.10–0.14 mg/day per adult (13); however, the Committee noted that the dietary iodine requirement is to be re-evaluated by WHO in the near future. For purposes of safety, the Committee set a provisional maximum tolerable daily intake of 1 mg of iodine (0.017 mg per kg of body weight) from all sources. The Committee further recommended that physicians and public health

authorities should be aware of the need to balance therapeutic need with potential iodine excess in relation to the use of iodine-containing drugs.

A toxicological monograph was prepared.

### *Methylmercury*

At the twenty-second meeting (Annex 1, reference 47), the Committee endorsed the recommendation of the sixteenth meeting (Annex 1, reference 30) in establishing a PTWI of 0.3 mg of total mercury per person, of which no more than 0.2 mg should be present as methylmercury. At its present meeting the Committee reassessed methylmercury as new data were available on this compound.

The Committee confirmed the previously recommended PTWI of 200 µg of methylmercury (3.3 µg per kg of body weight) for the general population, but noted that pregnant women and nursing mothers are likely to be at greater risk from the adverse effects of methylmercury. The Committee considered the available data insufficient for it to recommend a specific methylmercury intake for this population group, and it recommended that more detailed studies be undertaken. The Committee noted that a Task Group of the International Programme on Chemical Safety was also considering the effects of methylmercury on pregnant women and nursing mothers.

The Committee was aware of the variation in the levels of naturally occurring methylmercury in fish. This variation has been shown to correlate with a number of factors including the size and age of the fish, the species (e.g., predatory species normally contain higher mercury levels), the mercury content of the water and sediments, and the pH of the water. Thus, while most fish from unpolluted waters contain less than 0.4 µg of methylmercury per g, species such as swordfish, shark, and tuna may contain levels of up to several µg per g. Fish from contaminated waters can contain significantly higher levels of methylmercury.

The Committee noted the distinction between the elevated methylmercury levels found in certain fish from unpolluted waters and similar levels that can result from industrial pollution. In this regard, selenium and other naturally occurring trace constituents in fish from unpolluted waters may play an important role in moderating the effects of methylmercury. The Committee recommended that further investigation be made of this possibility.

Finally, the Committee noted that fish is nutritious and efforts are under way in many countries to increase fish consumption as an integral part of a well-balanced diet. Furthermore, the dietary habits of regional and ethnic groups have evolved over centuries in response to their needs and are entrenched in their culture. Any recommendations that imply the need to change these habits should be based on compelling arguments and must not overlook the possible implications. Efforts should continue, however, to minimize human exposure to methylmercury that results from industrial pollution.

An addendum to the toxicological monograph on methylmercury was prepared.

### *Tin*

Tin was considered at the twenty-second and twenty-sixth meetings of the Committee (Annex 1, references 47 and 59) when, in addition to reviewing information on the absorption, distribution, and excretion of tin, the Committee evaluated the results of toxicological studies and epidemiological data.

At its twenty-sixth meeting (Annex 1, reference 59), the Committee determined that gastric irritation was the main problem associated with excessive levels of tin in foods and concluded, on the basis of existing data, that the threshold for this effect was about 200 mg of tin per kg of food. The Committee noted that care should be taken to ensure that levels of tin in food are kept as low as practicable; to this end, consumers were advised not to store food in open tin-coated cans. The Committee allocated a provisional maximum tolerable daily intake for tin of 2 mg per kg of body weight.

At the present meeting, the Committee reaffirmed the previously established tolerable daily intake, but converted it to a PTWI of 14 mg of inorganic tin per kg of body weight,<sup>1</sup> and emphasized that this value was applicable to chronic tin exposure. As for acute toxicity due to tin exposure and in response to the request from the Codex Committee on Food Additives and Contaminants for further clarification of this matter, a re-examination of available data on human exposure was undertaken.

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<sup>1</sup> Includes tin derived from food additive use.

The Committee was aware that different types of canned food are consumed in varying amounts and that levels of tin are higher in unlacquered than in lacquered cans. Infants and small children are likely to consume higher levels of tin, on a body weight basis, from a single source, e.g., canned juice, than are adults. Furthermore, the Committee acknowledged that various factors may potentiate the adverse effects of tin or moderate potentially toxic effects. In the absence of more specific information on these factors and on the chemical forms of tin that cause acute gastric irritation, it was not possible for the Committee to incorporate such considerations into its evaluation. It was concluded from the limited data available on human exposure, including one incident involving canned beverages, that tin concentrations as low as 150 µg/g in canned beverages and 250 µg/g in other canned foods may produce acute manifestations of gastric irritation in certain individuals; however, it was also noted that some canned products containing levels of up to 700 µg of tin per g have not been reported to produce any detectable toxic effects.

Therefore, the Committee recommended that efforts be made to keep tin levels in canned foods as low as practicable. In this regard, tin concentrations in canned foods should be limited to those consistent with the application of good manufacturing practices (14).

An addendum to the toxicological monograph was prepared.

#### **4. REVISION OF CERTAIN SPECIFICATIONS**

##### **4.1 General**

Thirteen substances were evaluated for specifications only (see Annex 2), and the specifications for all thirteen were revised.

The revised specifications for lactitol, modified starches, and xanthan gum were designated "tentative", with a request for information intended to improve them; for xanthan gum, the Committee requested information on the methodology and limits for several microbiological requirements introduced into the specifications. The Committee agreed to delete the "tentative" qualification for the revised specifications for sorbitan monooleate.

For bone phosphate, the Committee deleted the specification for soluble fluoride because it provided no further limitation on quality than that afforded by the specification for total fluoride.

## 4.2 Polyols

In addition to the specifications for maltitol and maltitol syrup (hydrogenated glucose syrups—see section 3.1.5), the Committee considered the specifications for isomalt, lactitol, mannitol, sorbitol, sorbitol syrup, and xylitol. At its thirty-first meeting the Committee recommended that the specifications for four of these polyols should be reviewed with the aim of reducing the limits for lead. Information available to the Committee at its present meeting confirmed that the limits for lead could be reduced from 10 mg/kg to a maximum of 1 mg/kg for all six polyols. In reviewing this aspect of the specifications, the Committee considered the consistency among the existing specifications, and the need for other changes became apparent. The existing specifications for isomalt, mannitol, sorbitol, and sorbitol syrup were revised; the existing tentative specifications for xylitol were revised and the “tentative” qualification was deleted.

The existing specifications for lactitol establish limits for purity criteria on an anhydrous basis for articles of commerce that vary from solids to 50% solutions of lactitol. The Committee had difficulty in establishing methods appropriate for determining these limits because of the absence of a suitable method for determining the water content of products sold as solutions. In addition, there was no information available to support the need to use a method for reducing substances different from the one included in the general methods listed in the *Guide to specifications* (Annex 1, reference 65). The specifications for lactitol were revised and made tentative pending information on the maximum water content of products sold as solutions, a suitable method for determining the water content of lactitol solutions, and the applicability of the general methods for reducing substances as alternatives to the modified Luff-Schoorl method in the existing tentative specifications.

The tentative alternative method for “the determination of polyols by high pressure liquid chromatography”, adopted by the thirty-first meeting, was revised, but the “tentative” qualification was maintained.

## 5. SETTING PRIORITIES FOR THE SAFETY REVIEW OF FOOD FLAVOURING INGREDIENTS

The Committee has, for a number of years, recognized the need for a procedure to set priorities for the review of food flavouring

ingredients, primarily because of the large number of these substances in use. An *ad hoc* working group responded to this request by developing a suitable method, and a working paper describing the proposed method was presented to the Committee at the present meeting. (The method had been previously endorsed, at its twentieth session, by the Codex Committee on Food Additives and Contaminants, which recommended that the method be presented to the Joint FAO/WHO Expert Committee on Food Additives for its scientific review.)

The Committee considered the scientific basis for the proposed approach to setting priorities for the safety evaluation of flavours, including the use of structure–activity relationships, consideration of the natural occurrence of flavours in food and of the amounts of flavours added to food, and the use of existing toxicological data. The Committee endorsed the proposed method for ranking flavours, and agreed that the method should be used to begin bringing flavouring substances of high priority forward for the Committee's review. The method is described in Annex 4.

The Committee recognized that, in practice, the application of the method would require the relevant data used in setting priorities (e.g., the exposure estimates) to be as current as possible and also as representative as possible of the international situation. The Committee noted that it should be possible to update priority lists as more information becomes available from various parts of the world.

The Committee stated that it would be able to respond to new and relevant information on flavours as it became available, even if the flavours in question were out of sequence on the new priority list.

## 6. FUTURE WORK

1. Since specifications have been established for potassium iodate and the Committee has been informed of its use as a food additive, it should undergo toxicological evaluation.

2. The general methods section of the *Guide to specifications* (Annex 1, reference 65) should be updated. The methods adopted by the Committee since the *Guide to specifications* was published in 1983 should be evaluated for inclusion (see also section 2.3.5).

3. During its evaluation of specifications, the Committee became aware that infrared spectroscopy was used for identifying several

substances. As this technique is not included in the general methods section of the *Guide to specifications* (Annex 1, reference 65) the Committee should develop an appropriate general method.

## 7. RECOMMENDATIONS

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 regularly.

2. In recognition of the important role that accurate information on intakes of food additives and contaminants plays in the Committee's evaluations, FAO and WHO should encourage the development of food consumption surveys that will provide more accurate estimates of these intakes than do the dietary surveys commonly employed at present, which are intended for nutrient evaluation. Survey methods should include a mechanism for considering proprietary information on levels of use of food additives and on the total amounts used annually in the food supply.

### 3. *Arsenic*

- (a) In order to define more clearly levels of inorganic arsenic that may result in adverse effects, FAO and WHO should encourage further epidemiological study of populations exposed to elevated levels of inorganic arsenic compounds occurring naturally in drinking-water.
- (b) FAO and WHO should encourage the epidemiological study of consumers of large amounts of fish, to assess more fully the implications for human health of exposure to naturally occurring organoarsenic compounds in marine products.
- (c) Further investigations should be conducted of the types and levels of organoarsenic compounds naturally occurring in marine products.
- (d) As arsenic compounds of unknown toxicity are present in marine products, further animal studies of these compounds should be undertaken.

### 4. *Cadmium*

- (a) Efforts should continue to reduce human exposure to cadmium. To this end, care should be exercised in using cadmium-

containing materials, including cadmium-plated utensils in food processing and preparation, galvanized equipment in water-distribution and water-storage systems, cadmium-containing enamel and pottery glazes that come into contact with foods, and cadmium-based pigments in food-contact materials. In addition, the application of phosphate fertilizers and sewage sludge to land used for crops should be closely monitored to ensure that such practices do not result in any significant increase in cadmium levels in crops grown on treated lands.

- (b) Because of the relatively small margin between estimated human dietary exposure to cadmium and levels that produce adverse effects, FAO and WHO should encourage: (i) further biological monitoring to define more accurately the population critical concentration for cadmium; and (ii) further monitoring of foods to refine estimates of dietary cadmium intake.

#### 5. *Bis(2-ethylhexyl) phthalate*

- (a) To minimize human dietary exposure to bis(2-ethylhexyl) phthalate, efforts should be made to avoid using this substance for materials that come into contact with fatty foods.
- (b) Alternative plasticizers to bis(2-ethylhexyl) phthalate should be sought; the Committee stressed the importance of evaluating the safety of any such substitutes prior to their introduction and widespread use.

#### 6. *Iodine*

- (a) FAO and WHO should encourage appropriate studies in humans to determine more precisely the acceptable range of intakes in normal subjects and in iodine-sensitive individuals.
- (b) The Committee was aware that certain practices (e.g., the use of iodophors for sanitizing dairy equipment) have been associated with elevated iodine levels in foods. It recommended that such practices be investigated with the aim of preventing excessive levels of iodine in foods.
- (c) FAO and WHO should encourage further work to determine the bioavailability of iodine from various iodine compounds found in foods.

#### 7. *Methylmercury*

Because of the limited size of the available epidemiological studies on populations consuming methylmercury in fish from unpolluted

waters, FAO and WHO should encourage further studies, aimed at achieving a better understanding of whether low-level prenatal exposure to methylmercury in marine products results in adverse effects in infants (e.g., on the central nervous system). These studies should, where possible, assess the significance of other micro-constituents naturally occurring in fish (e.g., selenium) in moderating methylmercury toxicity.

#### 8. Tin

- (a) In light of the limited data available relating tin levels in food to acute toxicity in humans, FAO and WHO should encourage studies to:
  - identify the chemical forms of tin that cause acute gastric irritation; and
  - investigate what factors may play a role in potentiating or moderating the adverse effects of tin.
- (b) To minimize dietary exposure to tin, consumers should be advised not to store foods in opened cans, and in particular in unlacquered cans, for extended periods of time.
- (c) Efforts should continue through FAO, WHO, and other appropriate United Nations agencies to assist developing countries in implementing technological improvements in their canning industries.

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## 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 international 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).
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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.
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## Annex 2

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

Substance	Specifications <sup>1</sup>	Acceptable daily intake (ADI) for humans and other toxicological recommendations
<b>A. Food additives</b>		
<i>Antioxidant</i>		
Butylated hydroxyanisole	R	0–0.5 mg/kg of body weight
<i>Flavouring agents</i>		
trans-Anethole	R	0–1.2 mg/kg of body weight <sup>2</sup>
d- & l-Carvone	R	0–1.0 mg/kg of body weight <sup>2, 3</sup>
<i>Flour-treatment agent</i>		
Potassium bromate	S	0–60 mg bromate/kg of flour <sup>4</sup>
<i>Food colour</i>		
Erythrosine	R	0–0.05 mg/kg of body weight <sup>2</sup>
<i>Sweetening agents</i>		
Maltitol	N <sup>5</sup>	ADI not specified <sup>6</sup>
Maltitol syrup	R <sup>7</sup>	ADI not specified <sup>6, 8</sup>
Trichlorogalactosucrose <sup>9</sup>	N, T	0–3.5 mg/kg of body weight <sup>2</sup>
<i>Thickening agent</i>		
Karaya gum	S	ADI not specified <sup>6</sup>
<i>Miscellaneous food additives</i>		
Glycerol ester of wood rosin	R, T	No ADI allocated <sup>10</sup>
Mineral oil	R	ADI not specified <sup>2, 6, 11</sup>
Paraffin wax	R, T	No ADI allocated <sup>10</sup>
Petroleum jelly	S, T	No ADI allocated <sup>10</sup>
Sodium, potassium, and calcium salts of oleic acid	R	ADI not specified <sup>6</sup>
<b>B. Contaminants</b>		
Aluminium		7 mg/kg of body weight <sup>12</sup>
Arsenic (inorganic)		0.015 mg/kg of body weight
Cadmium		0.007 mg/kg of body weight
Bis(2-ethylhexyl) phthalate		Provisional acceptance <sup>13</sup>
Iodine		[0.017 mg/kg of body weight <sup>14</sup> ]
Methylmercury		0.0033 mg/kg of body weight <sup>15</sup>
Tin		14 mg/kg of body weight <sup>16</sup>

Specifications only <sup>1</sup>	
Bone phosphate	R
Insoluble polyvinylpyrrolidone	R
Isomalt	R
Lactitol	R, T
Mannitol	R
Modified starches	R, T <sup>17, 18</sup>
Potassium iodate	R
Saccharin	R
Sorbitan monooleate	R
Sorbitol	R
Sorbitol syrup	R
Xanthan gum	R, T
Xylitol	R

#### Notes to Annex 2

1. N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; and T, the existing, new, or revised specifications are tentative and comments are invited (see Annex 3).
2. Temporary acceptance (see Annex 3).
3. ADI applies to the two listed compounds, alone or in combination.
4. Acceptable level for treatment of flours for bread-making.
5. New specifications were developed for 98% pure maltitol separately from maltitol syrup.
6. 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 ADI expressed in numerical form is not deemed necessary.
7. Designated as "hydrogenated glucose syrups" at previous meetings.
8. The ADI previously allocated to hydrogenated glucose syrups applies to maltitol syrup meeting the revised specifications.
9. This compound was on the agenda under the name "sucralose".
10. Insufficient information available on the toxicology and/or chemical composition of the substance(s) to establish an ADI.
11. Applies only to those mineral oils currently in use as releasing agents and lubricants.
12. The PTWI includes food additive uses of aluminium salts.
13. The use of food-contact materials from which bis(2-ethylhexyl) phthalate may migrate is provisionally accepted, on condition that the quantity of the substance migrating into the food is reduced to the lowest level technically attainable.
14. Provisional maximum tolerable daily intake. The nutritional requirement for iodine is currently considered by WHO to be in the range of 0.10 to 0.14 mg per person per day for adults. The nutritional requirement for iodine is under review by WHO.
15. Applies to methylmercury. New data were not available on inorganic mercury.

16. Includes tin resulting from food additive uses. Efforts should be made to keep tin levels in canned foods as low as practicable, because of the possibility of gastric irritation.
17. Separate specifications for enzyme-treated starches were published in *FAO Food and Nutrition Paper, No. 4, 1978*.
18. The “tentative” qualification applies to oxidized starch and acetylated distarch adipate.

## **FURTHER TOXICOLOGICAL STUDIES AND OTHER INFORMATION REQUIRED OR DESIRED**

### **Antioxidant**

#### *Butylated hydroxyanisole*

Submission of the results of an ongoing reproduction-related study is desired.

### **Flavouring agents**

#### *trans-Anethole*

1. Submission of more details of the long-term rat study that was reviewed by the Committee. A review of the detailed study records and of the histopathological material should be undertaken by an independent institute in collaboration with WHO.<sup>1</sup>

2. Submission of the results of studies that are known to be under way that may clarify the significance of interspecies, intersex, and dose-dependent differences in metabolism for the induction of hepatic tumours.<sup>2</sup>

#### *d-Carvone*

Submission of the results of the carcinogenicity feeding studies in mice and rats that were completed in 1984.<sup>1</sup>

### **Food colour**

#### *Erythrosine*

Submission of the results of pharmacokinetic studies relating the amount of erythrosine absorbed to the amount ingested that would enable a correlation to be established between blood/tissue levels of erythrosine and effects on the thyroid; this may help elucidate the mechanism of thyroid effects.<sup>1</sup>

<sup>1</sup> Information required by 1990.

<sup>2</sup> To be submitted as soon as results become available.

## **Sweetening agents**

### *Trichlorogalactosucrose (sucralose)*

Submission of:<sup>1</sup>

1. Information on the absorption and metabolism of trichlorogalactosucrose in humans after prolonged oral dosing.
2. Results of studies to ensure that trichlorogalactosucrose produces no adverse effects in people with insulin-dependent and maturity-onset diabetes.
3. Results of further studies in rats on the elimination of trichlorogalactosucrose from pregnant animals and from the fetus, to exclude the possibility of bioaccumulation.
4. Results of a short-term study in rats on the metabolite 6-chlorofructose.

Information required relating to specifications includes: (1) the purity of the material used to prepare the infrared reference spectra; (2) the maxima in the spectra most relevant for identification; and (3) the nature of the material contributing to the sulfated ash.

## **Thickening agent**

### *Karaya gum*

Further detailed histopathological information is desired on the feeding study in monkeys.

## **Miscellaneous food additives**

### *Glycerol ester of wood rosin*

Information required relating to specifications includes: (1) the applicability of the general method for colour and the specification limit by that method; and (2) the availability of a more practical method for determining density than the proposed method.

### *Mineral oils*

Further studies to characterize accurately the mineral oils that have been tested toxicologically.<sup>1</sup> Until such studies have been completed, the Committee is unable to evaluate new mineral oil formulations.

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<sup>1</sup> Information required by 1990.

### *Paraffin wax*

Information required relating to specifications includes: (1) the actual composition of the hydrocarbons; (2) methods for identifying the individual hydrocarbons; (3) limits and methods of analysis for sulfur; and (4) the nature of the sulfur compounds present.

### *Petroleum jelly*

Information required relating to specifications includes: (1) the actual composition of the hydrocarbons; (2) method(s) for identifying the individual hydrocarbons; (3) limits and methods of analysis for sulfur, arsenic, lead, and heavy metals; and (4) the nature of the sulfur compounds present.

## **Contaminants**

### *Arsenic*

Further investigations of the type and levels of organoarsenic compounds naturally occurring in marine products and further animal studies of these compounds are highly desirable.

### *Cadmium*

It is desirable that biological monitoring of groups exposed to relatively high levels of cadmium be carried out to provide information to supplement that obtained from estimates of dietary intake.

### *Methylmercury*

More detailed studies are desirable of the effects of methylmercury on pregnant women and nursing mothers.

## **Specifications only**

### *Lactitol*

Information is required on: (1) the maximum water content of solutions of lactitol; (2) a method for determining the water content of solutions; and (3) the applicability of the general methods for reducing substances (listed in the *Guide to specifications*) as alternatives to the Luff-Schoorl method.

*Modified starches*

Methods of analysis are required for carboxyl groups in oxidized starch and free adipic acid in acetylated distarch adipate.

*Xanthan gum*

Information is required on the limits and methodology for microbiological criteria.

## **A METHOD FOR SETTING PRIORITIES FOR THE SAFETY REVIEW OF FOOD FLAVOURING INGREDIENTS**

### **Introduction**

The method for setting priorities among food flavouring ingredients consists of a set of simple procedures that, when applied to any inventory of flavours concurrently in use, results in a subset of convenient size that can be designated for more detailed review and evaluation. The Codex Committee on Food Additives and Contaminants may use this method to identify the flavouring ingredients of highest priority, which it may then recommend for review by the Joint FAO/WHO Expert Committee on Food Additives so that ADIs can be determined.

### **Basic principles**

It is emphasized that the purpose of this priority-setting process is not to determine safety, but rather to establish priorities for acquiring and reviewing the necessary information upon which a complete consideration of safety can be made.

The scheme is "risk-based" while giving appropriate weight to the ease with which risks can be diminished (1-3). It is applicable to a wide range of chemical entities and will differentiate one substance from another so that a subgroup of substances can be created of a size appropriate to the resources available for safety review. The scheme has been designed with computerization in mind so that it can be easily applied to large numbers of substances and so that the effect of new information on existing priority lists can be easily tested. Priorities can be set even if (as is often the case for flavouring ingredients) animal feeding studies have not been carried out, since the method permits the assessment of presumptive toxicity on the basis of chemical structure-activity relationships. The method also allows for consideration of available toxicological data, and is designed to make use of summary data from toxicological studies, of the type found in some modern computerized data bases, rather than in-depth analyses of original data.

These principles are consistent with those put forward in the recent monograph entitled *Principles for the safety assessment of food additives and contaminants in food* (4).

### **Description of the method**

The priority-setting method consists of the sequential application of a series of four steps:

#### *Step 1: Inventory of substances*

The first step is to create an inventory of candidate substances to be ranked. For this purpose, Chemical Abstracts Service Registry Numbers are employed as well as other current identification numbers such as those assigned by the Flavor and Extract Manufacturers' Association of the United States (FEMA). The method will initially be applied to a list of flavours prepared for the Twentieth Session of the Codex Committee on Food Additives and Contaminants (5).

#### *Step 2: Hybrid priority levels*

Because no toxicological feeding studies have been carried out for most flavours, the initial assignment of "presumptive concern" for each compound to be ranked (i.e., the degree of concern warranted by the flavour's likely toxicity and level of use) is based upon other data. Two established assignment methods are employed that make use of: (a) estimates of probable addition levels to food and (b) knowledge of each compound's chemical structure. The methods combine chemical structure information (in the form of assignments to discrete structure categories) with human exposure information to allow placement of all flavours into one of several "concern levels".

The first of these methods—the FEMA Decision Tree method—uses a decision tree made up of 33 questions to assign compounds into chemical structure categories (6). The second method—the US Food and Drug Administration (FDA) Redbook method—uses tables of chemical substructures to assign compounds into structure categories (7). In both cases, flavours are assigned to one of three chemical structure categories corresponding to "low", "intermediate", or "high" presumptive toxicity. These structure assignments are then combined with the estimates of human

exposure (via purposeful addition to food) to categorize compounds into one of several initial “concern levels”, four for the FEMA Decision Tree method (6) and three for the FDA Redbook method (7, 8).

The concern levels assigned by the two methods are combined into a single set of “hybrid priority levels”. The merging procedure is based upon the simple premise that any compound classified into the highest concern level by both the FEMA Decision Tree method and the FDA Redbook method ought to be assigned to the highest hybrid priority level. Conversely, a compound assigned to the lowest concern level by both methods ought to be assigned to the lowest hybrid priority level. Hybrid priority levels are thus defined as the sums of the respective numbers characterizing the separate concern levels, with level 7 being the highest (Table 1).

Table 1. Merging procedure for hybrid priority levels

Hybrid priority level	RCL <sup>a</sup>	FCL <sup>b</sup>
7	3	4
6	3	3
	2	4
5	3	2
	2	3
	1	4
4	3	1
	2	2
	1	3
3	2	1
	1	2
2	1	1

<sup>a</sup>Concern level defined by the FDA Redbook method.

<sup>b</sup>Concern level defined by the FEMA Decision Tree method.

### *Step 3: Application of consumption ratio*

The third step in setting priorities for flavours is to address the question of the ease of risk reduction, which is affected by the natural occurrence of certain flavours in food. Risk reduction is more difficult if intake of the flavour by humans is mainly from natural sources; safety evaluation may then be considered more urgent, but *only* if the flavour has a high hybrid priority level. The “consumption ratio” provides a convenient way of taking this into account. It is defined as the ratio of the per capita intake resulting from a flavour’s

natural occurrence in food to the per capita intake of the flavour from its intentional addition to food (1, 9, 10). Thus, a large consumption ratio signifies that the human intake from natural occurrence of the compound in food is much greater than the intake that results from its intentional addition to food. A consumption ratio of zero indicates that the compound does not occur naturally in food as far as is presently known. Consumption ratios other than zero range from  $1 \times 10^{-3}$  to values of the order of  $1 \times 10^5$ .

The effect of the consumption ratio on the assignment of flavours to priority levels should depend upon whether initial priority levels are high or low. If the hybrid priority level is low, a high consumption ratio will not affect the presumptive risk in such a way as to require immediate review of the flavouring substance. However, if the hybrid level of the flavour is initially high, a large value for the consumption ratio implies an even larger level of risk that demands scrutiny. For these reasons, the method employs the following use of the consumption ratio in modifying initial assignments to hybrid priority levels:

1. Any substance placed in hybrid priority level 7 should not have that priority reduced by the consumption ratio. The presumptive risk is in no way reduced by heavy intake of the flavour from natural sources, but is increased. However, there is no need for a higher priority than the highest already available. Thus, all substances in hybrid priority level 7 remain there.
2. Substances in hybrid priority level 6 with a consumption ratio higher than 100 should be moved to priority level 7, since intake of the substance from natural sources requires review. Consumption ratios of less than 100 should have no effect.
3. At level 5, the consumption ratio should be without effect.
4. At hybrid priority level 4 and below (and for consumption ratios  $\geq 3.2$ ), the hybrid level of concern should be reduced by the logarithm (base 10) of the consumption ratio rounded up or down to the nearest integer (Table 2).

#### *Step 4: Adjustment for toxicological data*

The following are general guidelines for adjusting the hybrid priority levels using existing toxicological data:

Table 2. Effect of consumption ratios on hybrid priority levels of 4 and below

Consumption ratio (CR)	Log consumption ratio	Level reduction
CR $\geq$ 3200	$\geq 4$	-4 <sup>a</sup>
320 $\leq$ CR < 3200	3	-3 <sup>a</sup>
32 $\leq$ CR < 320	2	-2
3.2 $\leq$ CR < 32	1	-1
CR < 3.2	< 1	0

<sup>a</sup>The priority level should not be reduced below zero.

1. Seriously adverse data not previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives raise the substance to the highest priority level (level 7).
2. Adverse data weigh much more heavily than favourable data of equal quality.
3. Suggestive adverse data not clearly overridden by substantially more data of higher quality raise the substance by three priority levels, or to the highest level.
4. Data from studies in which the flavour was administered by non-oral routes or to non-mammalian species are given weight only in the absence of data on the effects of oral administration, unless there is evidence indicating that the former data are relevant to ingestion of the flavour.
5. Data from short-term (mutagenicity) tests have no weight unless, in the absence of data on the effects of chronic administration of the flavour, the results from two or more different tests are positive for mutagenicity.
6. A prior review of the substance by the Joint FAO/WHO Expert Committee on Food Additives that resulted in the setting of a specific (not temporary) ADI or an ADI "not specified" reduces the priority level to zero, unless new adverse toxicological data have since become available (see guideline 1).
7. Data from chronic studies of at least moderate quality, showing no adverse effects at feeding levels one thousand times the probable daily intake, reduce the priority of the substance by three levels, but not below zero.
8. Data from subchronic studies of at least moderate quality, showing no adverse effects at feeding levels one thousand times the probable daily intake, reduce the priority of a substance in priority level five or below by three levels, but not below zero.

9. Data from LD<sub>50</sub> tests have weight only in the absence of data from repeated-dose studies, and then only if the LD<sub>50</sub> is less than 100 mg/kg of body weight, in which case the priority should be raised to the highest level.
10. "Mixed" data, generally favourable but of poor quality and thus raising or leaving some questions, have no impact.
11. Data of poor quality have no weight unless seriously adverse (see guideline 1).

### **Application to a trial list of flavours**

#### *The basic inventory*

The approach to the ranking of flavours discussed above was tested by applying it to a trial list of 1229 synthetic flavouring ingredients currently added to food in the USA. A data base was created by merging files on food chemicals from the FDA computer with computer files from FEMA and from the US National Academy of Sciences. The resulting file resides in a d-Base III data base accessible by microcomputer. For each substance, it contains the chemical name; the FEMA identification number; the Chemical Abstracts Service Registry Number (to assure a unique identification); the compound's "exposure value" (total number of pounds "disappearing annually into the US food supply") reported under FDA contract by an industry survey conducted every five years by the US National Academy of Sciences; the FEMA chemical structure category and the FEMA concern level; the Redbook structure category and Redbook concern level; and the consumption ratio when available.

#### *Initial assignment to hybrid priority levels*

When the initial assignment into hybrid priority levels was performed, the 1229 flavours in the trial inventory were assigned to the levels shown in the second column of Table 3.

As can be readily seen, the method assigns only relatively few compounds to the highest levels, while the great majority of compounds are assigned to the lowest level. Thus, even at this stage of application, the method separates out, from a large inventory of compounds, a relatively small proportion that might be considered to be of high presumptive concern.

Table 3. Numbers of flavours assigned to priority levels

Priority level	Initial assignment	After adjustment for consumption ratio	After adjustment for toxicological data
7	7	10	11
6	44	41	22
5	29	29	19
4	104	65	62
3	127	120	119
2	918	684	700
1	0	89	86
0	0	191	210
<b>Totals</b>	1229	1229	1229

*Adjustment for consumption ratio*

When adjustments are made for the consumption ratio, the flavours are assigned the priority levels shown in the third column of Table 3.

*Adjustment for toxicological data*

The fourth column of Table 3 shows the effect of applying, on a tentative basis, the eleven guidelines for adjusting priority-level assignment on the basis of available toxicological data.

**Summary and conclusions**

The priority-setting method described here can be used for bringing forward for review specific flavours requiring further evaluation and possible assignment of ADIs. The system is intended as a means of priority-setting, not to provide determinations of safety. It is designed to apply to an inventory, of any size, of discrete chemical substances, and relies on simple and straightforward procedures. The initial screening methods for flavours, based only on chemical structure, human exposure, and consumption ratio, are intended to be generally applicable even in the absence of toxicological data. The assigned priority levels are then adjusted in the final stage on the basis of available toxicological data, by a procedure that allows for the use of summary information without detailed examination of raw data.

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**MATTERS ARISING FROM THE REPORTS  
OF SESSIONS OF THE CODEX COMMITTEE  
ON FOOD ADDITIVES (AND CONTAMINANTS)**

**Matters arising from the Nineteenth Session**

*1. Nutritional status and tolerable intakes for contaminants*

The Codex Committee on Food Additives inquired whether the tolerable intakes for contaminants set by the Joint FAO/WHO Expert Committee on Food Additives would be equally applicable to both well-fed and undernourished populations.

The Expert Committee, responding to this inquiry, noted that the question was complex, since undernourishment can have many causes and can manifest itself in different ways. If information was available on specific nutrient deficiencies, this was taken into account when tolerable intakes for contaminants were set. The Committee agreed that it would continue to take nutritional factors into account whenever data were available on specific contaminants.

*2. Acute effects of tin*

The Codex Committee asked the Joint FAO/WHO Expert Committee on Food Additives to provide information on the level of tin in food at which no acute effects (e.g., gastric irritation) are observed, taking into consideration the possible combined effects of acidity and the presence of high levels of iron. The Expert Committee considered the issue at its present meeting (see section 3.2 of the main report).

*3. Evaluation of cadmium, bis(2-ethylhexyl) phthalate, mercury, and methylmercury*

The Expert Committee responded to the Codex Committee's request for a re-evaluation of cadmium, bis(2-ethylhexyl) phthalate, and methylmercury (see section 3.2 of the main report). However, the Expert Committee was unable to comply with the request of the Codex Committee for the re-evaluation of inorganic mercury, because no new toxicological information was available.

4. *Non-allocation of ADIs for (i) substances for which no specifications exist and (ii) substances for which specifications exist but that have no known food use*

At its twenty-ninth meeting (1), the Expert Committee expressed the view that it had difficulty in evaluating a number of substances because of the absence of specifications for food-grade material or the absence of information on actual food use. In response to the request from the Codex Committee, the Expert Committee agreed that it would seek information from the Codex Committee before deciding not to allocate an ADI or to withdraw an existing ADI for a substance on the basis of no known use. The Expert Committee does not allocate ADIs to substances which have no specifications.

**Matters arising from the Twentieth Session**

1. *Definition of ADI*

The Codex Committee on Food Additives and Contaminants noted that in the *Principles for the safety assessment of food additives and contaminants in food* (2) the ADI was defined as an estimate (by the Joint FAO/WHO Expert Committee on Food Additives) of “the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk”. The definition of ADI contained in earlier documents of the Expert Committee (for example reference 3) did not contain the word “appreciable”.

The Expert Committee expressed the view that the definition of ADI contained in the *Principles for the safety assessment of food additives and contaminants in food* (2) was essentially the same as that contained in its earlier documents and would be applicable to all the food additives reviewed earlier.

2. *Use of chlorine as a flour-treatment agent*

The Codex Committee wanted a clarification of what the Expert Committee meant in its twenty-ninth report (1) when it stated that “when restricted to use in cake flour, the use of chlorine at levels of up to 2.5 g/kg flour would be acceptable”. The Codex Committee pointed out that this was not the way an ADI was normally expressed.

The Expert Committee expressed the view that the level of chlorine that it stated would be acceptable, when used as a flour-treatment agent, was not an ADI but was a treatment level, the safety of which was established by a toxicological study of cake made from treated flour. From the study, it was reasonable to infer the safety of other baked products made from such flour.

### 3. *Priority-setting for flavour evaluation*

The Codex Committee requested the Expert Committee to consider a proposed system for priority ranking of flavouring substances and in particular whether the method of adjustment for toxicological data was appropriate. It also requested the Expert Committee to consider whether the safety of flavouring substances could be evaluated using criteria based on less extensive data than normally required for food additives.

The Expert Committee expressed the view that the adjustment for toxicological data in the system proposed by the Codex Committee for priority-setting for flavour evaluation was appropriate (see section 5 of the main report).

The Expert Committee reiterated that special considerations apply to the evaluation of flavourings, and noted that the principles for evaluating food flavouring agents were described in detail in section 6.1.2 of reference (2).

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