WHO Technical Report Series
884

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Forty-ninth report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
Geneva 1999

WHO Library Cataloguing in Publication Data

Joint FAO/WHO Expert Committee on Food Additives (1997 : Rome, Italy)

Evaluation of certain food additives and contaminants : forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives.

(WHO technical report series ; 884)

1.Food additives — toxicity 2.Food contamination I.Title II.Series

ISBN 92 4 120884 8 (NLM Classification: WA 712)
ISSN 0512-3054

Typeset in Hong Kong
Printed in Spain
98/12076 — Best-set/Fotojae — 6000

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Rome, 17–26 June 1997

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

Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 40, 1998.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, Addendum 5. FAO Food and Nutrition Paper, No. 52, Add. 5, 1997.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 17 to 26 June 1997. The meeting was opened by Dr H. de Haen, Assistant Director-General, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr de Haen emphasized the importance of the work of the Committee and its impact on international trade and stressed the necessity for transparency in its deliberations. Dr de Haen highlighted the significance of accurate, comprehensive and concise reporting of the proceedings and deliberations of the Committee's meetings. He also stated that the scientific committees that advise the Codex Alimentarius Commission must have adequate expertise and experience to enable them to perform accurate and scientifically sound evaluations. FAO and WHO make every effort to ensure that the process for the selection of Committee members is open and transparent, and that this process results in the selection of highly qualified scientists in the fields of competence needed to make important decisions that affect the safety of the world's food supply.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been 48 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the forty-sixth meeting (Annex 1, reference *122*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);
— to undertake toxicological evaluations of certain food additives, food ingredients, flavouring agents and contaminants (sections 3, 4 and 5 and Annex 2);
— to review and prepare specifications for selected food additives and flavouring agents (sections 3, 4 and 6 and Annex 2);
— to assess the risks associated with aflatoxin contamination (section 5); and
— to consider approaches to evaluate the intake of food additives in the light of the recommendations of the Twenty-ninth Session of the Codex Committee on Food Additives and Contaminants (*2*) (section 2.4.2).

2.1 Modification of the agenda

The flavouring agents isoamyl alcohol, isoamyl formate and isoamyl acetate were removed from the agenda for toxicological evaluation because they had been evaluated at the forty-sixth meeting of the Committee (Annex 1, reference *122*). The flavouring agent geranyl 2-ethylbutanoate (*trans*-3,7-dimethyl-2,6-octadien-1-yl 2-ethylbutanoate) was on the agenda under the esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids; however, it was evaluated with the esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids. The flavouring agent 4-hydroxy-3-methyloctanoic acid γ-lactone was added for toxicological evaluation under the aliphatic lactones.

Sixty flavouring agents included on the agenda under the saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids and the aliphatic lactones were not considered for specifications at the present meeting. The specifications for these substances will be reviewed at a future meeting of the Committee at which food additives and contaminants are considered.

The Twenty-ninth Session of the Codex Committee on Food Additives and Contaminants (*2*) reviewed the specifications of identity and purity of selected food additives that had been prepared at the forty-sixth meeting of the Expert Committee (Annex 1, reference *122*). The Codex Committee referred back to the Expert Committee the specifications of nine compounds: citric acid, propylene glycol, allyl cyclohexane propionate (2-propenyl cyclohexane propanoate), ethyl nonanoate, ethyl octanoate, isoamyl acetate (3-methylbutyl acetate), isoamyl butyrate (3-methylbutyl butanoate), isoamyl isobutyrate (3-methylbutyl 2-methylpropanoate) and isoamyl isovalerate (3-methylbutyl 3-methylbutanoate); these were added to the agenda of the present meeting.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives, food ingredients, flavouring agents and contaminants, the Committee took into consideration the principles established and contained in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated subsequently at meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107*, *116* and *122*), including the present one. Environmental Health Criteria, No. 70 (Annex 1, reference *76*) embraces the major observations, comments

and recommendations on the safety assessment of food additives and contaminants contained, up to the time of its publication, in the 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 *Procedure for the Safety Evaluation of Flavouring Agents*

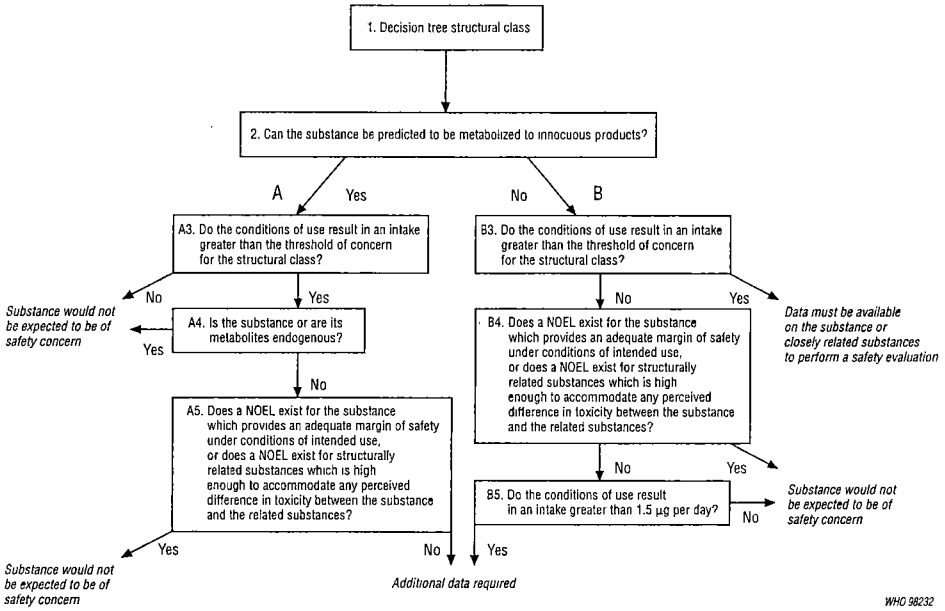
At its forty-sixth meeting (Annex 1, reference *116*), the Committee evaluated three groups of flavouring agents using a procedure based on that reviewed at its forty-fourth meeting (Annex 1, reference *122*). At the forty-sixth meeting, the Committee did not fully discuss the application of the last step on the right-hand side of the Procedure ("Do the conditions of use result in an intake greater than 1.5 μg per day?") to flavouring agents and this step was not considered. At that time, the Committee recommended that this step be considered at a future meeting at which food additives and contaminants were evaluated.

At its present meeting, the Committee considered the numbering of the various steps in the Procedure for the Safety Evaluation of Flavouring Agents. Concern was expressed about the numbering system used in the Procedure at the forty-sixth meeting, which implied that the two sides of the Procedure were parallel. To avoid this confusion, the Committee decided to prefix the steps on the left- and right-hand sides of the Procedure with the letters "A" and "B" respectively.

At its present meeting, the Committee also considered a paper that will be published in the WHO Food Additives Series (*3*) that provided further information relating to the derivation of the value of 1.5 μg per person per day. The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 μg per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ("Do the conditions of use result in an intake greater than 1.5 μg per day?") (Fig. 1). The Committee

Figure 1

Procedure for the Safety Evaluation of Flavouring Agents adopted by the Committee at its present meeting



recognized that flavouring agents with unresolved toxicity problems could be evaluated by steps B3, B4 and B5 of the Procedure, but reaffirmed its view, expressed at the forty-sixth meeting, that as with any scheme, its application calls for judgement, and it should not replace expert opinion; the Committee therefore reserved the right to use alternative approaches when data on specific flavouring agents warranted such action.

During its present meeting, the Committee used the Procedure for the Safety Evaluation of Flavouring Agents given in Fig. 1.

In applying the Procedure at the present meeting, a number of general issues were raised.

Consideration of flavouring agents as groups

The flavouring agents were evaluated by the Committee in groups of structurally and/or metabolically related substances. Systematic changes in structure are the basis for understanding the effect of structure on the chemical and biological properties of a substance (Annex 1, reference *117*, Annex 5). When the Procedure is being used, the evaluation of flavouring agents in groups facilitates the consideration of common pathways of metabolism which apply to

members of a group. For substances which share common metabolites, consideration should be given to the total intake from all related substances. The total intake of such related flavouring agents, either from within the same group or across groups, should be evaluated where assessment of the intake data and toxicological profile warrant a combined appraisal. Total intakes should be considered for substances which produce the same potentially toxic metabolite (for example the esters of allyl alcohol considered at the forty-sixth meeting of the Committee (Annex 1, reference *122*)). The Committee concluded that flavouring agents which produce metabolites that are innocuous and endogenous would not be of safety concern, providing that the total intake from all related substances was judged not to give rise to perturbations outside the normal physiological range. Evaluations of such theoretical combined intakes should also take into account, where possible, the likelihood of the different flavouring agents being consumed together.

Natural occurrence

Some substances used as flavouring agents also occur as natural constituents of food; the influence of natural occurrence on the application of the Procedure was considered at the forty-fourth meeting of the Committee (Annex 1, reference *117*, Annex 5). Intakes from use as flavouring agents should be considered relative to the intakes from natural sources. This is a complex issue and interpretation of data on natural occurrence is dependent on:

— the nature of the flavouring substance and its structural class (step 1);
— the natural source of the substance;
— the intake from natural sources; and
— the proportion of the total intake accounted for by its use as a flavouring agent.

As a consequence the intake of such naturally occurring substances should be considered on a case-by-case basis.

Data on intakes of flavouring agents

The only estimates of intake of flavouring agents available to the Committee were derived from surveys in Europe and the USA. The Committee would welcome additional information on intakes of flavouring agents from other geographical regions. The Committee noted that the evaluations performed to date using the Procedure have been based on intake estimates available at the meeting at which the flavouring agents were considered and that changes in intake might warrant re-evaluation of a flavouring agent. The Committee

recommended that information on intakes be updated periodically to ensure the validity of the safety evaluations, particularly for flavouring agents for which the annual volume of production is variable.

The Committee considered that the estimation of intakes based on production data is a practical and realistic approach. Further consideration of intake should be given to flavouring agents for which there are high reported levels of use in some foods or beverages, but low intakes when calculated from production data. This would be particularly important for flavouring agents with intakes calculated to be only slightly below one of the threshold criteria in the evaluation process (i.e. steps A3, B3 or B5). However, the Committee recognized that estimation of intakes of flavouring agents based on reported levels of use would require detailed information on the specific products in which the flavouring agent is used, the actual levels of use and the intake of the individual food products containing the flavouring agent by consumers of both average and above average quantities of these foods.

2.2.2 *Role of the Committee in the risk analysis process of the Codex Alimentarius Commission*

The Committee welcomed the acknowledgement by the Codex Alimentarius Commission of the continuing need for the Joint FAO/WHO Expert Committee on Food Additives and the Joint FAO/WHO Meeting on Pesticide Residues to provide risk assessments to the Codex Alimentarius Commission (*4*). The Committee wished to emphasize the essential role of the expert scientific judgements provided by scientific committees as the basis for risk assessment. Such expertise will be of increasing importance for future developments in understanding the scientific basis of risk assessment, such as mechanisms of toxicity, differences between test species and humans, and human diversity and genetic variability. The Committee will continue to welcome developments in methods of risk assessment which will provide a more sound scientific basis to the advice that it provides to the Codex Alimentarius Commission.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *Significance of identity and purity requirements*

The Committee noted that the specifications monographs contain requirements under two subheadings, "identity tests" and "purity tests", and it emphasized that substances should meet all require-

ments listed under these headings. The meanings of "identification" and "purity" are both clearly defined in FAO Food and Nutrition Paper No. 5, Rev. 2 (Annex 1, reference *100*).

2.3.2 *Limits for arsenic, lead and other heavy metals*

In keeping with its previously stated intentions (Annex 1, references *116* and *122*) regarding limits for arsenic, lead and other heavy metals, the Committee considered four issues:

— the lack of specificity in the current limit test for heavy metals (expressed as lead) and the potential loss of metals during the dry ashing procedure, both of which compromise the validity of the test;
— the need to replace the general test for heavy metals with tests for specific metals, particularly for lead, cadmium, mercury and arsenic;
— the need for more specific and sensitive analytical methods, such as atomic absorption spectroscopy (including the graphite furnace technique) and for improved methods of sample preparation; and
— the need to consider the amount of a food additive consumed and its potential for contamination by specific heavy metals.

In order to address these issues in greater depth the Committee will seek information on the specific content of heavy metals in food additives as well as on methods of analysis. At the present meeting, the Committee decided to delete specifications for limits for heavy metals (expressed as lead) from specifications monographs where a specification for lead was available.

2.3.3 *Analytical methods*

Alternative methods

The Committee's policy has been to describe only one analytical method for an analyte with a limit in the specifications. However, the Committee has now concluded that in some instances the inclusion of alternative methods may be desirable for reasons of economy or simplicity. For example, the use of nuclear magnetic resonance spectroscopy has been presented as an alternative to gas chromatography for the method of assay in the specifications monograph on salatrim, because of the comparative simplicity of the sample preparation and instrumental analysis.

Methods of determining residual solvents and other volatile substances

The Committee observed that a number of specifications require analysis for volatile substances such as residual solvents and reaction

by-products. However, many of the analytical methods are out of date. The Committee wishes to encourage the use of improved techniques such as headspace gas chromatography, and in the future will expect descriptions of such methods to be supplied as part of information for revised or new specifications.

References to standard methods

During the revision of existing specifications the Committee noted that several references have been made to published standard analytical procedures (e.g. American Society for Testing and Materials (ASTM) methods) instead of providing full descriptions of the methods. One such reference was also included in a new monograph prepared at this meeting. The Committee concluded that in future such references should be replaced by a complete description of the methods.

2.3.4 *Enzymes derived from genetically modified organisms*

The Committee designated as "tentative" new specifications for two enzyme preparations derived from genetically modified organisms. This decision was made because Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*, section 2.3.4), referred to in the specifications, is itself tentative. The Committee decided to review Appendix B at its next meeting in 1998 and subsequently to re-evaluate the specifications for enzyme preparations which refer to Appendix B.

The Committee requested comments on Appendix B, to be reviewed in 1998.

2.3.5 *Flavouring agents*

The Committee was asked to consider the specifications for 224 flavouring agents at the present meeting, of which 60 were transferred to the agenda for a future meeting. It decided to modify the tabular format for the specifications for flavouring agents adopted at the forty-sixth meeting (Annex 1, reference *124*). Special methods of analysis and spectra will continue to be included as appendices to the table of flavouring agents. Where a substance has a function in addition to that of a flavouring agent, a standard specification format will be included.

The common names, chemical names and synonyms will be used to index the substances. A new identification number was allocated to

each substance for the convenience of the Committee and an identification number will also be allocated to each substance evaluated in the future. The Committee proposed to develop a classification by chemical group, for ease of future safety evaluations.

2.4 Principles governing intake assessments of food additives and contaminants

The Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (*4*) recognized that assessments of the intake of food additives, contaminants and residues of pesticides and veterinary drugs should be considered an integral part of the risk assessment process for these substances. At its present meeting, the Committee also recognized the importance of assessments of dietary intake in characterizing any potential risks posed by food additives and contaminants.

2.4.1 *Methods for assessing dietary intake*

The Committee agreed with the conclusion of the FAO/WHO Consultation on Food Consumption and Exposure Assessment to Chemicals (*5*) that, in principle, the estimation of potential dietary intakes is the same for all food chemicals. However, because of differences in their occurrence in the food supply, assessments of intake of food additives and contaminants may be based on different types of data on consumption of food and on occurrence of chemicals in food. The procedures developed for pesticide residues are applicable to assessments of the dietary intake of contaminants which also occur in raw agricultural commodities (*6*). These procedures were employed in the assessment of the intake of aflatoxins (section 5).

In most cases, assessments of the intake of food additives are conducted using data on consumption of processed foods. For certain food additives, "poundage" data may be used to estimate per capita intake. Five main approaches for assessing dietary intake of food additives have been used by countries at the national level (*7*, *8*). These approaches usually overestimate chronic (long-term) daily intake, and this could compensate for potential differences in intake between population subgroups and for day-to-day fluctuations in individuals. The five approaches are summarized below.

The budget method

This method takes into account the physiological requirements for energy and fluid in estimating consumption of foods in solid and liquid form. The Committee emphasized that the budget method is

not a procedure for estimating food additive intake *per se*. However, because of its simplicity it is generally accepted as an appropriate screening tool at the international or national level for the identification of food additives that require further assessment.

The "poundage" approach
This approach uses statistics on usage of food additives, adjusted for imports, exports and non-food uses.

The food balance sheet/household survey approach
This method is based on food available for consumption either at a national or household level. Food balance sheets are adjusted for the proportion of each raw commodity that is processed and likely to contain the food additive being studied.

The model diet approach
This method is used to construct a model diet from information on food consumption for a selected population subgroup.

Individual dietary records
These methods use data from representative national surveys of individual food consumption.

These approaches are listed in the order of their increasing ability to accurately predict dietary intake. However, increased accuracy requires more comprehensive data on food consumption and use of food additives as well as greater resources for the assessment of dietary intake. Other approaches for assessing intake such as duplicate diet studies and total diet studies may also be used.

2.4.2 *Assessment of dietary intake of specific additives*

The Committee was requested at the Twenty-ninth Session of the Codex Committee on Food Additives and Contaminants (*2*) to perform assessments of the intake of five food additives: benzoic acid and its salts, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), *tert*-butylhydroquinone (TBHQ) and sulfites. These food additives have been identified for priority assessment by the Codex Committee because initial assessments indicate that intakes of these food additives may approach or exceed the ADIs established by the Expert Committee.

Information on national assessments of the intake of these five food additives will be requested from countries based on procedures developed by the Committee. The Committee recommended that an evaluation of intake assessments from various countries should be

undertaken at the next meeting of the Committee at which food additives and contaminants are considered. The likely intakes of these substances on a global basis will be assessed to respond to the request of the Codex Committee to provide guidance on the potential for the intakes of these food additives to exceed their ADIs.

3. Specific food additives and food ingredients

The Committee evaluated three food additives and one food ingredient for the first time and re-evaluated several food additives and aflatoxins considered at previous meetings. In addition, the Committee evaluated a large number of flavouring agents using the Procedure for the Safety Evaluation of Flavouring Agents (section 2.2.1). Information on the evaluations and on specifications is summarized in Annex 2.

3.1 Antioxidant: *tert*-butylhydroquinone (TBHQ)

tert-Butylhydroquinone (TBHQ) was previously evaluated by the Committee at its nineteenth, twenty-first, thirtieth, thirty-seventh and forty-fourth meetings (Annex 1, references *38*, *44*, *73*, *94* and *116*). At the forty-fourth meeting, the previously established temporary ADI of 0–0.2 mg/kg of body weight was extended, pending results from long-term toxicity studies in rodents. This ADI was derived from a no-observed-effect level (NOEL) of 1500 mg/kg in the diet (equivalent to 37.5 mg/kg of body weight per day) in a 117-week feeding study in dogs on the basis of haematological changes observed at the next highest dose level of 5000 mg/kg in the diet. At its present meeting, the Committee reviewed the results of the long-term toxicity studies in mice and rats. In addition, new information relating to the metabolism of TBHQ, its effects on the induction of enzymes, and its short-term and reproductive toxicity in rodents was available for review. The results from the long-term study in dogs and the genotoxicity studies relating to the clastogenic potential of TBHQ were also re-evaluated.

In studies reviewed at earlier meetings of the Committee (Annex 1, references *39* and *117*), TBHQ was shown to be extensively absorbed and rapidly excreted following ingestion by rats, dogs and humans. The major urinary metabolites in all three species were the *O*-sulfate and *O*-glucuronide conjugates, with the former predominating. In numerous *in vitro* studies, TBHQ was shown to induce the activity of phase II enzymes, including glucuronosyl transferase and glutathione transferase, by a mechanism independent of the *Ah* receptor.

Induction of hepatic glutathione transferase activity was also demonstrated following short-term administration of TBHQ in the diet of female mice.

TBHQ also undergoes redox cycling with the corresponding quinone, accompanied by the production of reactive oxygen species. In a study reviewed at the present meeting, three glutathione conjugates of TBHQ were identified in the bile of male rats and sulfur-containing metabolites of TBHQ were detected in the urine. In other studies, glutathione conjugates of TBHQ demonstrated higher redox cycling activity than unconjugated TBHQ, and were toxic to the kidney and bladder when administered intravenously to male rats.

In a new 13-week feeding study conducted in mice, significant treatment-related effects were noted in both sexes. These effects were decreased body-weight gain and hyperplasia of the mucosal epithelium of the forestomach. The latter effect was noted only at very high doses of TBHQ; 20 g/kg in the diet (equal to 4000 mg/kg of body weight per day) and above. The NOEL was 870 mg/kg of body weight per day. In a 13-week feeding study conducted in rats continuously exposed to TBHQ, starting *in utero*, treatment-related haemosiderin pigmentation of the spleen was noted in both sexes. In addition, there was a treatment-related increase in atrophy of the red pulp of the spleen in female rats receiving 2.5 and 5 g/kg in the diet. Bone marrow and haematological parameters were not altered at these doses. Hyperplasia of the forestomach was not observed in this study, even at the highest dose tested; 10 g/kg in the diet (equal to 800 mg/kg of body weight per day), although it has been noted in another study in adult rats following short-term administration of TBHQ at 20 g/kg in the diet. Treatment with TBHQ had no effect on the estrous cycle or on the histological appearance of the reproductive organs. Because pigmentation of the spleen was noted in female rats at the lowest dose tested, a NOEL could not be established, but the lowest-observed-effect level (LOEL) was 190 mg/kg of body weight per day. Irritation and hyperplasia observed in the nasal epithelium of both rats and mice and on the skin of mice were considered to be the consequence of direct contact with TBHQ from the diet.

The results of two recently conducted carcinogenicity studies were reviewed. In female mice, TBHQ induced an increase in the incidence of hyperplasia of the thyroid follicular cells at all dose levels. A non-significant increase in follicular cell adenomas was reported at the highest dose of 5 g/kg in the diet (equal to 600 mg/kg of body weight per day) but the incidence was within the range of historical controls. No follicular cell carcinomas were observed. Decreased body-weight

gains were also observed at the highest dose in both sexes. Since the Committee was aware that hydroquinone (the unsubstituted parent compound) induces thyrotoxicity in mice, but not rats (*9*), it considered that the hyperplasia of the follicular cells observed with TBHQ in this study might be a toxicologically significant effect. Consequently, it concluded that a NOEL could not be identified in this study and that the lowest dose of 1.25 g/kg in the diet, equal to 130 mg/kg of body weight per day, represented the LOEL. In the study in rats, toxicologically significant effects were noted only at the highest dose tested, 5 g/kg in the diet (equal to 220 mg/kg of body weight per day); these effects were an increase in the incidence of hyperplasia of transitional cells and suppurative inflammation of the kidneys of male rats and haemosiderin pigmentation of the spleen of the females. The Committee considered that 2500 mg/kg in the diet, equal to 110 mg/kg of body weight per day, represented the NOEL and that TBHQ was not carcinogenic in mice or rats.

The 117-week study on dogs in which the temporary ADI had been based was re-evaluated in the light of supplementary information requested from its authors. On the basis of actual intake data, nominal levels of 500, 1580 and 5000 mg/kg in the diet were equal to doses of 21, 72 and 260 mg/kg of body weight per day. In dogs of both sexes given the highest dose, statistically significant reductions in haemoglobin concentrations and erythrocyte volume fractions were observed at several sampling intervals throughout the study, although the values were within the ranges in historical controls. Red blood cell counts were also significantly decreased in male and female dogs in the highest-dose group at week 112, the only time at which measurement of this parameter was reported. Increases in the reticulocyte count (as a percentage of red blood cells) and the presence of immature red blood cell forms in the peripheral blood of animals from all treated groups, reported to occur late in the study, were not dose-related nor were they accompanied by changes in red blood cell parameters at 500 and 1580 mg/kg in the diet. On the basis of this re-evaluation, the Committee confirmed that the NOEL for long-term toxicity in dogs was 1580 mg/kg in the diet, equal to 72 mg/kg of body weight per day.

In view of the conflicting results of the genotoxicity assays reviewed at previous meetings of the Committee, many of the studies of TBHQ were re-evaluated at the present meeting with respect to the validity of the protocol and interpretation of data. The conclusions of a number of the studies could no longer be supported. The results of the well conducted studies indicated that TBHQ was clastogenic *in vitro* in the absence or presence of metabolic activation, but did not induce

the formation of micronuclei *in vivo*. In sister chromatid exchange assays, TBHQ was positive in mice *in vivo* and in an *in vitro* system. The results from several studies suggested that damage to DNA resulting from exposure to TBHQ, including chromosome loss and breakage, was secondary to the production of reactive oxygen species. In the light of this information, and the fact that TBHQ was not carcinogenic in rats or mice, the Committee concluded that TBHQ was unlikely to be genotoxic *in vivo* under conditions of use as an antioxidant, and that further genotoxicity studies were unnecessary.

The results of four reproductive toxicity studies in rats were evaluated. Taken together, the results of these studies indicated an adverse effect of TBHQ on the survival and/or body weight of pups at levels of 5 g/kg in the diet or higher. The effect on pup body weight occurred late in the lactation period. The NOEL was 2.5 g/kg in the diet, equivalent to 125 mg/kg of body weight per day.

On the basis of the data reviewed at the present meeting, the Committee concluded that TBHQ was not carcinogenic in rats or mice. After reviewing the long-term toxicity studies in mice, rats and dogs and the reproductive toxicity studies in rats, the Committee concluded that the most sensitive species was the dog. The Committee allocated an ADI of 0–0.7 mg/kg of body weight for TBHQ, based on the NOEL of 72 mg/kg of body weight per day and a safety factor of 100. The NOEL was rounded to one significant figure, as is the usual practice.

A toxicological monograph incorporating new information and relevant information from the earlier toxicological monographs and monograph addenda was prepared. The existing specifications were revised, with minor changes.

3.2 Emulsifiers

3.2.1 *Microcrystalline cellulose*

Microcrystalline cellulose was evaluated at the fifteenth, seventeenth and nineteenth meetings of the Committee (Annex 1, references *26*, *32* and *38*). At the nineteenth meeting, an ADI "not specified" was allocated. In the light of concern about possible persorption and consequential adverse effects of fine particles, the substance was re-evaluated at the present meeting.

In early studies persorption of microcrystalline cellulose was reported in various species including rats. A recent study in which a special

preparation of fine particle size of microcrystalline cellulose (median diameter 6 μm) was administered orally to rats (5 g/kg of body weight per day) for 90 days has failed to confirm the earlier observations. In this study precautions were taken to ensure that there was no cross-contamination of the tissues with fine particulate matter at autopsy.

In various acute toxicity studies in animals given microcrystalline cellulose parenterally there have been signs consistent with a tissue response to foreign particles. Similarly microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously by drug abusers. No such lesions have been described as a consequence of oral ingestion of microcrystalline cellulose by rats or humans.

In 90-day toxicity tests during which microcrystalline cellulose was administered to rats at concentrations of 25 g/kg to 500 g/kg in the diet, increased consumption of food to compensate for the low energy content of this material was observed. Although this may have some adverse effects on mineral absorption there was, in general, no compound-related systemic toxicity. The NOEL was 50 g/kg in the diet, equal to 3.8 g/kg of body weight per day.

A 2-year study in rats, which were fed microcrystalline cellulose in the diet, was brought to the attention of the Committee. Despite a lack of evidence of toxic effects, the Committee considered that the execution and reporting of the study were not adequate to identify a NOEL. *In vitro* and *in vivo* genotoxicity studies were negative.

In a 3-generation reproductive toxicity study in rats that had been reviewed by the Committee at its fifteenth meeting (Annex 1, reference *27*), there were some effects in animals given microcrystalline cellulose at 300 g/kg in the diet; these were considered to be a consequence of the quantity of material reducing the energy density of the diet. In recent embryotoxicity and teratogenicity studies in rats, there was no evidence of treatment-related effects at levels of up to 50 g/kg in the diet (equal to 4.6 g/kg of body weight per day), given on days 6 to 15 of pregnancy.

In some studies in humans there have been reports of alterations in gastrointestinal function following ingestion of microcrystalline cellulose. The changes do not appear to be related to systemic toxicity. The Committee concluded that the toxicological data from humans and animals provided no evidence that the ingestion of microcrystalline cellulose can cause toxic effects in humans when used in foods according to good manufacturing practice.

It is recognized that small particles of other materials may be persorbed and that the extent of persorption is greater with very small particles (<1 μm in diameter). Despite the absence of any demonstrated persorption of microcrystalline cellulose in the recent study in rats, the Committee, as a precautionary measure, revised the specifications for microcrystalline cellulose at the present meeting to limit the content of particles less than 5 μm in diameter. The Committee retained the ADI "not specified" for microcrystalline cellulose conforming to these specifications.

A toxicological monograph that incorporated the updated earlier monograph and summaries of studies reviewed for the first time at the present meeting was prepared. The existing specifications were revised and the requirement for particle size was changed from "greater than 5 μm" to "not more than 10% of the material has a particle size of less than 5 μm".

3.2.2 *Sucrose esters of fatty acids and sucroglycerides*

Sucrose esters of fatty acids and sucroglycerides were previously reviewed by the Committee at its thirteenth, seventeenth, twentieth, twenty-fourth, thirty-fifth, thirty-ninth and forty-fourth meetings (Annex 1, references *19*, *32*, *41*, *53*, *88*, *101* and *116*). At the forty-fourth meeting, the NOEL from a new long-term toxicity/carcinogenicity study in rats was used as the basis for the ADI. The sucrose ester formulations used in this study contained no monoglycerides or diglycerides and the highest dose tested was 50 g/kg in the diet, equal to 1970 mg/kg of body weight per day. Because the results from a tolerance study in humans raised some concerns about potential laxative effects and related abdominal symptoms, a temporary group ADI of 0–20 mg/kg of body weight was established for the sucrose ester content of sucrose esters of fatty acids and sucroglycerides, based on the long-term toxicity study in rats and a safety factor of 100. The results of a well designed and conducted tolerance study in humans were requested for review in 1997.

In the previous study in humans, single doses of 1.5–3.0 g, or divided doses of 3.0–4.5 g per day for 5–7 days, induced laxation and related abdominal symptoms. The results from a new study in humans indicated an absence of effects of sucrose esters of fatty acids on the frequency and appearance of faeces and related abdominal symptoms in men and women ingesting a divided daily dose of 1.5 g of sucrose esters of fatty acids (equal to 27 and 29 mg/kg of body weight per day, respectively) for 5 days. Even though the deficiencies in design noted in the earlier study, i.e. the small number of subjects and the lack of

proper controls, were corrected in the new study only a single dose level was used, which was below that previously associated with gastrointestinal disturbances. Consequently, it was not possible to confirm that the effects observed in the previous study were the result of treatment with sucrose esters of fatty acids.

The Committee noted that no systemic effects were observed in a well conducted long-term toxicity study in rats up to the highest dose tested, 1970 mg/kg of body weight per day. Consequently, a group ADI of 0–30 mg/kg of body weight for sucrose esters of fatty acids and sucroglycerides was allocated on the basis of the new study in humans without the application of a safety factor.

An addendum to the toxicological monograph was prepared. The existing specifications for sucrose esters of fatty acids and sucroglycerides were revised, with minor changes.

3.3 Enzyme preparations

3.3.1 *α-Acetolactate decarboxylase*

α-Acetolactate decarboxylase is an enzyme produced by submerged fermentation of *Bacillus subtilis* carrying the gene coding for α-acetolactate decarboxylase from *B. brevis*. It is used as a processing aid in the brewing and alcohol industry to avoid formation of the unpleasant tasting α-diacetyl from α-acetolactate during fermentation.

α-Acetolactate decarboxylase expressed in *B. subtilis* has not been previously evaluated by the Committee.

Data reviewed by the Committee included information on the pathogenicity of the source and donor organisms as well as short-term toxicity and genotoxicity studies on the enzyme preparation.

Two forms of α-acetolactate decarboxylase have been used in the toxicity studies, namely, an unstabilized form and a glutaraldehyde-stabilized form, which is the form used in the final commercial product.

The available data indicate that both the source organism, *B. subtilis*, and the donor organism, *B. brevis*, are considered to be non-pathogenic species. *B. subtilis* was grown under properly controlled conditions in media containing ingredients commonly used in the production of food-grade substances by fermentation. The vector, pUB110, is a plasmid commonly used in the construction of recombinant microorganisms in the production of enzymes and was not considered to be of toxicological concern.

The pathogenicity of four strains of *B. subtilis* involved either in the construction of the recombinant strain or in the production of α-acetolactate decarboxylase was tested in a study in mice given a single dose by the intraperitoneal route. There were no clinical symptoms related to treatment, and no pathological changes were noted at the end of the study that could be associated with treatment.

The Committee considered the recombinant DNA procedures used, and concluded that the recombinant strain of *B. subtilis* should be regarded as a safe source of α-acetolactate decarboxylase.

Administration of α-acetolactate decarboxylase in the diet to rats in a 14-day and a 13-week study was not associated with any signs of toxicity at dietary levels equivalent to 2500 mg/kg in the feed (14-day study) or 500 mg/kg in the feed (13-week study) for either the unstabilized or stabilized enzyme. No long-term toxicity studies were available. In genotoxicity studies, negative results were obtained with both unstabilized and stabilized α-acetolactate decarboxylase in *in vitro* gene mutation assays in bacteria and mammalian cells and in a chromosomal aberration assay in human lymphocytes.

On the basis of the toxicological data, the Committee concluded that α-acetolactate decarboxylase is an enzyme of low toxicity and that no further studies are required to assess its safety.

The Committee established a temporary ADI "not specified" for α-acetolactate decarboxylase from this recombinant strain of *B. subtilis* when the preparation is used in accordance with good manufacturing practice. A temporary ADI was allocated, pending consideration of the "tentative" qualification of the specifications.

A toxicological monograph was prepared. New specifications were prepared and designated as "tentative" because of the tentative qualification of Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*, section 2.3.4).

3.3.2 *Maltogenic amylase*

The enzyme under evaluation is a maltogenic amylase produced by submerged fermentation of a non-pathogenic and non-toxicogenic strain of *Bacillus subtilis* which contains the *amy*M gene from *B. stearothermophilus* coding for maltogenic amylase.

Maltogenic amylase expressed in *B. subtilis* has not been previously evaluated by the Committee.

Formulations of maltogenic amylase are used in the baking and starch industry. It is an exo-acting maltogenic amylase enzyme (EC 3.2.1.133, glucan 1,4-α-maltohydrolase), which catalyses the hydrolysis of 1,4-α-glucosidic linkages in amylose, amylopectin and related glucose polymers. Maltose units are successively removed from the non-reducing end of the polymer chain until the molecule is degraded or, in the case of amylopectin, until a branch point is reached. The Committee noted that the human intake of this recombinant maltogenic amylase resulting from its intended use in the baking and starch industry would be low and that the material consumed would not be the active maltogenic amylase but a heated, denatured material.

The data reviewed included the genetic modification procedures employed, characterization of the producing organisms, the fermentation process, acute and short-term toxicity studies in animals, and genotoxicity studies.

The Committee noted that well documented non-pathogenic and non-toxicogenic strains of microorganisms (*Bacillus subtilis*, *Escherichia coli* K12 and *B. stearothermophilus*) had been used in the genetic modification procedures. The final vector used (pUB110) is well characterized and has been used for several years as a cloning vehicle for *B. subtilis*. The plasmid construct pDN1413, containing the *amy*M gene, was introduced into *B. subtilis* (a derivative of strain 168) using standard transformation procedures. Although the plasmid pDN1413 carries the gene for kanamycin resistance, it is unlikely that this gene can be transferred, since it is well integrated into the host genome and no plasmid DNA could be detected in the end-product. The entire DNA sequence of pDN1413 was determined, which confirmed that genes coding for shiga-like toxins are not present.

B. subtilis was grown under properly controlled conditions in media containing ingredients commonly used in the production of food-grade substances by fermentation.

From the evaluation of the recombinant DNA procedures being employed, the Committee concluded that the final construct should be regarded as a safe source of maltogenic amylase.

The product tested in the toxicological studies was a concentrated material with an enzyme activity of 35900 units/g. It was produced according to the standard production process except that the formulation/standardization step was omitted and the product was lyophilized.

In a 90-day study in which the lyophilized test compound was administered in the diet of rats, the highest dose, 50 g/kg in the diet, caused a significant reduction in body-weight gain accompanied by a slight decrease in food consumption in both males and females. A significant decrease in thyroid weights was also seen in both males and females. At the next dose, 15 mg/kg in the diet, no statistically significant treatment-related findings were observed. The NOEL in this study was 15 g/kg in the diet, equal to 1200 mg/kg of body weight per day.

The test compound had no effects in *in vitro* gene mutation studies in bacteria or mammalian cells, and the results of chromosomal aberration tests *in vivo* and *in vitro* were consistently negative.

The test compound did not cause skin or eye irritation in rabbits and did not produce skin sensitization in a delayed-contact hypersensitivity assay in guinea-pigs.

The Committee allocated a temporary ADI "not specified" to maltogenic amylase derived from this recombinant strain, pending deletion of the "tentative" qualification of the specifications.

A toxicological monograph was prepared. New specifications were prepared and designated as "tentative" because of the tentative qualification of Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*, section 2.3.4).

3.4 Flavouring agent: *trans*-anethole

trans-Anethole was previously reviewed by the Committee at its eleventh, twenty-third, twenty-seventh, twenty-eighth, thirty-first, thirty-third, thirty-seventh and thirty-ninth meetings (Annex 1, references *14*, *50*, *62*, *66*, *77*, *83*, *94* and *101*). At the thirty-seventh meeting, a temporary ADI of 0–0.6 mg/kg of body weight was allocated on the basis of the results of a long-term toxicity/carcinogenicity study in Sprague–Dawley rats. In this study, a dose-related increase in the incidence of non-neoplastic proliferative lesions in the liver was observed in both males and females at all doses. In addition, a clear increase in the incidence of hepatocellular adenomas and carcinomas was observed in female rats receiving *trans*-anethole at the highest level, 10 g/kg in the diet (equal to 550 mg/kg of body weight per day). In male animals a slight increase in the incidence of hepatocellular adenomas but not carcinomas was observed at 10 g/kg in the diet (equal to 400 mg/kg of body weight per day).

At the thirty-ninth meeting, the Committee was informed that comparative metabolic studies in mice and rats, studies on the effects of long-term dietary administration of *trans*-anethole on hepatic enzyme induction and cell proliferation in these species and on enzyme induction in humans, and *in vitro* cytotoxicity and genotoxicity studies were in progress. The temporary ADI was extended to 1997, pending the completion of these studies and the results of a long-term study in mice at appropriate levels to establish a no-effect level.

Not all of the requested studies were available for review at the present meeting. The Committee was informed that further studies would be available by 1998.

The Committee extended the previously allocated temporary ADI of 0–0.6 mg/kg of body weight until 1998, pending the submission of the results of the remaining studies.

No toxicological monograph was prepared. The specifications were revised and, as *trans*-anethole is used only as a flavouring agent, they were transferred to the list of flavouring agents in the *Compendium of food additive specifications, Addendum 5* (FAO Food and Nutrition Paper, No. 52, Add. 5, 1997).

3.5 Glazing agent: hydrogenated poly-1-decene

Hydrogenated poly-1-decene has not been previously evaluated by the Committee. It is used as a glazing and releasing agent.

The Committee considered that the data available from a 28-day range-finding study and a 90-day study in which hydrogenated poly-1-decene was administered in the feed of rats were inadequate to support the use of this product as a food additive. Considering the potentially high intake from its use, the Committee concluded that adequate data are required to establish that oily coats observed in rats fed hydrogenated poly-1-decene are not the result of systemic absorption. In addition, data in humans that clearly demonstrate the lack of absorption of this substance should be provided. In the absence of these data, long-term toxicity and reproductive toxicity studies and information on the metabolism, distribution and excretion of hydrogenated poly-1-decene would be required.

A toxicological monograph was not prepared. New specifications were prepared.

3.6 Sweetening agent: maltitol syrup

At the present meeting, the Committee reviewed a request for the amendment of the specifications for maltitol syrup in the context of its

toxicological implications. The current specifications (Annex 1, reference *124*) to which the ADI "not specified" applies (Annex 1, references *83* and *107*) require that maltitol syrup has a maltitol content of no less than 50%, a sorbitol content of no more than 8%, a maltotriitol content of no more than 25% and a content of hydrogenated polysaccharides containing more than three glucose or glucitol units of no more than 30%. An ADI "not specified" was allocated to maltitol syrup produced from glucose syrups that meet these specifications at the thirty-third meeting of the Committee (Annex 1, reference *83*) and confirmed at the forty-first meeting (Annex 1, reference *107*).

The proposed amendment would support the use of a broader range of starch hydrogenation products than are currently permitted. By deletion of the specification tests for hydrogenated saccharides other than maltitol, while still requiring a maltitol content of no less than 50.0% and a total polyol content of no less than 99.0%, the content of any of these components in malititol syrup (sorbitol, maltotriitol and higher-order polyols) could theoretically be as high as 49%. Since an ADI "not specified" has been established for both sorbitol and maltitol, the toxicological review concentrated on the consequences of high concentrations of the higher-order hydrogenated saccharides.

The results of metabolic studies in rats and humans indicated that the higher-order polyol components in hydrogenated starch hydrolysates of differing composition were efficiently hydrolysed in the gastrointestinal tract to glucose and a small amount of maltitol. Maltitol was hydrolysed less readily by endogenous enzymes and a considerable portion undergoes fermentation in the lower gastrointestinal tract. The small amount that is absorbed is rapidly excreted unchanged in the urine.

Studies in animals treated with maltitol syrup composed of up to 41% higher-order polyols were reviewed at the twenty-ninth meeting of the Committee (Annex 1, reference *70*). At its present meeting, the Committee reviewed the toxic potential of two materials that contain more than 49% of the hydrogenated polysaccharides, the first containing 10% sorbitol, 8% maltitol and 82% higher-order polyols and the second containing 100% hydrogenated dextrin, were evaluated in studies in which they were fed to animals, and the mutagenic potential of hydrogenated dextrin was also examined in bacterial assays. A study in rats showed that ingestion of up to 5.2 g/kg of body weight per day of hydrogenated dextrin for 13 weeks did not result in any treatment-related effects. No treatment-related toxicity was seen in

rats or dogs when the material containing 10% sorbitol, 8% maltitol and 82% higher-order polyols was administered in the diet at dosages of up to 18 and 43 g/kg of body weight per day, respectively, for 90 days. Hydrogenated dextrin was not mutagenic in either *Salmonella typhimurium* or *Escherichia coli* strains in the absence or presence of rat S9 microsomal fraction.

On the basis of the above considerations, the Committee confirmed the previous ADI "not specified" and concluded that it could be applied to maltitol syrup meeting the revised specifications.

An addendum to the toxicological monograph was prepared. In reviewing the specifications for maltitol syrup, the Committee considered the specifications for "hydrogenated saccharides other than maltitol" to be unnecessary and deleted the reference and respective purity test.

3.7 Miscellaneous substance: salatrim (short- and long-chain acyltriglyceride molecules)

Salatrim has not been previously reviewed by the Committee. Salatrim is a family of structured triglycerides containing, on average, one or two long-chain fatty acid moieties (usually stearic acid), the remainder being short-chain fatty acids. It is intended for use as a reduced-calorie replacement for conventional fats and oils.

The Committee evaluated studies on the caloric value of salatrim, being aware that short-chain fatty acids supply fewer kilocalories per gram than long-chain fatty acids. However, the claim of poor absorption of stearic acid from salatrim has not been proven for humans. Because there is no specific formulation for salatrim, it is not possible to assign a single caloric value to this product. The Committee noted that the specifications for salatrim that were elaborated at the present meeting permit formulations that include up to 0.87 g of stearate per g of fat. The biological data available do not provide information on materials with such compositions. If future studies determine that stearic acid is poorly absorbed from such formulations, the Committee considered that the consequences of this will need to be determined.

In evaluating the safety of salatrim, the Committee considered various studies. An *in vitro* study with porcine pancreatic lipase demonstrated that a wide range of the salatrim triacylglycerides are hydrolysed rapidly. In rats, the *in vivo* metabolism of a specific salatrim formulation indicated that it was metabolized in an analogous manner to triolein.

Salatrim products do not contain any structural features suggestive of potential mutagenicity, and no evidence of genotoxicity was observed in an adequate range of *in vitro* or *in vivo* studies.

Five 90-day studies in rats, each using a different salatrim formulation administered at concentrations of up to 100 g/kg in the diet, showed no toxicologically significant effects. A 28-day study in minipigs of a specific salatrim formulation was carried out using dose levels of 30, 60 and 100 g/kg in the diet, and also showed no toxicologically significant effects. These studies were not designed to detect potential nutritional effects, and the study in minipigs was of insufficient duration. The Committee concluded that these limitations meant that the studies did not provide an adequate basis for a nutritional or toxicological evaluation.

Because of the high projected intake of salatrim products (90th percentile levels for "all ages" and for 3–5-year-olds are 37 and 26 g per day, respectively) and given that no systemic effects were seen in animal studies, the Committee paid particular attention to the results of the five studies in humans. Of these, one was a free-living trial, the other four were clinic-based with different experimental designs.

In the four clinic-based studies the experimental protocols provided intakes of up to 60 g of salatrim per person per day for periods of 1, 4 or 7 days. Although these studies provided some indication that the consumption of salatrim in the diet was associated with an increased incidence of mild gastrointestinal symptoms and significantly elevated serum enzymes, the treatment periods were short and the numbers of study participants were few.

The free-living study was a randomized, double-blind, multiple-dose, parallel comparison between diets in which the fat was replaced by salatrim oil (23SO, 4SO or 43SO) and control diets in which the fat was soy oil. At least 12 women and 12 men were recruited for each of the two control groups and each of the five treatment groups which received 30, 45 or 60 g per day of 23SO, 60 g per day of 4SO or 60 g per day of 43SO. The total duration of the study was 6 weeks. Subjects in the treatment groups received soy oil during weeks 1 and 6 and salatrim during weeks 2–5, while those in the control groups received soy oil throughout the study.

A total of 183 subjects started the study; 34 dropped out, four of whom were controls. Of those who dropped out, 20 had received salatrim and recorded adverse effects as the reason for leaving the study. The Committee noted inconsistencies between the published

and unpublished reports of the study in that there were differences in the recorded numbers of subjects dropping out.

The consumption of 60 g of salatrim per day was associated with more reports (compared to controls) of stomach cramps and nausea in a substantial number of subjects. Transient elevations of the levels of alanine aminotransferase and aspartate aminotransferase were recorded. Due to the short duration of the study, the high drop-out rate and the modest number of participants, the Committee concluded that it was not possible to determine whether these observations were clinically significant.

The Committee concluded that the available studies did not provide an adequate basis for evaluating the safety and nutritional effects of salatrim. The Committee recommended that additional appropriately designed studies be performed to assess fully both the safety and nutritional consequences of ingestion of salatrim.

A monograph addressing the safety and nutritional effects of salatrim, which included an analysis of the caloric content of the salatrim family, was prepared.

The Committee considered salatrim to be a replacement for conventional fats and oils and therefore regarded it as a food ingredient and not as a food additive. At the request of the Codex Committee on Food Additives and Contaminants the Committee nevertheless prepared new specifications to describe this food ingredient.

4. Substances evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

Six groups of flavouring agents were evaluated using the Procedure for the Safety Evaluation of Flavouring Agents as modified at the present meeting (section 2.2.1 and Fig. 1).

The Committee noted that in applying the Procedure, the substance is first assigned to a structural class as identified at the forty-sixth meeting of the Committee (Annex 1, reference *122*). The structural classes are as follows:

- Class I. Substances that have simple chemical structures and efficient modes of metabolism which would suggest a low order of oral toxicity.
- Class II. Substances that have structural features that are less innocuous than those of substances in class I, but are not suggestive

of toxicity. Substances in this class may contain reactive functional groups.

- Class III. Substances that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity.

A key element of the Procedure involves determining whether a flavouring agent and the product(s) of its metabolism are innocuous and/or endogenous substances. For the purpose of the evaluations, the Committee used the following definitions adapted from the report of its forty-sixth meeting.

Innocuous metabolic products are defined as products that are known or readily predicted to be harmless to humans at the estimated intake of the flavouring agent.

Endogenous substances are intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included. The estimated intake of a flavouring agent that is, or is metabolized to, an endogenous substance should be judged not to give rise to perturbations outside the physiological range.

The Committee first considered the metabolic pathways common to the groups of flavouring agents evaluated at the present meeting.

Hydrolysis of esters

Linear alkyl esters are hydrolysed rapidly to their component alcohols and carboxylic acids in the intestinal tract, blood and liver, and most tissues throughout the body. Hydrolysis is catalysed by classes of enzymes recognized as carboxylesterases or esterases. For simple linear esters, as considered at this meeting, the rate of hydrolysis increases with increased chain length of either the acid or alcohol component. The rate of hydrolysis of straight-chain esters is approximately 100 times that of branched-chain esters. The rates of hydrolysis of the alkenyl esters citronellyl acetate (3,7-dimethyl-6-octen-1-yl acetate) and citronellyl phenylacetate, by artificial pancreatic juice, were similar to the rates for simple branched-chain esters.

Oxidation of alkyl primary alcohols and aldehydes

Most linear and branched-chain, saturated and unsaturated primary alcohols are oxidized rapidly to their corresponding aldehydes by alcohol dehydrogenase. The rate of oxidation increases with increased chain length, and the presence of a double bond.

The subsequent oxidation of the aldehydes to their corresponding acids is catalysed by dehydrogenase and oxidase enzymes. The most active is a NAD^+/NADH-dependent aldehyde dehydrogenase present in the cytosol, the activity of which increases with increasing relative molecular mass of the aldehyde substrate. Aldehydes may also be reduced to alcohols or conjugated with sulfhydryl-containing substances, such as glutathione. Aldehyde dehydrogenase-catalysed oxidation of aldehydes of low relative molecular mass requires glutathione, which suggests that the free aldehyde may be conjugated rapidly with glutathione *in vivo* to form a thiohemiacetal that is subsequently oxidized to the corresponding acid. Branched-chain aldehydes are rapidly oxidized by aldehyde dehydrogenase, and the rate of oxidation of 2-methylpropanal is similar to that of acetaldehyde.

Oxidation of linear saturated carboxylic acids

Aliphatic linear saturated carboxylic acids are metabolized in the fatty acid β-oxidation pathway, the tricarboxylic acid cycle, or the C_1-tetrahydrofolate pathway. Oxidation of formic acid to carbon dioxide and water occurs primarily in the liver and is catalysed by tetrahydrofolate in humans and other primates.

Other carboxylic acids are condensed with coenzyme A (CoA) to yield thioesters that undergo β-cleavage to acetyl CoA. Carboxylic acids containing an even number of carbon atoms give acetyl CoA, whereas those containing an odd number yield acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly, whereas propionyl CoA is first converted to succinyl CoA.

Oxidation of branched-chain saturated carboxylic acids

Short-chain (containing six or fewer carbon atoms) branched-chain saturated aliphatic acids undergo β-oxidation preferentially in the longer chain, followed by cleavage to yield linear acid fragments that are metabolized via the fatty acid pathway or the tricarboxylic acid cycle. Isobutyric acid (2-methylpropanoic acid), isovaleric acid (3-methylbutanoic acid) and 2-methylbutyric acid (2-methylbutanoic acid) are formed during the oxidative deamination of endogenous branched-chain amino acids and are metabolized by normal pathways of intermediary metabolism. At high dose levels, longer branched-chain acids may undergo ω-oxidation to yield diacids that undergo further oxidation and cleavage.

Acids with a methyl substituent are extensively metabolized to carbon dioxide via β-oxidation, unless the methyl group is located at the β-position (e.g. 3-methylpentanoic acid), in which case α-oxidation

occurs, yielding short-chain acid fragments capable of being completely metabolized.

The presence of a 2-ethyl substituent prevents the β-oxidation of aliphatic carboxylic acids, and these compounds undergo ω-oxidation and ω-1 oxidation to yield polar metabolites that are excreted primarily in the urine. Saturation of this ω-oxidation pathway may lead to formation of the 2-substituted carboxylic acid that may be excreted as the glucuronic acid conjugate.

4.1 Allyl 2-furoate

Twenty-one allyl esters used as flavouring agents in food were evaluated by the Committee at its forty-sixth meeting using the Procedure for the Safety Evaluation of Flavouring Agents modified at that meeting (Annex 1, reference *122*). The Committee concluded that the use of 20 of the 21 allyl esters that were evaluated posed no safety concerns at their estimated levels of intake. The evaluation of one of the flavouring agents in the group, allyl 2-furoate (2-propenyl furan-2-carboxylate), was postponed pending consideration of the last step on the right-hand side of the Procedure in which a decision criterion of 1.5 μg per person per day is applied to a substance for which adequate data on metabolism and toxicity are lacking. At the present meeting, allyl 2-furoate was evaluated in accordance with the Procedure inclusive of this step (see Fig. 1).

Intake data

On the basis of a reported annual volume of production of 1 kg in Europe (International Organization of the Flavor Industry, personal communication, 1995) and <0.01 kg in the USA (*10*), the estimated daily per capita intake of allyl 2-furoate is 0.14 μg in Europe and <0.01 μg in the USA. These estimates were calculated assuming under-reporting of the poundage data and consumption by 10% of the population as described in Annex 5 of WHO Food Additives Series, No. 35 (Annex 1, reference *117*).

Information on absorption, metabolism and elimination

No data on the metabolism of allyl 2-furoate, an ester of allyl alcohol and 2-furoic acid, were available. The Committee recognized that allyl esters are generally hydrolysed to allyl alcohol and their corresponding carboxylic acids. At its forty-sixth meeting, however, the Committee determined that there was insufficient evidence to conclude that allyl 2-furoate would be rapidly and completely hydrolysed in humans.

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1) to allyl 2-furoate, the Committee assigned the compound to structural class III (*11*).

Step 2. No data on the metabolism of allyl 2-furoate were available and the substance could not be predicted to be metabolized to innocuous products. Accordingly, the right-hand side of the decision tree was further considered.

Step B3. The intake estimates for allyl 2-furoate were below the threshold for class III (90 μg per day).

Step B4. There were no toxicity data on allyl 2-furoate or on a structurally related substance to provide a NOEL to indicate whether an adequate margin of safety exists under conditions of intended use.

Step B5. The conditions of use of allyl 2-furoate do not result in an intake greater than 1.5 μg per day. The estimated intake is approximately one-tenth of this value.

Conclusion

No multiple-dose toxicity studies on allyl 2-furoate were available. At its forty-sixth meeting, the Committee considered the available toxicity data on the other allyl esters as inapplicable to the evaluation of allyl 2-furoate, because they were all expected to be rapidly and completely hydrolysed in humans.

If hydrolysis of allyl 2-furoate were assumed, the ADI for allyl alcohol and knowledge of the metabolism of 2-furoic acid would support a conclusion of no safety concern for this substance. In accordance with the Procedure, the Committee concluded that allyl 2-furoate would not be expected to present a safety concern at the estimated level of current intake.

A toxicological monograph was not prepared. The tentative specifications prepared at the forty-sixth meeting of the Committee were maintained.

4.2 Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids

The Committee evaluated a group of 38 flavouring agents that included selected saturated aliphatic acyclic linear primary alcohols, aldehydes and acids of chain length C_{1-18} (Table 1) using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

Table 1
Summary of the results of safety evaluations of 38 saturated aliphatic acyclic linear primary alcohols, aldehydes and acids[a]

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Comments	Conclusion based on levels of current intake
Formic acid[c]	0079	No Europe: 800 USA: 160	NR	Formic acid is produced endogenously in humans and is a normal component of intermediate metabolism	No safety concern
Acetaldehyde	0080	Yes Europe: 11000 USA: 9700	Yes	Acetaldehyde is oxidized to acetic acid which is metabolized via the citric acid cycle; acetaldehyde can also be reduced to ethanol	
Acetic acid[c]	0081	Yes Europe: ND USA: 360000	Yes	Acetic acid is metabolized to carbon dioxide; it acetylates amines and can be incorporated into proteins	
Propyl alcohol	0082	Yes Europe: 420 USA: 2700	Yes	Propyl alcohol is oxidized to propionaldehyde which is oxidized to propionic acid; propionic acid is metabolized via the citric acid cycle	
Propionaldehyde	0083	No Europe: 33 USA: 140	NR	Propionaldehyde is oxidized to propionic acid which is metabolized via the citric acid cycle	

Propionic acid[c]	0084	Yes Europe: 1100 USA: 5200	Yes	Propionic acid is metabolized via the citric acid cycle	No safety concern
Butyl alcohol	0085	Yes Europe: 1900 USA: 8100	Yes	Butyl alcohol is oxidized to butyraldehyde which is oxidized to butyric acid; butyric acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Butyraldehyde	0086	No Europe: 26 USA: 17	NR	Butyraldehyde is oxidized to butyric acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Butyric acid	0087	Yes Europe: 10000 USA: 5900	Yes	Butyric acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Amyl alcohol	0088	No Europe: 97 USA: 44	NR	Amyl alcohol is oxidized to valeraldehyde which is rapidly oxidized to valeric acid; valeric acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Valeraldehyde	0089	Yes Europe: 3000 USA: 8.8	Yes	Valeraldehyde is rapidly oxidized to valeric acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Valeric acid	0090	No Europe: 140 USA: 850	NR	Valeric acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Hexyl alcohol	0091	Yes Europe: 1900 USA: 800	Yes	Hexyl alcohol is oxidized to hexanal which is rapidly oxidized to hexanoic acid; hexanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Hexanal	0092	No Europe: 780 USA: 260	NR	Hexanal is rapidly oxidized to hexanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Hexanoic acid	0093	Yes Europe: 3500 USA: 1300	Yes	Hexanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	

Table 1 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Comments	Conclusion based on current levels of intake
Heptyl alcohol	0094	No Europe: 12 USA: 7	NR	Heptyl alcohol is oxidized to heptanal which is rapidly oxidized to heptanoic acid; heptanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	No safety concern
Heptanal	0095	No Europe: 200 USA: 3.2	NR	Heptanal is rapidly oxidized to heptanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Heptanoic acid	0096	No Europe: 170 USA: 5.3	NR	Heptanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
1-Octanol	0097	No Europe: 230 USA: 32	NR	1-Octanol is oxidized to octanal which is rapidly oxidized to octanoic acid; octanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Octanal[c]	0098	No Europe: 170 USA: 90	NR	Octanal is rapidly oxidized to octanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Octanoic acid	0099	Yes Europe: 3800 USA: 650	Yes	Octanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Nonyl alcohol	0100	No Europe: 8.1 USA: 2.1	NR	Nonyl alcohol is oxidized to nonanal which is rapidly oxidized to nonanoic acid; nonanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Nonanal[c]	0101	No Europe: 130 USA: 17	NR	Nonanal is rapidly oxidized to nonanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	

Nonanoic acid	0102	No Europe: 64 USA: 63	NR	Nonanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	No safety concern
1-Decanol	0103	No Europe: 290 USA: 7	NR	1-Decanol is oxidized to decanal which is rapidly oxidized to decanoic acid; decanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Decanal	0104	No Europe: 288 USA: 61	NR	Decanal is rapidly oxidized to decanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Decanoic acid	0105	No Europe: 1400 USA: 980	NR	Decanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways; at high concentrations, it undergoes ω-oxidation	
Undecyl alcohol	0106	No Europe: 0.9 USA: 11	NR	Undecyl alcohol is oxidized to undecanal which is rapidly oxidized to undecanoic acid; undecanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Undecanal	0107	No Europe: 480 USA: 1.5	NR	Undecanal is rapidly oxidized to undecanoic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Undecanoic acid	0108	No Europe: 4.6 USA: 8.8	NR	Undecanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Lauryl alcohol	0109	No Europe: 170 USA: 80	NR	Lauryl alcohol is oxidized to lauric aldehyde which is rapidly oxidized to lauric acid; lauric acid is metabolized via the fatty acid and tricarboxylic acid pathways	

Table 1 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Comments	Conclusion based on current levels of intake
Lauric aldehyde	0110	No Europe: 52 USA: 21	NR	Lauric aldehyde is rapidly oxidized to lauric acid which is metabolized via the fatty acid and tricarboxylic acid pathways	No safety concern
Lauric acid	0111	No Europe: 590 USA: 1200	NR	Lauric acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Myristaldehyde	0112	No Europe: 9.4 USA: 25	NR	Myristaldehyde is rapidly oxidized to myristic acid which is metabolized via the fatty acid and tricarboxylic acid pathways	
Myristic acid	0113	No Europe: 160 USA: 72	NR	Myristic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
1-Hexadecanol	0114	No Europe: 3.6 USA: 0.2	NR	1-Hexadecanol is oxidized to hexadecanal which is rapidly oxidized to hexadecanoic acid; hexadecanoic acid is metabolized via the fatty acid and tricarboxylic acid pathways	
Palmitic acid	0115	No Europe: 89 USA: 234	NR	β-oxidation of palmitic acid yields 2-carbon units which enter the tricarboxylic acid cycle	
Stearic acid	0116	Yes Europe: 58 USA: 1900	Yes	β-oxidation of stearic acid yields 2-carbon units which enter the tricarboxylic acid cycle	

NR: Not required for evaluation because consumption of the substance was determined to be of no safety concern at step A3 of the procedure. ND: no intake data reported

[a] *Step 1*: All of the substances in this group are in structural class I, the human intake threshold of which is 1800 μg per day.
Step 2: All of the substances in this group are metabolized to innocuous products.

[b] All intake values are expressed in μg per day.

[c] The ADI for this substance was maintained.

Several substances in the group have been evaluated previously by the Committee. At the seventeenth meeting, group ADIs "not limited" were allocated to acetic acid and its potassium and sodium salts and to propionic acid (propanoic acid) and its calcium, potassium and sodium salts, and an ADI of 0–3 mg/kg of body weight was allocated to formic acid (Annex 1, reference *32*), which was made a group ADI with ethyl formate at the twenty-third meeting (Annex 1, reference *50*). A group ADI of 0–0.1 mg/kg of body weight was established for octanal and nonanal, singly or in combination, at the twenty-eighth meeting (Annex 1, reference *66*). An ADI "not limited" was allocated to the aluminium, ammonium, calcium, magnesium, potassium and sodium salts of myristic (tetradecanoic), palmitic (hexadecanoic) and stearic (octadecanoic) acids at the seventeenth meeting (Annex 1, reference *32*). At the twenty-ninth meeting, the Committee did not establish ADIs for these acids due to lack of information on the manufacture and use of the food-grade material, but noted that they are normal constituents of coconut oil, butter and other edible oils. ADIs have not been allocated to butyl alcohol (1-butanol), decanal or propyl alcohol (1-propanol) because the data were considered to be inadequate (Annex 1, references *38*, *14* and *56* respectively).

The intake of one substance, ethyl alcohol (ethanol), which is structurally related to the group was considered at the forty-sixth meeting (Annex 1, reference *122*), when the Committee evaluated ethyl esters used as flavouring agents. At that time, the Committee concluded that ethyl alcohol posed no safety concern at its current level of intake when ethyl esters are used as flavouring agents.

Intake data

The total annual volume of production of the 38 substances from their use as flavouring agents is approximately 2100 tonnes in the USA. Approximately 90% of the total volume is accounted for by acetic acid, which includes the amount produced for uses (acidulant or solvent) in food other than as a flavouring agent. No specific data were available on the use of acetic acid as a flavouring agent in Europe. Disregarding acetic acid, the total reported annual volume of production of the remaining 37 aliphatic substances used as flavouring agents is approximately 300 tonnes in Europe and 200 tonnes in the USA.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, acetaldehyde (ethanal), butyl alcohol and butyric acid (butanoic acid) are the most important substances in this group. Acetaldehyde and butyric acid account for

about 50% of the daily per capita intake in Europe, and acetaldehyde and butyl alcohol account for about 46% of the daily per capita intake in the USA. Other flavouring agents in this group with high intake levels (i.e. >1800 μg per person per day) include octanoic acid, hexanoic acid, valeraldehyde (pentanal), butyl alcohol and hexyl alcohol (1-hexanol) in Europe and butyric acid, propionic acid, propyl alcohol and stearic acid in the USA (Table 1).

Saturated linear aliphatic alcohols, aldehydes and acids are ubiquitous in nature. Alcohols and acids of low relative molecular mass have been detected in almost every known fruit and vegetable. There are a limited number of reports of the natural occurrence of the corresponding aldehydes. In the USA, the available quantitative data indicate that the dietary consumption of saturated linear aliphatic alcohols, aldehydes and acids from naturally occurring sources exceeds their consumption from use as flavouring substances.

Information on absorption, metabolism and elimination

Linear aliphatic acyclic alcohols, aldehydes and carboxylic acids are absorbed through the gastrointestinal tract. Their half-lives in plasma are difficult to measure since many alcohols of low relative molecular mass (e.g. ethyl alcohol), aldehydes and carboxylic acids (e.g. acetic acid and propionic acid) are endogenous in humans. Acetaldehyde has been detected in whole blood (<0.2 mg/l) and acetate is a blood buffer.

The flavouring agents in this group of selected saturated aliphatic linear alcohols, aldehydes and acids are all metabolized via the fatty acid and tricarboxylic acid pathways (see pages 26–27).

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned saturated aliphatic linear alcohols, aldehydes and acids, the Committee assigned all 38 substances to structural class I.

Step 2. All of the flavouring agents in this group are known to be, or can be readily predicted to be, efficiently metabolized to innocuous substances. Accordingly, the left-hand side of the decision tree was further considered.

Step A3. The intake estimates for 27 substances in this group fall below the threshold for human intake for class I (1800 μg per day); therefore, these substances were considered to be of no safety concern.

Step A4. The intake estimates for 11 substances in this group exceeded the threshold for human intake for class I. In all cases, the substances could be predicted to undergo complete metabolism to endogenous products via the fatty acid and tricarboxylic acid pathways. In the opinion of the Committee, the endogenous levels of metabolites from these substances would not give rise to perturbations outside the physiological range. Therefore, these 11 substances were also considered to be of no safety concern.

Table 1 summarizes the evaluation of the 38 saturated aliphatic acyclic linear primary alcohols, aldehydes and acids using the Procedure.

Consideration of combined intakes

In the unlikely event that all foods containing all of the 38 substances in this group were consumed simultaneously on a daily basis, the estimated daily per capita intake in Europe and the USA (excluding intakes of acetic acid and propionic acid which have ADIs "not limited") would be approximately 40 mg and 30 mg respectively, i.e. above the threshold for human intake for substances in class I.

All of the substances in this group and their metabolites are innocuous and endogenous and their combined intake was judged by the Committee not to give rise to perturbations outside the physiological range.

Conclusion

The Committee concluded that the substances in this group would not present safety concerns at the estimated current levels of intake.

No toxicity data were required for the application of the Procedure. However, the Committee noted that the toxicity data that were available were consistent with the results of using the Procedure. In cases where ADIs had been established previously, they were maintained at the present meeting.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.3 Saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids

The Committee evaluated a group of 25 flavouring agents that included selected saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids (see Table 2) using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

Table 2
Summary of the results of safety evaluations of 25 saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids[a]

Substance	No.	*Step A3* Does intake exceed the threshold for human intake?[b]	Conclusion based on current levels of intake
Structural class I: methyl-substituted saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids			
Isobutyl alcohol	0251	No Europe: 530 USA: 290	
Isobutyraldehyde	0252	No Europe: 130 USA:100	
Isobutyric acid	0253	No Europe: 820 USA: 140	
2-Methylbutyraldehyde	0254	No Europe: 4.9 USA: 370	
2-Methylbutyric acid	0255	No Europe: 1200 USA: 480	
3-Methylbutyraldehyde	0258	No Europe: 110 USA: 140	
Isovaleric acid	0259	No Europe: 480 USA: 96	
2-Methylpentanal	0260	No Europe: 12 USA: 8.5	No safety concern
2-Methylvaleric acid	0261	No Europe: 680 USA: 2.3	
3-Methylpentanoic acid	0262	No Europe: 2.9 USA: 8.8	
3-Methyl-1-pentanol	0263	No Europe: 5.9 USA: 4.2	
4-Methylpentanoic acid	0264	No Europe: 1.6 USA: 55	
2-Methylhexanoic acid	0265	No Europe: 15 USA: 2.3	
5-Methylhexanoic acid	0266	No Europe: 0.0 USA: 8.6	
3,5,5-Trimethyl-1-hexanol	0268	No Europe: 13 USA: 0.76	

Table 2 (*continued*)

Substance	No.	*Step A3* Does intake exceed the threshold for human intake?[b]	Conclusion based on current levels of intake
3,5,5-Trimethylhexanal	0269	No Europe: 0.29 USA: 150	
2-Methyloctanal	0270	No Europe: 0.14 USA: 0.95	
4-Methyloctanoic acid	0271	No Europe: 11 USA: 0.10	
3,7-Dimethyl-1-octanol	0272	No Europe: 94 USA: 2.9	No safety concern
2,6-Dimethyloctanal	0273	No Europe: 0.01 USA: 6.7	
4-Methylnonanoic acid	0274	No Europe: 1.00 USA: 1.5	
2-Methylundecanal	0275	No Europe: 0.61 USA: 0.10	
Structural class II: ethyl-substituted saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids			
2-Ethylbutyraldehyde[c]	0256	No Europe: 0.57 USA: 0.17	
2-Ethylbutyric acid[c]	0257	No Europe: 60 USA: 31	No safety concern
2-Ethyl-1-hexanol[c, d]	0267	No Europe: 86 USA: 40	

[a] *Step 2:* All of the substances in this group are metabolized to innocuous products.
[b] The thresholds for human intake for classes I and II are 1800 µg per day and 540 µg per day, respectively. All intake values are expressed in µg per day.
[c] The 2-ethyl substituent inhibits the β-oxidation of aliphatic alcohols, aldehydes and carboxylic acids. These compounds undergo ω- and ω-1-oxidation to yield polar metabolites which are primarily excreted in urine.
[d] The ADI for this substance was maintained.

Twenty-two of these substances contain one or more methyl substituents and the remaining three have ethyl substituents in the α-position.

Two of the substances have been evaluated previously by the Committee. Isobutyl alcohol (2-methyl-1-propanol) was considered at the twenty-third meeting, when an ADI was not allocated because of a

lack of information (Annex 1, reference *50*). An ADI of 0–0.5 mg per kg of body weight was allocated to 2-ethyl-1-hexanol at the forty-first meeting (Annex 1, reference *107*).

Intake data

The total annual volume of production of the 22 methyl-substituted saturated aliphatic branched-chain primary alcohols, aldehydes and acids from their use as flavouring substances is approximately 29 tonnes in Europe and 9.8 tonnes in the USA. In Europe, more than 85% of the total annual volume is accounted for by five substances (isobutyl alcohol, isobutyric acid, 2-methylbutyric acid, isovaleric acid and 2-methylvaleric acid (2-methylpentanoic acid)). In the USA more than 80% of the total annual volume is accounted for by seven substances (isobutyl alcohol, isobutyraldehyde (2-methylpropanal), isobutyric acid, 2-methylbutyraldehyde (2-methylbutanal), 2-methylbutyric acid, 3-methylbutyraldehyde (3-methylbutanal) and isovaleric acid).

The total reported annual volume of production of the three 2-ethyl substituted substances for use as flavouring agents is 1000 kg in Europe and 370 kg in the USA.

Saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids have been detected as natural components of a wide variety of foods such as cheese, fruits, vinegar and alcoholic beverages. Quantitative data on the natural occurrence of these flavouring agents has been reported for 11 of the 25 substances in the group and their total annual consumption in food is estimated at 1.5 million kg per year.

Information on absorption, metabolism and elimination

The metabolism of methyl- and ethyl-substituted saturated aliphatic acyclic branched-chain alcohols, aldehydes and carboxylic acids is described on pages 26–27.

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids, the Committee assigned all 22 methyl-substituted substances to structural class I. The three ethyl-substituted substances (2-ethylbutyraldehyde (2-ethylbutanal), 2-ethylbutyric acid (2-ethylbutanoic

acid) and 2-ethyl-1-hexanol) contain sterically hindered functional groups and were therefore assigned to structural class II.

Step 2. At their current levels of intake from use as flavouring agents (see Table 2), the 22 methyl-substituted alcohols, aldehydes and carboxylic acids and the three ethyl-substituted alcohols, aldehydes and carboxylic acids would not be expected to saturate the metabolic pathways and all the compounds were predicted to be metabolized to innocuous products.

Step A3. The intake estimates for all the 22 methyl-substituted substances in this group in both Europe and the USA are below the threshold for human intake for class I (1800 μg per day). Therefore, these substances were considered to be of no safety concern when used as flavouring agents at current estimated levels of intake.

The intake estimates for the three ethyl-substituted substances (2-ethylbutyraldehyde, 2-ethylbutyric acid and 2-ethyl-1-hexanol) in this group in both Europe and the USA are below the threshold for human intake for class II (540 μg per day). Therefore, these substances were also considered to be of no safety concern when used as flavouring agents at current estimated levels of intake.

Table 2 summarizes the evaluation of the 25 saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and carboxylic acids using the Procedure.

Consideration of combined intake

In the unlikely event that all foods containing all 22 methyl-substituted alcohols, aldehydes and acids as flavouring agents were consumed simultaneously on a daily basis, the estimated total daily per capita intake of these substances would be 410 μg in Europe and 1900 μg in the USA.

In the unlikely event that all foods containing all three ethyl-substituted alcohols, aldehydes and acids were consumed simultaneously on a daily basis, the estimated total daily per capita intake of these three substances would be less than 145 μg in Europe and less than 71 μg in the USA.

The Committee judged that the combined intake of substances in this group is of no safety concern, since all the substances are expected to be efficiently metabolized and the combined level of intake is not expected to saturate metabolic pathways.

Conclusion

The Committee concluded that the use of the above-mentioned substances as flavouring agents would not present safety concerns at the estimated current levels of intake.

No toxicity data were required for the application of the Procedure. However, the Committee noted that where toxicity data were available they were consistent with the results of the Procedure. The ADI established previously for 2-ethyl-1-hexanol was maintained.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.4 Aliphatic lactones

The Committee evaluated a group of 35 aliphatic lactones used as flavouring agents in food (Table 3) using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

Two substances in the group, γ-nonalactone and γ-undecalactone, were previously evaluated by the Committee at its eleventh meeting, when ADIs of 0–1.25 mg/kg of body weight were established for each substance (Annex 1, reference *14*).

Intake data

The total annual volume of production of the 35 substances from their use as flavouring agents is approximately 160 tonnes in Europe and 27 tonnes in the USA. The estimated total daily per capita intakes of all aliphatic lactones resulting from their use as flavouring agents are 30.3 mg in Europe and less than 5.3 mg in the USA. In Europe, γ-decalactone and δ-dodecalactone account for two-thirds of the daily per capita intake of lactones used as flavouring agents. In the USA, four substances (γ-decalactone, δ-decalactone, γ-dodecalactone and δ-dodecalactone) account for most of the daily per capita intake of aliphatic lactones used as flavouring agents.

The four lactones that are α,β-unsaturated (5-hydroxy-2,4-decadienoic acid δ-lactone, 5-hydroxy-2-decenoic acid δ-lactone, 5-hydroxy-2-dodecenoic acid δ-lactone, and a mixture of 5-hydroxy-2-decenoic acid δ-lactone, 5-hydroxy-2-dodecenoic acid δ-lactone and 5-hydroxy-2-tetradecenoic acid δ-lactone) and the two hydroxyfuranones (5-ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone and 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one) are estimated to have very low total daily per capita intakes. The combined estimated per capita intakes of these six substances from their use in food is 27 μg in Europe and less than 9 μg in the USA.

Table 3
Summary of the results of safety evaluations of 35 aliphatic lactones

Substance	No.	*Step 2* Metabolized to innocuous products?	*Step A3/B3*[a] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step B4/A5* Adequate NOEL for substance or related substance?	Conclusion based on current levels of intake
Structural class I						
4-Hydroxybutyric acid lactone (γ-butyrolactone)	0219	Yes	No Europe: 130 USA: 100	NA	NA	
γ-Valerolactone	0220	Yes	No Europe: 140 USA: 57	NA	NA	
γ-Hexalactone	0223	Yes	No Europe: 190 USA: 19	NA	NA	No safety concern
δ-Hexalactone	0224	Yes	No Europe: 380 USA: 2.5	NA	NA	
γ-Heptalactone	0225	Yes	No Europe: 190 USA: 41	NA	NA	

Table 3 (*continued*)

Substance	No.	*Step 2* Metabolized to innocuous products?	*Step A3/B3*[a] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step B4/A5* Adequate NOEL for substance or related substance?	Conclusion based on current levels of intake
γ-Octalactone	0226	Yes	No Europe: 490 USA: 90	NA	NA	No safety concern
δ-Octalactone	0228	Yes	No Europe: 270 USA: 17	NA	NA	
γ-Nonalactone[b]	0229	Yes	No Europe: 1200 USA: 470	NA	NA	
Hydroxynonanoic acid δ-lactone	0230	Yes	No Europe: 150 USA: 11	NA	NA	
γ-Decalactone	0231	Yes	Yes Europe: 1800 USA: 370	No	Yes	
δ-Decalactone	0232	Yes	Yes Europe: 8400 USA: 1900	No	Yes	
ε-Decalactone	0241	Yes	No Europe: 0.01 USA: 0	NA	NA	
γ-Undecalactone[b]	0233	Yes	No Europe: 1400 USA: 550	NA	NA	

5-Hydroxyundecanoic acid δ-lactone	0234	Yes	No Europe: 350 USA: 180	NA	NA	No safety concern
γ-Dodecalactone	0235	Yes	No Europe: 220 USA: 110	NA	NA	
δ-Dodecalactone	0236	Yes	Yes Europe: 6800 USA: 1140	No	Yes	
ε-Dodecalactone	0242	Yes	No Europe: 0.01 USA: 0.17	NA	NA	
δ-Tetradecalactone	0238	Yes	No Europe: 120 USA: 2.5	NA	NA	
ω-Pentadecalactone	0239	Yes	No Europe: 84 USA: 51	NA	NA	
4-Hydroxy-3-pentenoic acid lactone	0221	Yes	No Europe: NR USA: 4.8	NA	NA	
5-Hydroxy-7-decenoic acid δ-lactone	0247	Yes	No Europe: 0.26 USA: 0.10	NA	NA	

Table 3 (*continued*)

Substance	No.	*Step 2* Metabolized to innocuous products?	*Step A3/B3*[a] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step B4/A5* Adequate NOEL for substance or related substance?	Conclusion based on current levels of intake
5-Hydroxy-8-undecenoic acid δ-lactone	0248	Yes	No Europe: 0.01 USA: 8.6	NA	NA	No safety concern
1,4-Dodec-6-enolactone	0249	Yes	No Europe: 0.01 USA: 8.6	NA	NA	
ω-6-Hexadecenlactone	0240	Yes	No Europe: 6 USA: 0.10	NA	NA	
4,4-Dibutyl-γ-butyrolactone	0227	Yes	No Europe: 0.14 USA: 0.10	NA	NA	
3-Heptyldihydro-5-methyl-2(3*H*)-furanone	0244	Yes	No Europe: 0.04 USA: 0.1	NA	NA	
4-Hydroxy-3-methyloctanoic acid γ-lactone	0437	Yes	No Europe: 0 USA: 8.6	NA	NA	
6-Hydroxy-3,7-dimethyloctanoic acid lactone	0237	Yes	No Europe: 0.1 USA: 0	NA	NA	
γ-Methyldecalactone	0250	Yes	No Europe: 0 USA: 43	NA	NA	

Structural class III						
5-Hydroxy-2-decenoic acid δ-lactone	0246	No	No Europe: 12 USA: 0.10	NA	Insufficient information	Not evaluated[c]
5-Hydroxy-2,4-decadienoic acid δ-lactone	0245	No	No Europe: 0.33 USA: 0.10	NA	Insufficient information	
Mixture of 5-hydroxy-2-decenoic acid δ-lactone, 5-hydroxy-2-dodecenoic acid δ-lactone and 5-hydroxy-2-tetradecenoic acid δ-lactone	0276	No	— Europe: 0 USA: 2	NA	Insufficient information	
5-Hydroxy-2-dodecenoic acid δ-lactone	0438	No	— Europe: 0 USA: 8.6	NA	Insufficient information	
5-Ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone	0222	No	No Europe: 13 USA: 6.1	NA	Yes	No safety concern
4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one	0243	No	No Europe: 2.1 USA: 0.1	NA	Yes	

NA: not applicable.
[a] The thresholds for human intake for classes I and III are 1800 μg per day and 90 μg per day, respectively. All intake values are expressed in μg per day.
[b] The ADI for this substance was maintained.
[c] Evaluation deferred, pending consideration of other α,β-unsaturated compounds.

Most of the aliphatic lactones have been reported to occur naturally in traditional foods. The four aliphatic lactones that are used most as flavouring agents (γ-decalactone, δ-decalactone, γ-dodecalactone and δ-dodecalactone) are ubiquitous in food, occurring mainly in fruits, alcoholic beverages, meats and dairy products.

Information on absorption, metabolism and elimination

Lactones are generally formed by acid-catalysed intramolecular cyclization of hydroxycarboxylic acids. In an aqueous environment, a pH-dependent equilibrium is established between the open-chain hydroxycarboxylate anion and the lactone ring. In basic media, such as blood, the open-chain hydroxycarboxylate anion is favoured while in acidic media, such as urine, the lactone ring is favoured. Both the aliphatic lactones and the ring-opened hydroxycarboxylic acids can be absorbed from the gastrointestinal tract.

The aliphatic lactones in this group can be divided into three subgroups on the basis of their predicted metabolism, namely, lactones derived from linear and branched-chain hydroxycarboxylic acids, lactones which are α,β-unsaturated, and the two hydroxyfuranones. The metabolism of the members of each of these subgroups is discussed below.

Lactones derived from linear saturated 5-hydroxycarboxylic acids. Linear saturated 5-hydroxycarboxylic acids (formed from δ-lactones) are converted, via acetyl CoA, to hydroxythioesters which then undergo β-oxidation and cleavage to yield an acetyl CoA fragment and a new β-hydroxythioester reduced by two carbons. Acids containing even numbers of carbon atoms continue to be oxidized and cleaved to yield acetyl CoA while those containing odd numbers of carbon atoms yield acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly while propionyl CoA is transformed into succinyl CoA which then enters the citric acid cycle.

Lactones derived from linear saturated 4- or 6-hydroxycarboxylic acids. Linear saturated 4- or 6-hydroxycarboxylic acids (formed from γ- or ε-lactones) participate in the same pathway as described above for linear saturated 5-hydroxycarboxylic acids; however, loss of an acetyl CoA fragment produces an α-hydroxythioester which undergoes α-oxidation and α-decarboxylation to yield a linear carboxylic acid and eventually carbon dioxide. γ-Butyrolactone, the only lactone in this group formed from a primary alcohol, may participate in an alternative oxidation pathway, namely, oxidation by alcohol dehydrogenase and succinate-semialdehyde dehydrogenase to succinate which then enters the citric acid cycle.

Lactones derived from linear unsaturated hydroxycarboxylic acids. If the lactone is formed from a linear hydroxycarboxylic acid which is unsaturated, cleavage of acetyl CoA units continues along the carbon chain until the position of unsaturation is reached. If the unsaturation begins at an odd-numbered carbon, acetyl CoA fragmentation will eventually yield a 3-enoyl CoA which is converted to the *trans*-Δ^2-enoyl CoA before entering the fatty acid pathway. If unsaturation begins at an even-numbered carbon, acetyl CoA fragmentation yields a Δ^2-enoyl CoA product which is a substrate for further fatty acid oxidation. If the stereochemistry of the double bond is *cis*, hydration yields (*R*)-3-hydroxyacyl CoA which is isomerized to (*S*)-3-hydroxyacyl CoA by 3-hydroxyacyl CoA epimerase prior to entering the fatty acid pathway.

Lactones derived from branched-chain hydroxycarboxylic acids. For branched-chain hydroxycarboxylic acids, the principal metabolic pathways utilized for detoxication are influenced by the chain length and the position and size of the alkyl substituents. Short-chain (< six carbon atoms) branched aliphatic hydroxycarboxylic acids may be excreted unchanged as the glucuronic acid conjugate, or undergo α- or β-oxidation followed by cleavage and complete metabolism to carbon dioxide via the fatty acid pathway and the tricarboxylic acid cycle. Alternatively, as chain length, substitution and lipophilicity increase, the hydroxycarboxylic acid may undergo a combination of ω-, ω-1 and β-oxidation to yield polar hydroxyacid, ketoacid and hydroxydiacid metabolites which are excreted as the glucuronic acid or sulfate conjugates in the urine and, to a lesser extent, in the faeces. These metabolites are considered to be innocuous.

α,β-Unsaturated lactones. For the four substances which are α,β-unsaturated there was no direct evidence of hydrolysis. While hydrolysis to the corresponding ring-opened α,β-unsaturated hydroxycarboxylic acids may occur, no information was available on the four substances considered to enable the Committee to predict that this is the major route of metabolism. If hydrolysis to the corresponding ring-opened form occurs, condensation of the α,β-unsaturated hydroxycarboxylic acid with acetyl CoA would yield a Δ^2-enoyl CoA product, which is a substrate in the fatty acid pathway. Since the stereochemistry of the double bond in a lactone is *cis*, hydration would yield (*R*)-3-hydroxyacyl CoA, which is then isomerized to (*S*)-3-hydroxyacyl CoA by 3-hydroxyacyl CoA epimerase prior to entering the fatty acid pathway.

Alternatively, the lactones which are α,β-unsaturated may conjugate with glutathione and be excreted as cysteine or mercapturic acid

derivatives. Evidence for this alternative pathway comes from two structurally related lactones which are α,β-unsaturated. The Committee considered that further information was required in order to clarify the metabolic route(s) of these substances.

Hydroxyfuranones. There was no direct evidence available of hydrolysis of the two hydroxyfuranones (nos 0222 and 0243, see Table 3) to the corresponding ring-opened compound. The Committee considered that alternative metabolic pathways are likely and that no prediction of a metabolic route is possible for these substances.

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the aliphatic lactones, the Committee assigned 29 substances to structural class I; the four α,β-unsaturated substances and the two hydroxyfuranones were assigned to structural class III.

Step 2. The available data indicate that for the 29 lactones in class I derived from saturated linear and branched-chain hydroxycarboxylic acids, the corresponding aliphatic hydroxycarboxylic acids are metabolized via the fatty acid pathway. For these substances, the evaluation should proceed via the left-hand side of the decision-tree. For the four lactones in class III which are α,β-unsaturated, metabolism may occur either via hydrolysis followed by β-oxidation or via conjugation with glutathione. There was insufficient information available to predict the route of metabolism of these four substances with confidence. The Committee considered that further information on their metabolism was required and that they should be evaluated together with other α,β-unsaturated substances and that their evaluation should therefore be deferred. No information was available to indicate the route of metabolism for the two lactones in class III which are hydroxyfuranones and therefore the evaluation of these two substances should proceed via the right-hand side of the decision-tree.

Step A3/B3. For the 29 lactones derived from saturated linear and branched-chain hydroxycarboxylic acids in class I, three lactones (γ-decalactone, δ-decalactone and δ-dodecalactone) had intake estimates equal to or greater than the threshold for class I (1800 μg per day). The evaluation of these three substances therefore proceeded to step A4. For the other 26 lactones of similar structure the intake estimates are below the threshold for class I and they would therefore not be expected to be of safety concern. For the two hydroxyfuranones in class III, the intake estimates are well below the

threshold for class III (90 μg per day). The evaluation of these substances therefore proceeded to step B4.

Step A4. None of the three lactones derived from saturated linear hydroxycarboxylic acids (γ-decalactone, δ-decalactone and δ-dodecalactone) are known to be endogenous or to be metabolized to endogenous substances. The safety evaluation of these substances therefore proceeded to step A5.

Step A5. Although adequate studies on which to base a NOEL for the three lactones derived from saturated linear hydroxycarboxylic acids were not available, the following NOELs have been reported for structurally related lactones in 2-year studies in rats: 250 mg/kg of body weight per day for γ-nonalactone and γ-undecalactone and 110 mg/kg of body weight per day for γ-butyrolactone. In a 2-year study in mice with γ-butyrolactone a NOEL of 260 mg/kg of body weight per day was found. The studies on γ-nonalactone and γ-undecalactone were considered previously by the Committee and ADIs were established at the eleventh meeting (Annex 1, reference *14*). Although these studies were not conducted according to modern standards, the results are considered to be valid. These NOELs provide an adequate margin of safety (>1000) for γ-decalactone, δ-decalactone and δ-dodecalactone and therefore these substances would not be expected to be of safety concern.

Step B4. The Committee considered the results of studies on the two hydroxyfuranones in class III. In a 90-day study in rats administered 5-ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone in the diet, the NOEL was 1.3 mg/kg of body weight per day, and in a 1-year study in rats administered 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one in the diet, the NOEL was 46 mg/kg of body weight per day. These NOELs provide an adequate margin of safety (>1000) for these substances and therefore they would not be expected to be of safety concern.

Table 3 summarizes the evaluation of the 35 aliphatic lactones using the Procedure.

Consideration of combined intakes

From the available data, the 29 lactones derived from linear and branched-chain hydroxycarboxylic acids would be expected to be efficiently metabolized via commonly known biochemical pathways to innocuous substances. In the unlikely event that all foods containing all 29 substances as flavouring agents were consumed simultaneously on a daily basis, the estimated daily per capita consumption in Europe and the USA would exceed the threshold for human intake for substances in class I but, in the opinion of the Committee, this

would not give rise to perturbations outside the physiological range.

For the two hydroxyfuranones whose route of metabolism is unknown, their combined estimated intake was very low (15 μg per day) compared to the known NOELs for each of these substances and was not considered to present a safety concern.

Conclusions

The Committee concluded that the evaluation of the four substances which are α,β-unsaturated should be deferred, pending consideration of other α,β-unsaturated substances. The safety evaluation of the two hydroxyfuranones proceeded because of the existence of supporting data from toxicity studies.

On the basis of the results of the evaluation of the 29 lactones derived from linear and branched-chain hydroxycarboxylic acids and the substances 5-ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone and 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one, the Committee concluded that the use of these substances as flavouring agents would not present safety concerns at the estimated current levels of intake.

In using the Procedure, the Committee noted that where toxicity data were available, they were consistent with the results of the safety evaluation.

The ADIs for γ-nonalactone and γ-undecalactone were maintained.

A monograph summarizing the safety data available on this group of flavouring agents was prepared.

4.5 Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids

The Committee evaluated a group of 32 flavouring agents that included selected esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids (Table 4) using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

The Committee had previously evaluated one member of the group, ethyl isovalerate, at its eleventh meeting (Annex 1, reference *14*), but because of a lack of data, was unable to allocate an ADI.

Intake data

The total annual volume of production of the 32 esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids from their use as flavouring substances is approximately 32 tonnes in Europe and 16 tonnes in the USA. In Europe, more than 90% of the

Table 4

Summary of the results of safety evaluations of 32 esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids[a]

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Methyl isobutyrate	0185	No Europe: 23 USA: 270	NR	No safety concern
Ethyl isobutyrate	0186	No Europe: 750 USA: 470	NR	
Propyl isobutyrate	0187	No Europe: 15 USA: 0.08	NR	
Butyl isobutyrate	0188	No Europe: 2.7 USA: 1.9	NR	
Hexyl isobutyrate	0189	No Europe: 3.00 USA: 0.57	NR	
Heptyl isobutyrate	0190	No Europe: 0.00 USA: 3.0	NR	
trans-3-Heptenyl 2-methylpropanoate	0191	No Europe: 0.01 USA: 2.3	NR	
Octyl isobutyrate	0192	No Europe: 11 USA: 5.0	NR	
Dodecyl isobutyrate	0193	No Europe: 50 USA: 0.76	NR	
Isobutyl isobutyrate	0194	No Europe: 65 USA: 2.3	NR	
Methyl isovalerate	0195	No Europe: 7.8 USA: 110	NR	
Ethyl isovalerate	0196	No Europe: 760 USA: 540	NR	
Propyl isovalerate	0197	No Europe: 2.00 USA: 0.10	NR	
Butyl isovalerate	0198	No Europe: 94 USA: 500	NR	
Hexyl 3-methyl-butanoate	0199	No Europe: 2.3 USA: 3.1	NR	
Octyl isovalerate	0200	No Europe: 7.3 USA: 0.57	NR	
Nonyl isovalerate	0201	No Europe: 0.01 USA: 0.08	NR	

Table 4 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
3-Hexenyl 3-methylbutanoate	0202	No Europe: 9.4 USA: 30	NR	No safety concern
2-Methylpropyl 3-methylbutyrate	0203	No Europe: 78 USA: 130	NR	
2-Methylbutyl 3-methylbutanoate	0204	No Europe: 0.86 USA: 0.95	NR	
Methyl 2-methylbutyrate	0205	No Europe: 390 USA: 69	NR	
Ethyl 2-methylbutyrate[c]	0206	Yes Europe: 2200 USA: 560	Yes	
n-Butyl 2-methylbutyrate	0207	No Europe: 26 USA: 0.02	NR	
Hexyl 2-methylbutanoate	0208	No Europe: 4.9 USA: 8.6	NR	
Octyl 2-methylbutyrate	0209	No Europe: 0.01 USA: 0.10	NR	
Isopropyl 2-methylbutyrate	0210	No Europe: 4.9 USA: 0.10	NR	
3-Hexenyl 2-methylbutanoate	0211	No Europe: 5 USA: 8.8	NR	
2-Methylbutyl 2-methylbutyrate	0212	No Europe: 3.6 USA: 0.04	NR	
Methyl 2-methylpentanoate	0213	No Europe: 0.17 USA: 0.02	NR	
Ethyl 2-methylpentanoate	0214	No Europe: 7.6 USA: 320	NR	
Ethyl 3-methylpentanoate	0215	No Europe: 0.31 USA: 5.90	NR	
Methyl 4-methylvalerate	0216	No Europe: 0.03 USA: 0.10	NR	

NR: not required for evaluation because consumption of the substance was determined to be of no safety concern at step A3 of the procedure.

[a] *Step 1*: All of the esters in this group are in structural class I.
Step 2: All of the esters in this group are metabolized to innocuous products.

[b] The threshold for human intake for class I is 1800 µg per day. All intake values are expressed in µg per day.

[c] The components ethanol and 2-methylbutyric acid are endogenous. The acid is an intermediate in the metabolism of the amino acid.

total annual volume is accounted for by ethyl isobutyrate (ethyl 2-methylpropanoate), ethyl isovalerate (ethyl 3-methylbutanoate), ethyl 2-methylbutyrate (ethyl 2-methylbutanoate) and methyl 2-methylbutyrate (methyl 2-methylbutanoate). In the USA, approximately 67% of the total annual volume is accounted for by ethyl isobutyrate, ethyl isovalerate, butyl isovalerate (butyl 3-methylbutanoate) and ethyl 2-methylbutyrate.

Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids have been detected as natural components of a wide variety of foods. The available quantitative data on the natural occurrence of these esters indicate that the total intake from natural food sources is approximately 14 tonnes per year. This estimated intake is approximately equal to the estimated intake from their use as flavouring substances. In the USA, the consumption of isobutyrate esters from natural food sources is equivalent to their consumption from use as flavouring substances. The consumption of isovalerate esters and 2-methylbutyrate esters from natural food sources is several orders of magnitude higher than that from their use as flavouring agents.

Information on absorption, metabolism and elimination

It is expected that the esters in this group will be readily hydrolysed to their component alcohols and carboxylic acids in the intestinal tract, blood and liver. The metabolism of the hydrolysis products is discussed on pages 26–27.

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids, the Committee assigned all 32 substances to structural class I.

Step 2. At the estimated current levels of intake (see Table 4), these esters would not be expected to saturate the metabolic pathways, and they were all predicted to be metabolized to innocuous products. The left-hand side of the decision-tree was therefore considered.

Step A3. The estimated daily per capita intakes of all but one of the 32 esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids in Europe and the USA were below the threshold for class I (1800 μg per day), so that they were considered to be of no safety concern when used at estimated current levels of

intake as flavouring agents. Only ethyl 2-methylbutyrate has an estimated intake greater than the threshold for class I.

Step A4. Ethyl 2-methylbutyrate is expected to be hydrolysed to ethyl alcohol and 2-methylbutyric acid, which are endogenous. Therefore, this substance was determined to be of no safety concern on the basis of its structural class and known metabolism.

Table 4 summarizes the evaluation of the 32 esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids used as flavouring substances.

Consideration of combined intakes

In the unlikely event that all foods containing all of the substances in this group as flavouring agents were consumed simultaneously on a daily basis, the estimated total daily per capita intake would be 4.6 mg in Europe and 3 mg in the USA. The estimated daily per capita intake of the branched-chain acids (i.e. isobutyric acid, isovaleric acid and 2-methylbutyric acid) formed via hydrolysis of these esters is 3.1 mg in Europe and 2 mg in the USA.

These estimated combined intakes would exceed the threshold for class I. Since all the 32 substances in this group are expected to be efficiently metabolized, they would not be expected to saturate the metabolic pathways. On the basis of the evaluation of the collective data, the Committee concluded that combined intake of these substances would not be expected to be of safety concern.

Conclusion

The Committee concluded that the substances in this group would not present safety concerns at the estimated current levels of intake.

No toxicity data were required for application of the Procedure. However, the Committee noted that where toxicity data were available, they were consistent with the results of the Procedure.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.6 Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids

The Committee evaluated a group of 67 esters of aliphatic linear and branched-chain saturated and monounsaturated primary alcohols

with aliphatic linear saturated carboxylic acids (see Table 5) using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

One member of the group, butyl acetate, had been previously evaluated at the eleventh meeting of the Committee, but no ADI was established due to a lack of data (Annex 1, reference *14*).

Intake data

The total annual volume of production of the 67 esters in this group for use as flavouring agents is approximately 65 tonnes in Europe and 19 tonnes in the USA. In Europe, more than 75% of the total annual volume of production is accounted for by butyl butyrate (*n*-butyl *n*-butanoate), *n*-amyl butyrate (pentyl butanoate) and the acetate esters of methyl alcohol (methanol), butyl alcohol, hexyl alcohol, *cis*-3-hexenol and isobutyl alcohol. In the USA, more than 70% of the total annual volume of production is accounted for by *n*-amyl butyrate, *cis*-3- and *trans*-2-hexenyl propionate (*cis*-3- and *trans*-2-hexenyl propanoate) and the acetate esters of propyl alcohol, isobutyl alcohol and 2-methylbutyl alcohol (2-methylbutanol). On the basis of the reported annual volume of production in Europe and the USA, the total estimated daily per capita intake of the 67 esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids from their use as flavouring agents is 9.2 mg in Europe and 3.8 mg in the USA. The use of seven of the esters (heptyl formate, octyl propionate (octyl propanoate), decyl propionate (decyl propanoate), decyl butyrate (decyl butanoate), butyl heptanoate, butyl laurate (butyl dodecanoate), and *cis*-3- and *trans*-2-hexenyl propionate) has been reported in the USA but not in Europe.

Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids are principal components of alcoholic beverages and of a wide variety of fruits. Quantitative data on the natural occurrence in food for 37 substances in the group have been reported from the USA, which indicate that the intake of these substances from natural sources exceeds the intake from their use as flavouring agents.

Information on absorption, metabolism and elimination

In general, it is expected that esters of aliphatic linear and branched-chain primary alcohols with aliphatic linear saturated carboxylic acids would be hydrolysed to their component alcohols and carboxylic acids. The metabolism of the saturated acids and alcohols is described on pages 26–27.

Esters of the three monounsaturated alcohols in this group are expected to be oxidized via their corresponding aldehydes to carboxylic

Table 5
Summary of the results of safety evaluations of 67 esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids[a]

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Propyl formate	0117	No Europe: 5.0 USA: 0.38	NA	
Butyl formate	0118	No Europe: 21 USA: 0.17	NA	
n-Amyl formate	0119	No Europe: 29 USA: 110	NA	
Hexyl formate	0120	No Europe: 8.7 USA: 8.0	NA	
Heptyl formate	0121	No Europe: 0.00 USA: 0.10	NA	
Octyl formate	0122	No Europe: 0.14 USA: 0.95	NA	
cis-3-Hexenyl formate	0123	No Europe: 43 USA: 1.7	NA	
Isobutyl formate	0124	No Europe: 4.7 USA: 1.5	NA	
Methyl acetate	0125	No Europe: 460 USA: 110	NA	No safety concern
Propyl acetate	0126	No Europe: 180 USA: 440	NA	
Butyl acetate	0127	No Europe: 1200 USA: 170	NA	
Hexyl acetate	0128	Yes Europe: 3200 USA: 160	Yes[c]	
Heptyl acetate	0129	No Europe: 56 USA: 2.3	NA	
Octyl acetate	0130	No Europe: 83 USA: 9.5	NA	
Nonyl acetate	0131	No Europe: 6.6 USA: 2.5	NA	
Decyl acetate	0132	No Europe: 7.3 USA: 21	NA	

Table 5 (*continued*)

Substance	No.	*Step A3*[a] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Lauryl acetate	0133	No Europe: 9.3 USA: 0.57	NA	No safety concern
cis-3-Hexenyl acetate	0134	No Europe: 640 USA: 57	NA	
trans-3-Heptenyl acetate	0135	No Europe: 0.24 USA: 0.76	NA	
10-Undecen-1-yl acetate	0136	No Europe: 0.83 USA: 0.10	NA	
Isobutyl acetate	0137	No Europe: 1200 USA: 1300	NA	
2-Methylbutyl acetate	0138	No Europe: 130 USA: 360	NA	
2-Ethylbutyl acetate	0140	No Europe: 4.0 USA: 0.17	NA	
Methyl propionate	0141	No Europe: 9.3 USA: 30	NA	
Propyl propionate	0142	No Europe: 9.6 USA: 44	NA	
Butyl propionate	0143	No Europe: 10 USA: 1.1	NA	
Hexyl propionate	0144	No Europe: 5.7 USA: 3.0	NA	
Octyl propionate	0145	No Europe: 0.00 USA: 0.02	NA	
Decyl propionate	0146	No Europe: 0.00 USA: 0.95	NA	
cis-3-Hexenyl propionate and *trans*-2-hexenyl propionate	0147	No Europe: 0.00 USA: 430	NA	Not evaluated[c]
Isobutyl propionate	0148	No Europe: 12 USA: 6.5	NA	No safety concern
Methyl butyrate	0149	No Europe: 220 USA: 44	NA	

Table 5 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Propyl butyrate	0150	No Europe: 75 USA: 38	NA	
Butyl butyrate	0151	No Europe: 390 USA: 63	NA	
n-Amyl butyrate	0152	No Europe: 450 USA: 200	NA	
Hexyl butyrate	0153	No Europe: 110 USA: 27	NA	
Heptyl butyrate	0154	No Europe: 6.0 USA: 3.8	NA	
Octyl butyrate	0155	No Europe: 16 USA: 0.38	NA	
Decyl butyrate	0156	No Europe: 0.00 USA: 0.08	NA	
cis-3-Hexenyl butyrate	0157	No Europe: 160 USA: 4.8	NA	
Isobutyl butyrate	0158	No Europe: 47 USA: 7.4	NA	No safety concern
Methyl valerate	0159	No Europe: 30 USA: 11	NA	
Butyl valerate	0160	No Europe: 3.7 USA: 0.10	NA	
Propyl hexanoate	0161	No Europe: 14 USA: 0.17	NA	
Butyl hexanoate	0162	No Europe: 15 USA: 1.9	NA	
n-Amyl hexanoate	0163	No Europe: 8.7 USA: 8.8	NA	
Hexyl hexanoate	0164	No Europe: 150 USA: 13	NA	
cis-3-Hexenyl hexanoate	0165	No Europe: 42 USA: 1.3	NA	

Table 5 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Isobutyl hexanoate	0166	No Europe: 6.1 USA: 1.7	NA	
Methyl heptanoate	0167	No Europe: 5.7 USA: 0.10	NA	
Propyl heptanoate	0168	No Europe: 0.14 USA: 0.38	NA	
Butyl heptanoate	0169	No Europe: 0.00 USA: 4.4	NA	
n-Amyl heptanoate	0170	No Europe: 0.61 USA: 0.02	NA	
Octyl heptanoate	0171	No Europe: 0.21 USA: 0.38	NA	
Isobutyl heptanoate	0172	No Europe: 0.01 USA: 1.9	NA	
Methyl octanoate	0173	No Europe: 9.7 USA: 0.17	NA	
n-Amyl octanoate	0174	No Europe: 3.4 USA: 1.9	NA	No safety concern
Hexyl octanoate	0175	No Europe: 1.3 USA: 0.95	NA	
Heptyl octanoate	0176	No Europe: 0.71 USA: 0.95	NA	
Octyl octanoate	0177	No Europe: 0.03 USA: 2.3	NA	
Nonyl octanoate	0178	No Europe: 0.14 USA: 0.95	NA	
Methyl nonanoate	0179	No Europe: 0.86 USA: 2.3	NA	
Methyl laurate	0180	No Europe: 5.1 USA: 0.76	NA	
Butyl laurate	0181	No Europe: 0.00 USA: 0.10	NA	

Table 5 (*continued*)

Substance	No.	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Endogenous or metabolized to endogenous substances?	Conclusion based on current levels of intake
Isoamyl laurate	0182	No Europe: 0.14 USA: 0.57	NA	No safety concern
Methyl myristate	0183	No Europe: 62 USA: 46	NA	
Butyl stearate	0184	No Europe: 5.1 USA: 5.5	NA	

[a] *Step 1*: All of the esters in this group are in structural class I except 2-ethylbutyl acetate, which is in structural class II.
Step 2: Evaluation of *cis*-3- and *trans*-2-hexenyl propionate was postponed. All of the other substances in this group are metabolized to innocuous products.
[b] The thresholds for human intake for classes I and II are 1800 μg per day and 540 μg per day, respectively. All intake values are expressed in μg per day.
[c] Hexanoic acid, the metabolite of the component hexyl alcohol, and acetic acid are endogenous in humans.
[d] Evaluation postponed, pending consideration of other α,β-unsaturated carbonyl compounds.

acids, which then undergo β-oxidation in the fatty acid and other well-known metabolic pathways.

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids, the Committee assigned all but one of the 67 esters to structural class I. 2-Ethylbutyl acetate contains a sterically hindered functional group and was therefore assigned to structural class II.

Step 2. At this step the evaluation of *cis*-3- and *trans*-2-hexenyl propionate was postponed, pending consideration of other α,β-unsaturated carbonyl compounds.

The available data indicate that the remaining esters in this group would be hydrolysed in humans to their component alcohols and carboxylic acids. The aliphatic acyclic primary alcohols are oxidized to their corresponding carboxylic acids, which are either conjugated and excreted in the urine, or undergo β-oxidation and cleavage. The aliphatic linear saturated carboxylic acids are endogenous in humans. At the current levels of per capita intake these esters would not be expected to saturate the metabolic pathways. Therefore, the remaining 66 esters of aliphatic acyclic primary alcohols with aliphatic linear

saturated carboxylic acids were predicted to be metabolized to innocuous products. Accordingly, the Committee considered the left-hand side of the decision-tree.

Step A3. The estimated daily per capita intakes of all but one of the remaining 65 class I esters in this group in Europe and the USA were below the threshold for human intake (1800 μg). Only hexyl acetate had an estimated daily per capita intake greater than the threshold for class I. The estimated daily per capita intake of 2-ethylbutyl acetate in Europe and the USA was below the threshold for human intake for class II (540 μg).

Step A4. This step was considered only for hexyl acetate which was the only substance in this group for which the estimated level of intake exceeded the threshold for class I. The component hexyl alcohol is oxidized to hexanoic acid which is endogenous as it is an intermediary metabolite in the fatty acid pathway, and acetate is a component of the tricarboxylic acid cycle. In the opinion of the Committee the endogenous levels of these two metabolites would not give rise to perturbations outside the physiological range. Therefore, hexyl acetate was also determined to be of no safety concern on the basis of its structural class and known metabolism.

Table 5 summarizes the evaluation of the 67 esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids used as flavouring substances.

Consideration of combined intakes

In the unlikely event that all foods containing all of the 66 esters evaluated as flavouring substances were consumed simultaneously on a daily basis, the estimated daily per capita intake in Europe and the USA would exceed the threshold for human intake for substances in class I. All the flavouring agents in this group of esters are expected to be metabolized via well-known biochemical pathways to innocuous metabolites and/or endogenous substances and in the opinion of the Committee the endogenous levels of these metabolites would not give rise to perturbations outside the physiological range. Accordingly, the combined intake of these substances was considered to be of no safety concern.

Conclusions

On the basis of the results of the Procedure, the Committee concluded that the 66 esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids evaluated pose no safety concern when used at the estimated levels of current intake as

flavouring agents. The evaluation of *cis*-3- and *trans*-2-hexenyl propionate was postponed, pending consideration of other α,β-unsaturated carbonyl compounds.

No toxicity data were required for the application of the Procedure for this group of esters. However, the Committee noted that where toxicity data were available, they were consistent with the results of the Procedure.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.7 Esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids

A safety evaluation of a group of 26 terpenoid esters used as flavouring agents (see Table 6) was conducted using the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1).

One member of the group, geranyl acetate (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate), was previously evaluated at the twenty-third meeting of the Committee (Annex 1, reference *50*). It was evaluated as part of a group of other terpenoid flavouring substances, citral, citronellol and linalool, which have close chemical, biochemical and toxicological relationships. The Committee allocated a group ADI of 0–0.5 mg/kg of body weight, expressed as citral, to these substances on the basis of their clearly defined metabolism and their low toxicity in short-term toxicity studies.

Intake data

The total annual volume of production of the 26 terpenoid esters used as flavouring agents is approximately 13 tonnes in Europe and 2 tonnes in the USA. In both Europe and the USA approximately 60% of the total annual volume is accounted for by the acetate and butyrate esters of citronellol, geraniol and nerol. On the basis of these annual volumes of production, the total estimated daily per capita intake of the 26 terpenoid esters used as flavouring substances is 1800 μg in Europe and 410 μg in the USA. The total estimated daily per capita intake of the terpenoid alcohols (i.e. citronellol, geraniol, nerol and rhodinol) formed via hydrolysis of these esters is 1400 μg in Europe and 320 μg in the USA.

Terpenoid esters are principal flavour components of citrus fruit and citrus peel oils, and have also been detected in a wide variety of other fruits, spices and vegetables. The terpenoid esters are usually found at concentrations of up to 1 mg/kg in citrus fruit juices, 20 g/kg in citrus

Table 6
Summary of the results of safety evaluations of 26 esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids[a]

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	Conclusion based on current levels of intake
Citronellyl formate	0053	No Europe: 103 USA: 2.5	
Geranyl formate	0054	No Europe: 330 USA: 48	
Neryl formate	0055	No Europe: 0.01 USA: 0.04	
Rhodinyl formate	0056	No Europe: ND USA: 0.10	
Citronellyl acetate	0057	No Europe: 217 USA: 36	
Geranyl acetate[c]	0058	No Europe: 580 USA: 205	
Neryl acetate	0059	No Europe: 180 USA: 63	
Rhodinyl acetate	0060	No Europe: 1.1 USA: 0.8	
Citronellyl propionate	0061	No Europe: 41 USA: 1.5	No safety concern
Geranyl propionate	0062	No Europe: 81 USA: 11	
Neryl propionate	0063	No Europe: 4.3 USA: 1.1	
Rhodinyl propionate	0064	No Europe: ND USA: 0.02	
Citronellyl butyrate	0065	No Europe: 32 USA: 5	
Geranyl butyrate	0066	No Europe: 60 USA: 25	
Neryl butyrate	0067	No Europe: 0.4 USA: 0.02	
Rhodinyl butyrate	0068	No Europe: ND USA: 1.0	

Table 6 (*continued*)

Substance	No.	*Step A3*[b] Does intake exceed the threshold for human intake?	Conclusion based on current levels of intake
Citronellyl valerate	0069	No Europe: 0.7 USA: 4.0	
Geranyl hexanoate	0070	No Europe: 0.07 USA: 0.5	
Citronellyl isobutyrate	0071	No Europe: 13 USA: 1.3	
Geranyl isobutyrate	0072	No Europe: 124 USA: 3.0	
Neryl isobutyrate	0073	No Europe: 2.0 USA: 0.4	
Rhodinyl isobutyrate	0074	No Europe: 0.03 USA: 0.04	No safety concern
Geranyl isovalerate	0075	No Europe: 43 USA: 1.7	
Neryl isovalerate	0076	No Europe: 0.03 USA: 0.04	
Rhodinyl isovalerate	0077	No Europe: 0.01 USA: 0.02	
Geranyl 2-ethylbutanoate	0078	No Europe: 0.6 USA: 0	

ND, no data reported.
[a] *Step 1*: All of the esters in this group are in structural class I.
Step 2: All of the esters in this group are metabolized to innocuous products.
[b] The threshold for human intake for class I is 1800 µg per day. All intake values are expressed in µg per day.
[c] The ADI for this substance was maintained.

peel oils and 50 g/kg in spices. In the USA terpenoid esters are consumed predominantly as components of traditional foods and the total annual volume of consumption of the most common terpenoid esters as natural components of food is estimated to be approximately 300 tonnes (Stofberg & Grundschober, personal communication, 1987).

Information on absorption, metabolism and elimination

The terpenoid esters are hydrolysed to their corresponding terpenoid alcohols (geraniol, citronellol, nerol and rhodinol) and aliphatic carboxylic acids (formic, acetic, propionic, butyric, valeric, hexanoic,

isobutyric and isovaleric acids). Both the hydrolysis and the metabolism of aliphatic carboxylic acids are discussed on pages 26–27.

Following hydrolysis, the terpenoid alcohols undergo a complex pattern of alcohol oxidation, ω-oxidation, hydration, selective hydrogenation and subsequent conjugation to form oxygenated polar metabolites which are excreted primarily in the urine. Geraniol, related terpenoid alcohols (citronellol and nerol) and the aldehydes (geranial and neral) follow similar metabolic pathways in animals (Fig. 2).

Application of the Procedure

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned terpenoid esters, the Committee assigned all 26 esters to structural class I.

Step 2. The esters in this group are expected to be readily hydrolysed to their component alcohols and carboxylic acids, which are considered to be innocuous. The terpenoid alcohols are expected to undergo ω-oxidation and functional group oxidation to yield polar metabolites which are excreted as the glucuronic acid conjugate in the urine. Eight of the nine component carboxylic acids are endogenous in humans and are metabolized in the fatty acid β-oxidation pathway, amino acid pathways, the citric acid cycle or the C_1-tetrahydrofolate pathway to eventually yield carbon dioxide and water. The remaining carboxylic acid, 2-ethylbutyric acid, undergoes oxidation to polar metabolites which are conjugated with glucuronic acid and excreted. At current levels of intake these esters and their component terpenoid alcohols and aliphatic carboxylic acids would not be expected to saturate these metabolic pathways.

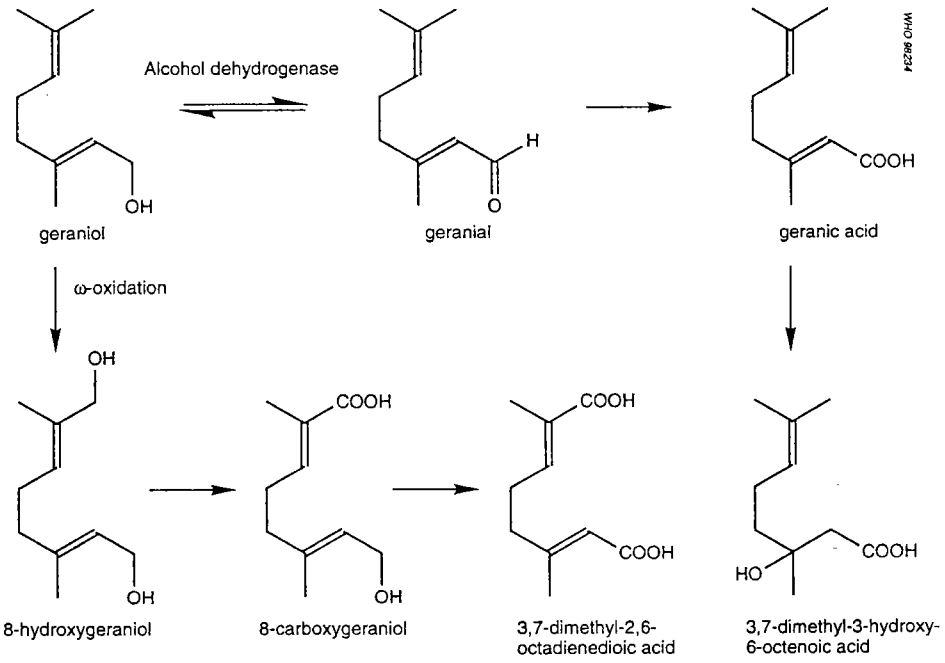
Step A3. The daily per capita intakes of each of the 26 terpenoid esters in both Europe and the USA are below the threshold for class I (1800 μg). Therefore none of the 26 terpenoid esters evaluated were considered to pose a safety concern when used at current levels of intake as flavouring substances.

Table 6 summarizes the evaluation of the 26 terpenoid esters used as flavouring substances.

Consideration of combined intake

In the unlikely event that all foods containing these 26 terpenoid esters used as flavouring agents were consumed simultaneously on a daily basis, the estimated total daily per capita intake would still be below the threshold for human intake for class I (1800 μg). The

Figure 2
Metabolism of geraniol in rats



Committee noted that the terpene alcohols, geraniol, citronellol and linalool, are used as flavouring agents and that the combined intakes of these alcohols and esters would be less than the group ADI.

Conclusions

The Committee concluded that the esters derived from branched-chain terpenoid alcohols and aliphatic acyclic linear and branched-chain carboxylic acids present no safety concern at the estimated levels of current intake.

No toxicity data were required for the application of the Procedure. However, the Committee noted that where toxicity data were available, they were consistent with the results of the Procedure.

The Committee noted that some of the esters are metabolized to α,β-unsaturated carbonyl compounds, but concluded that these had been adequately evaluated previously (Annex 1, reference *50*). The Committee maintained the group ADI of 0–0.5 mg/kg of body weight for geranyl acetate, citral, citronellol and linalool.

A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.8 Specifications for flavouring agents

The specifications for 173 flavouring agents on the modified agenda were reviewed. New specifications were prepared for 153 flavouring agents, 28 of which were designated as "tentative". The existing specifications for 11 flavouring agents reviewed toxicologically and for two flavouring agents reviewed for specifications only (see section 6) were revised. In addition, the existing specifications for the 52 flavouring agents in FAO Food and Nutrition Paper, No. 52, Add. 4 (Annex 1, reference *124*) were given identification numbers.

5. Contaminants: aflatoxins

Aflatoxins B_1, B_2, G_1 and G_2 are mycotoxins that may be produced by three species of *Aspergillus*: *A. flavus*, *A. parasiticus* and *A. nomius*, which contaminate plants and plant products. Aflatoxins M_1 and M_2, the hydroxylated metabolites of aflatoxins B_1 and B_2, may be found in milk or milk products obtained from livestock that have ingested contaminated feed. Of these six aflatoxins, aflatoxin B_1 is the most frequently present in contaminated samples and aflatoxins B_2, G_1 and G_2 are generally not reported in the absence of aflatoxin B_1. Most of the toxicological data relate to aflatoxin B_1. Intake of aflatoxins in the diet arises mainly from eating contaminated maize and groundnuts and their products.

The aflatoxins were evaluated at the thirty-first meeting of the Committee (Annex 1, reference *77*). At that time, the Committee considered aflatoxins to be potential human carcinogens. Sufficient information was not available to establish a figure for a tolerable level of intake. The Committee urged that the intake of dietary aflatoxins be reduced to the lowest practicable levels so as to reduce the potential risk as far as possible. A working group convened by the International Agency for Research on Cancer also concluded that naturally occurring aflatoxins are carcinogenic to humans (*12*).

At its forty-sixth meeting (Annex 1, reference *122*), the Committee considered estimates of the carcinogenic potency of aflatoxins and the potential risks associated with their intake. In view of the value of such estimates, the Committee recommended that this task be continued at its next meeting and that a monograph be published summarizing the data and analyses.

At its present meeting, the Committee reviewed a wide range of studies in both animals and humans that provided qualitative and quantitative information on the hepatocarcinogenicity of aflatoxins. The Committee evaluated the potency of these contaminants, linked these potencies to intake estimates and discussed the impact of hypothetical standards on sample populations and their overall risks.

Carcinogenicity

The aflatoxins are among the most potent mutagenic and carcinogenic substances known. Extensive experimental evidence from test species shows that aflatoxins are capable of inducing liver cancer in most animal species studied. In addition, most epidemiological studies show a correlation between exposure to aflatoxin B_1 and an increased incidence of liver cancer. Aflatoxins are metabolized in humans and test species to the corresponding epoxide which is usually considered to be the ultimate reactive intermediate. There is some evidence suggesting that humans are at substantially lower risk from exposure to aflatoxins than test species. The Committee was aware of epidemiological studies which suggest that intake of aflatoxins poses no detectable independent risk and of studies which suggest that they pose risks only in the presence of other risk factors such as hepatitis B infection. Several current studies are likely to allow more accurate estimates of the risks to humans from the intake of aflatoxins, most notably cohort studies in China (Qidong and Shanghai) and Thailand and hepatitis B vaccination trials in China (Qidong and Taiwan) and the Gambia. When these studies are complete, the Committee may wish to re-evaluate the risks of aflatoxins in humans.

A number of factors influence the risk of primary liver cancer, most notably carriage of hepatitis B virus as determined by the presence in serum of the hepatitis B surface antigen (presence denoted $HBsAg^+$ and absence denoted $HbsAg^-$). The potency of aflatoxin B_1 appears to be significantly enhanced in individuals with simultaneous hepatitis B infection. This interaction makes it difficult to interpret the epidemiological studies to determine the extent to which aflatoxins act as independent risk factors. The conclusions of the Committee regarding the carcinogenic potency of aflatoxins are therefore contingent upon the dynamics of hepatitis B infection in a human population.

The identification of hepatitis C virus is an important recent advance in understanding the etiology of liver cancer. Two studies have inves-

tigated interactions between hepatitis C infection, aflatoxins and liver cancer, but the results so far are inconclusive. It is estimated that between 50 and 100% of cases of liver cancer are associated with persistent infection with hepatitis B and/or hepatitis C.

The Committee considered that the weight of scientific evidence, which includes epidemiological data, studies in laboratory animals and *in vivo* and *in vitro* studies of metabolism, supports a conclusion that aflatoxins should be treated as carcinogenic food contaminants, the intake of which should be reduced to levels as low as reasonably achievable.

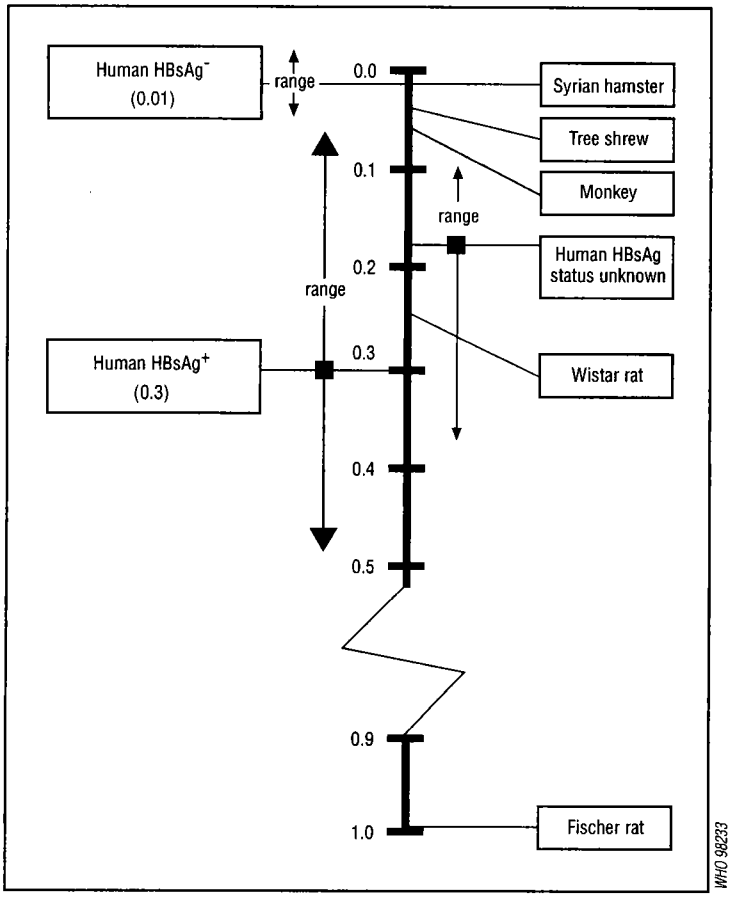
Carcinogenic potency

The Committee reviewed dose–response analyses that have been performed on aflatoxins. All of these analyses have limitations, three of which predominate. First, all of the epidemiological data from which a dose–response relationship can be determined are confounded by concurrent infection with hepatitis B. The epidemiological data are from geographical areas where both the prevalence of $HBsAg^+$ individuals and of contamination with aflatoxins are high; the relationship between these risk factors in areas in which aflatoxin contamination and prevalence of hepatitis B are low is unknown. Second, the reliability and precision of the estimates of exposure to aflatoxins in the relevant study populations are unknown. For example, aflatoxin biomarkers in humans do not reflect long-term intake of aflatoxins; analyses of crops for aflatoxins do not reflect the levels of aflatoxins consumed in foods after selection and processing. Finally, the shape of the dose–response curve is unknown and this introduces an additional element of uncertainty when choosing mathematical models for interpolation.

Observations concerning the interaction between hepatitis B infection and aflatoxins suggest two separate aflatoxin potencies; one is apparent in populations in which chronic hepatitis infections are common, the other in populations in which chronic hepatitis infections are rare. In analyses based on toxicological and epidemiological data, potency estimates for aflatoxins were divided into two basic groups, potencies applicable to individuals without hepatitis B infection and those applicable to individuals with chronic hepatitis B infection. The Committee found these estimates useful even though, through the use of differing mathematical models, they covered a broad range of possible values (Fig. 3). Potencies calculated from epidemiological studies in which hepatitis B infection status was unknown were in the range of potencies found in individuals with and without hepatitis B infection. The review also considered the extrapolation of animal data

Figure 3

Potency estimates for human liver cancer resulting from exposure to aflatoxin B_1 (cases per year/100 000 people per ng of aflatoxin B_1/kg of body weight per day), based on epidemiological and toxicological studies



HBsAg⁺: Hepatitis B surface antigen detected in serum; HBsAg⁻: hepatitis B surface antigen not detected in serum.

to estimate potency in humans; these estimates also generally fell within the range of the potency estimates derived from the epidemiological data.

There are several potential biases in the potency estimates depicted in Fig. 3:

- Only studies showing a positive association between aflatoxins and liver cancer were used as opposed to considering all studies (negative as well as positive); this leads to overestimation of the aflatoxin potency.

- When current levels of intake (i.e. using biomarkers or dietary surveys) are related to current levels of liver cancer (which presumably has a long induction period), historical levels of intake are ignored, and since intakes are likely to have been higher in the past, aflatoxin potency will be overestimated.
- The earliest studies systematically underestimated the prevalence of hepatitis B infection in patients with liver cancer by as much as 20–30% due to limitations in the methodology used to detect hepatitis B virus, which also leads to an overestimate of the relative potency of any other factor, including aflatoxins.
- Histological confirmation of the cases of liver cancer is limited in most epidemiological studies, allowing the possibility that cases of non-primary liver cancer have been included, which could lead to an underestimation or overestimation of the aflatoxin potency.

When these biases are taken into account, the values in Fig. 3 should be viewed as overestimates of the potency of the aflatoxins, leading to the hypothesis that it is possible that humans are in fact less sensitive to aflatoxins than the animal species tested in laboratory experiments.

The Committee reviewed the extensive data available on the metabolism of aflatoxins in various species. It was agreed that differences in the carcinogenic potency of aflatoxins between species can be partially attributed to differences in metabolism. However, there was insufficient quantitative information available about competing aspects of metabolic activation and detoxification of aflatoxin B_1 in various species to identify an adequate animal model for humans and to explain the apparent differences in potency between species.

The intake assessments used in many of the epidemiological studies ignored the contributions to total aflatoxin intake made by milk and milk products. Thus, the potencies shown in Fig. 3 do not generally apply to aflatoxin M_1. The results of a comparative toxicity study in rats suggest that aflatoxin M_1 has a potency approximately one order of magnitude less than that of aflatoxin B_1 in this species.

The Committee reviewed the potency estimates from the epidemiological studies which showed a positive association between aflatoxins and liver cancer and chose separate potency estimates and ranges for $HBsAg^+$ and $HBsAg^-$ individuals. Potency values of 0.3 cancers per year/100 000 population per ng of aflatoxins/kg of body weight per day (range 0.05–0.5) for $HBsAg^+$ individuals and of 0.01 cancers per year/100 000 population per ng of aflatoxins/kg of body weight per day (range 0.002–0.03) in $HBsAg^-$ individuals were chosen.

Population risks

The fraction of the incidence of liver cancer in a population attributable to intake of aflatoxins was derived by combining estimates of aflatoxin potency (risk per unit dose) and estimates of aflatoxin intake (dose per person). The Committee reviewed the frequency and amount of aflatoxin contamination in a variety of products (e.g. groundnuts, cereals and maize) in numerous countries. Many of the data on levels of aflatoxin contamination were derived from non-random samples which appeared to be biased upwards because monitoring studies focus on products that are thought to be contaminated. Some of the data on levels of contamination are not likely to be based on current Codex Alimentarius Commission sampling recommendations for aflatoxins. Accordingly, data on levels of contamination should be interpreted with caution and used only to infer patterns of importance in setting standards and not to provide exact contamination estimates.

The Committee considered the possible impact of applying hypothetical standards to aflatoxin contamination. It noted that the magnitude of the difference between two hypothetical standards is substantially larger than the magnitude of the difference in the mean contamination levels resulting from application of the separate standards. For example, in the case of maize from the USA, which has a mean level of aflatoxin contamination of 4.7 μg/kg, application of a hypothetical standard of 20 μg/kg would result in rejection of 3.9% of the crop and a mean level of aflatoxin contamination of 0.9 μg/kg. Imposition of a stricter hypothetical standard of 10 μg/kg would result in rejection of 6.2% of the crop and reduce the mean level of aflatoxin contamination by 0.3 μg/kg to 0.6 μg/kg (Table 7). Similar results would be obtained if aflatoxin B_1 levels in maize and total aflatoxins or aflatoxin B levels in groundnuts were examined.

Using the Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme regional diets combined with data on levels of aflatoxin contamination, the Committee was able to provide relative estimates of the mean dietary intake of aflatoxins for various regions. If these intakes are linked to the potency estimates shown in Fig. 3, it is possible to calculate the overall population risks on the basis of the prevalence of hepatitis B infection in various regions.

From its analysis the Committee noted that the application of a standard would prevent human consumption of the most highly contaminated samples, thus greatly reducing average estimated intakes of aflatoxins. The use of standards by all countries should be encour-

Table 7
Distribution of total aflatoxin contamination in maize from the USA and comparison of the impact of two different hypothetical standards on the percentage of samples rejected and the mean contamination level

Concentration of total aflatoxins in maize (µg/kg)	Percentile	Impact of hypothetical standard on percentage of samples rejected and mean contamination level[a]
0.1	10.0	
0.2	30.0	
0.3	50.0	
0.4	70.0	
0.5	80.0	
1.0	88.0	
5.0	90.6	
10	93.8	6.2% of samples rejected at a standard of 10 µg/kg (mean contamination level = 0.6 µg/kg)
15	95.0	
20	96.1	3.9% of samples rejected at a standard of 20 µg/kg (mean contamination level = 0.9 µg/kg)
30	96.8	
40	97.6	
50	98.0	

[a] The mean level of aflatoxin contamination with no standard was 4.7 µg/kg.

aged. The Committee considered the effect of modifying a given standard through the use of several hypothetical calculations. Two illustrations are given below.

The first example pertains to areas in which the level of contamination of food by aflatoxins is low and the proportion of the population who are $HBsAg^+$ is small. For this purpose, monitoring data from Europe on aflatoxin B_1 levels in groundnuts, maize[1] and their products were used. In this example, 1% of the population were assumed to be $HBsAg^+$. From the potency estimates given earlier (see Fig. 3), this yields an estimated potency for this population of $0.01 \times 99\% + 0.3 \times 1\% = 0.013$ cancers per year/100 000 people per ng of aflatoxins/kg of body weight per day (range 0.002–0.035). If it is assumed that all samples with levels of contamination above 20 µg/kg are removed and that these foods are ingested according to the "European diet", the mean estimated intake of aflatoxins is 19 ng per person per day. Assuming that an adult human weighs 60 kg, the estimated population

[1] The Committee noted that the aflatoxin data for Europe were for "all cereals". However, in these calculations, it was assumed that the aflatoxin level for "all cereals" applied to maize only.

risk (potency × intake) is 0.0041 cancers per year per 100000 people (range 0.0006–0.01). In contrast, if the same assumptions are used but a hypothetical standard of 10 μg/kg is applied, the average aflatoxin intake is 18 ng per person per day, resulting in an estimated population risk of 0.0039 cancers per year per 100000 people (range 0.0006–0.01). Thus, reducing the hypothetical standard from 20 μg/kg to 10 μg/kg yields a reduction in the estimated population risk of approximately two cancers per year per 1000 million people.

The second example pertains to areas with higher levels of aflatoxin contamination (for these purposes monitoring data from China on aflatoxin B_1 levels in groundnuts, maize and their products were used) and where a larger percentage of the population are carriers (in this case, 25% were assumed to be $HBsAg^+$). The estimated potency for this population is $0.01 \times 75\% + 0.3 \times 25\% = 0.083$ cancers per year per ng of aflatoxins ingested/kg of body weight per day (range 0.014–0.15). If a hypothetical standard of 20 μg/kg and the "Far Eastern diet" are used, the average estimated intake is 125 ng per person per day, yielding an average population risk of 0.17 cancers per year per 100000 people (range 0.03–0.3). If a hypothetical standard of 10 μg/kg is used, the average estimated intake falls to 103 ng per person per day, yielding an estimated population risk of 0.14 cancers per year per 100000 people (range 0.02–0.3). Thus, reducing the hypothetical standard for this population from 20 μg/kg to 10 μg/kg yields a reduction in the estimated population risk of 300 cancers per year per 1000 million people.

Conclusions

1. Aflatoxins are considered to be human liver carcinogens. Aflatoxin B_1 is the most potent carcinogen of the aflatoxins and most of the toxicological data available are related to aflatoxin B_1. Aflatoxin M_1, the hydroxylated metabolite of B_1, has a potency approximately one order of magnitude less than that of B_1.
2. The potency of aflatoxins in $HBsAg^+$ individuals is substantially higher than in $HBsAg^-$ individuals. Thus, reduction of the intake of aflatoxins in populations with a high prevalence of $HBsAg^+$ individuals will result in a greater reduction in liver cancer rates than reduction of the intake of aflatoxins in populations with a low prevalence of $HBsAg^+$ individuals.
3. Vaccination against hepatitis B will reduce the number of carriers of the virus. The present analysis suggests that reducing the number of carriers would reduce the potency of the aflatoxins in vaccinated populations and consequently reduce the risk of liver cancer.

4. Analyses of the application of hypothetical standards for aflatoxin contamination in food (10 μg/kg or 20 μg/kg) to model populations indicates that:
   (a) populations in which the prevalence of $HBsAg^+$ individuals is low and/or in which the mean intake of aflatoxins is low (less than 1 ng/kg of body weight per day) are unlikely to exhibit detectable[1] differences in population risks;
   (b) populations in which both the prevalence of $HBsAg^+$ and the intake of aflatoxins are high would benefit from reductions in aflatoxin intake.
5. The Committee has previously noted that reductions in the intake of aflatoxins can be achieved through avoidance measures such as improved farming and proper storage practices and/or through enforcing standards for levels of contamination in food or feed within countries and across borders (Annex 1, reference 77).
6. When two alternative standards for aflatoxin contamination in food are being considered, if the fraction of the samples excluded under the two standards is similar, the higher standard will yield essentially the same risk of liver cancer as the lower standard. When a substantial fraction of the current food supply is heavily contaminated with aflatoxins, reducing the levels of contamination may result in a detectable[1] reduction in rates of liver cancer. Conversely, when only a small fraction of the current food supply is heavily contaminated, reducing the standard by an apparently substantial amount may have little appreciable effect on health.

6. Revision of certain specifications

A total of 40 substances were examined for specifications only (see Annex 2), and the specifications for 30 were revised.

The specifications for agar, carthamus yellow, microcrystalline wax, propylene glycol, propylene glycol alginate and gellan gum were revised, with minor changes.

The specifications for alginic acid, ammonium alginate, calcium alginate, potassium alginate and sodium alginate were revised and the requirements for relative molecular mass range were changed in

[1] In the context of this statement "detectable" refers to an aflatoxin-induced change in liver cancer rates which exceeds the year-to-year variability around the current incidence and mortality rates. Hence "detectable" refers to the ability to observe a significant effect on the occurrence of liver cancer following intervention and will depend on the quality of the data available on historical trends in incidence and mortality.

order to reflect more precisely the products on the market. Some minor changes were also made.

The specifications for aluminium powder, mixed carotenoids, ethyl hydroxyethyl cellulose, propylene glycol esters of fatty acids and talc were revised and the "tentative" qualifications were deleted.

The specifications for citric acid, calcium propionate (calcium propanoate), potassium propionate (potassium propanoate) and sodium propionate (sodium propanoate) were revised, with minor changes. Citric acid was also added to the section on flavouring agents in the specifications monograph.

The specifications for propionic acid used as a preservative and an antimould and antirope agent were revised and designated as "tentative". The Committee requested information on the method of analysis and levels of readily oxidizable substances.

The Committee agreed to revise the specifications for modified starches to include enzyme treatment as an alternative method for modifying food starches. In addition, the Committee agreed to delete the minimum and maximum levels of reagents used in the processing of the starches since the end-product specifications were deemed sufficient to assure the quality and safety of the various modified starches. As a result of these recommendations, the existing tentative monograph for enzyme-treated starches was withdrawn.

The specifications for allyl cyclohexane propionate, ethyl octanoate, ethyl nonanoate, isoamyl acetate, isoamyl butyrate, isoamyl isobutyrate and isoamyl isovalerate used as flavouring agents were reviewed and given identification numbers. The specifications for isoamyl acetate used as a carrier solvent were revised in order to reflect that the substance is a mixture.

The existing tentative specifications for carbon dioxide and sulfur dioxide were revised in order to define purer products and the "tentative" designation was deleted.

The specifications for gum arabic obtained from certain species of acacia trees were last revised at the forty-fourth meeting of the Committee (Annex 1, reference *116*). In revising the specifications for gum arabic at its present meeting, the Committee considered two new extensive project reports from FAO (*13*, *14*) on the production, marketing and physicochemical characterization of this substance. The reports demonstrated that chemometric analysis of analytical compositional data is a suitable procedure for evaluating the chemical rela-

tionship of gums obtained from various acacia species. In the light of these reports, the Committee reiterated that gum from other acacia species closely related to *Acacia senegal* and meeting the newly revised specifications would adequately reflect the materials that had been toxicologically evaluated. The specifications were revised to make a clear distinction between gum arabic obtained from *A. seyal* and from *A. senegal.*

New specifications for enzyme-hydrolysed sodium carboxymethyl cellulose were prepared and designated as "tentative". The Committee requested information on the physical state of the substance as manufactured, the nature and proportion of material of low relative molecular mass present in the substance, and tests that distinguish the substance from sodium carboxymethyl cellulose.

The existing tentative specifications for carthamus red were revised and the "tentative" designation was maintained. The Committee requested information on the content of carthamin and method of assay.

The existing tentative specifications for petroleum jelly were revised, with minor corrections, and the "tentative" designation was maintained. The Committee requested information on the method of analysis and levels of viscosity at 100 °C, carbon number at 5% distillation point, average relative molecular mass and oil content. Unless this information was received by 31 March 1998, the specifications would be withdrawn.

The Committee compared the specifications for "diacetyltartaric and fatty acid esters of glycerol" (DATEM) with the existing tentative specifications for "tartaric, acetic and fatty acid esters of glycerol, mixed" and noted that the substances appear very similar. Both substances were toxicologically evaluated at the seventeenth meeting of the Committee in 1973 (Annex 1, reference *32*). At that meeting, DATEM was assigned an ADI of 0–50 mg/kg of body weight, whereas the mixed tartaric, acetic and fatty acids of glycerol were assigned an ADI "not limited". The Committee has not received information which would allow these substances to be distinguished analytically. The Committee decided to maintain the tentative status of the existing specifications for "tartaric, acetic and fatty acid esters of glycerol, mixed" and requested data that would distinguish this substance from DATEM. Unless such data were provided by 31 March 1998, the Committee would consider combining the two specifications. The existing specifications of DATEM were revised.

The Committee withdrew the tentative specifications for anoxomer since none of the information requested at its twenty-sixth meeting (Annex 1, reference *59*) has been submitted. The Committee was informed that anoxomer has been neither produced nor used for many years.

The specifications for turmeric as a food colour were on the agenda for revision. However, as the use of this substance was considered to be as a spice and not as a food colour, the Committee decided to withdraw the specifications.

7. Recommendations

1. In view of the large number of food additives, food ingredients and contaminants requiring evaluation or re-evaluation, the important role that the recommendations of the Committee play in the development of international food standards and of regulations in many countries, and the need for maintaining consistency and continuity within the Committee, it is strongly recommended that meetings of the Joint FAO/WHO Expert Committee on Food Additives continue to be held at least once yearly to evaluate these substances.
2. One of the substances referred to the present meeting for evaluation is an example of materials that have been defined as "novel foods" by some countries and organizations. The Committee recommended that FAO and WHO arrange at future meetings of the Committee for the review of procedures outlined in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) for the safety evaluation of these types of products and for the development of guidelines for assessing their safety and wholesomeness, taking into account guidelines developed by other organizations.

Acknowledgement

The Committee wishes to thank Dr P. Jenkins, International Programme on Chemical Safety, WHO, Geneva, Switzerland, for his assistance in the preparation of the report.

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Annex 1

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Annex 2

Acceptable Daily Intakes, other toxicological information, and information on specifications

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg/kg of body weight and other toxicological recommendations
Antioxidant		
tert-Butylhydroquinone (TBHQ)	R	0–0.7
Emulsifiers		
Microcrystalline cellulose	R	Not specified[b, c]
Sucrose esters of fatty acids and sucroglycerides	R	0–30 (group ADI)
Enzyme preparations		
α-Acetolactate decarboxylase	N, T	Not specified (temporary)[b, d]
Maltogenic amylase	N, T	Not specified (temporary)[b, d]
Flavouring agent		
trans-Anethole	R	0–0.6 (temporary)[e]
Glazing agent		
Hydrogenated poly-1-decene	N	No ADI allocated because insufficient data were available
Sweetening agent		
Maltitol syrup	R	Not specified[b, c]
Miscellaneous substance		
Salatrim (short- and long-chain acyltriglyceride molecules)	N	Adequate information was not available to evaluate its safety and nutritional effects

[a] N, new specifications prepared; R, existing specifications revised; T, the existing, new or revised specifications are tentative and comments are invited.

[b] ADI "not specified" is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

[c] This ADI applies to the substance conforming to the revised specifications.

[d] Temporary ADI, pending consideration of the "tentative" qualification of the specifications. The "tentative" qualification of Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Rome, Food and Agriculture Organization of the United Nations, 1992) will be reviewed in 1998.

[e] Temporary ADI extended to 1998, pending the submission of the results of studies currently underway that were requested at earlier meetings of the Committee.

Flavouring agents

The substances listed here were evaluated using the Procedure for the Evaluation of Flavouring Agents. For further details, see section 2.2.1 of the main report.

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
Allyl ester			
Allyl 2-furoate (2-propenyl furan-2-carboxylate)	0021	S, T	No safety concern
Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids			
Formic acid[c]	0079	R	
Acetaldehyde (ethanal)	0080	N	
Acetic acid[c]	0081	R	
Propyl alcohol (1-propanol)	0082	R	
Propionaldehyde (propanal)	0083	N	
Propionic acid[c] (propanoic acid)	0084	N	
Butyl alcohol (1-butanol)	0085	R	
Butyraldehyde (butanal)	0086	N	
Butyric acid (butanoic acid)	0087	N	
Amyl alcohol (1-pentanol)	0088	N	
Valeraldehyde (pentanal)	0089	N	
Valeric acid (pentanoic acid)	0090	N	
Hexyl alcohol (1-hexanol)	0091	N	
Hexanal	0092	N	
Hexanoic acid	0093	N	
Heptyl alcohol (1-heptanol)	0094	N	
Heptanal	0095	N	
Heptanoic acid	0096	N	
1-Octanol	0097	N	No safety concern
Octanal[c]	0098	R	
Octanoic acid	0099	N	
Nonyl alcohol (1-nonanol)	0100	N	
Nonanal[c]	0101	R	
Nonanoic acid	0102	N	
1-Decanol	0103	N	
Decanal	0104	R	
Decanoic acid	0105	N	
Undecyl alcohol (1-undecanol)	0106	N	
Undecanal	0107	N	
Undecanoic acid	0108	N	
Lauryl alcohol (1-dodecanol)	0109	N	
Lauric aldehyde (dodecanal)	0110	N	
Lauric acid (dodecanoic acid)	0111	N	
Myristaldehyde (tetradecanal)	0112	N	
Myristic acid (tetradecanoic acid)	0113	N	
1-Hexadecanol	0114	N	
Palmitic acid (hexadecanoic acid)	0115	N	
Stearic acid (octadecanoic acid)	0116	N	
Saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids			
Structural class I: methyl-substituted saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids			
Isobutyl alcohol (2-methyl-1-propanol)	0251	NR	No safety concern
Isobutyraldehyde (2-methylpropanal)	0252	NR	
Isobutyric acid (2-methylpropanoic acid)	0253	NR	
2-Methylbutyraldehyde (2-methylbutanal)	0254	NR	

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
2-Methylbutyric acid (2-methylbutanoic acid)	0255	NR	No safety concern
3-Methylbutyraldehyde (3-methylbutanal)	0258	NR	
Isovaleric acid (3-methylbutanoic acid)	0259	NR	
2-Methylpentanal	0260	NR	
2-Methylvaleric acid (2-methylpentanoic acid)	0261	NR	
3-Methylpentanoic acid	0262	NR	
3-Methyl-1-pentanol	0263	NR	
4-Methylpentanoic acid	0264	NR	
2-Methylhexanoic acid	0265	NR	
5-Methylhexanoic acid	0266	NR	
3,5,5-Trimethyl-1-hexanol	0268	NR	
3,5,5-Trimethylhexanal	0269	NR	
2-Methyloctanal	0270	NR	
4-Methyloctanoic acid	0271	NR	
3,7-Dimethyl-1-octanol	0272	NR	
2,6-Dimethyloctanal	0273	NR	
4-Methylnonanoic acid	0274	NR	
2-Methylundecanal	0275	NR	
Structural class II: ethyl-substituted saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids			
2-Ethylbutyraldehyde (2-ethylbutanal)	0256	NR	No safety concern
2-Ethylbutyric acid (2-ethylbutanoic acid)	0257	NR	
2-Ethyl-1-hexanol[c]	0267	NR	
Aliphatic lactones			
Structural class I			
4-Hydroxybutyric acid lactone (γ-butyrolactone)	0219	NR	No safety concern
γ-Valerolactone	0220	NR	
γ-Hexalactone	0223	NR	
δ-Hexalactone	0224	NR	
γ-Heptalactone	0225	NR	
γ-Octalactone	0226	NR	
δ-Octalactone	0228	NR	
γ-Nonalactone[c]	0229	NR	
Hydroxynonanoic acid δ-lactone	0230	NR	
γ-Decalactone	0231	NR	
δ-Decalactone	0232	NR	
ε-Decalactone	0241	NR	
γ-Undecalactone[c]	0233	NR	
5-Hydroxyundecanoic acid δ-lactone	0234	NR	
γ-Dodecalactone	0235	NR	
δ-Dodecalactone	0236	NR	
ε-Dodecalactone	0242	NR	
δ-Tetradecalactone	0238	NR	
ω-Pentadecalactone	0239	NR	
4-Hydroxy-3-pentenoic acid lactone	0221	NR	
5-Hydroxy-7-decenoic acid δ-lactone	0247	NR	
5-Hydroxy-8-undecenoic acid δ-lactone	0248	NR	
1,4-Dodec-6-enolactone	0249	NR	
ω-6-Hexadecenlactone	0240	NR	
4,4-Dibutyl-γ-butyrolactone	0227	NR	

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
3-Heptyldihydro-5-methyl-2(3*H*)-furanone	0244	NR	No safety concern
4-Hydroxy-3-methyloctanoic acid γ-lactone	0437	NR	
6-Hydroxy-3,7-dimethyloctanoic acid lactone	0237	NR	
γ-Methyldecalactone	0250	NR	
Structural class III			
5-Hydroxy-2-decenoic acid δ-lactone	0246	NR	
5-Hydroxy-2,4-decadienoic acid δ-lactone	0245	NR	
Mixture of 5-hydroxy-2-decenoic acid δ-lactone, 5-hydroxy-2-dodecenoic acid δ-lactone and 5-hydroxy-2-tetradecenoic acid δ-lactone	0276	NR	Not evaluated[d]
5-Hydroxy-2-dodecenoic acid δ-lactone	0438	NR	
5-Ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone	0222	NR	No safety concern
4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one	0243	NR	
Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids			
Methyl isobutyrate (methyl 2-methylpropanoate)	0185	N	No safety concern
Ethyl isobutyrate (ethyl 2-methylpropanoate)	0186	N	
Propyl isobutyrate (*n*-propyl 2-methylpropanoate)	0187	N	
Butyl isobutyrate (butyl 2-methylpropanoate)	0188	N	
Hexyl isobutyrate (hexyl 2-methylpropanoate)	0189	N	
Heptyl isobutyrate (heptyl 2-methylpropanoate)	0190	N	
trans-3-Heptenyl 2-methylpropanoate	0191	N	
Octyl isobutyrate (octyl 2-methylpropanoate)	0192	N	
Dodecyl isobutyrate (dodecyl 2-methylpropanoate)	0193	N	
Isobutyl isobutyrate (2-methylpropyl 2-methylpropanoate)	0194	N	
Methyl isovalerate (methyl 3-methylbutanoate)	0195	N	
Ethyl isovalerate (ethyl 3-methylbutanoate)	0196	R	
Propyl isovalerate (propyl 3-methylbutanoate)	0197	N	
Butyl isovalerate (butyl 3-methylbutanoate)	0198	N	
Hexyl 3-methylbutanoate	0199	N	
Octyl isovalerate (octyl 3-methylbutanoate)	0200	N	
Nonyl isovalerate (nonyl 3-methylbutanoate)	0201	N	
3-Hexenyl 3-methylbutanoate	0202	N	
2-Methylpropyl 3-methylbutyrate (2-methylpropyl 3-methylbutanoate)	0203	N	
2-Methylbutyl 3-methylbutanoate	0204	N, T	
Methyl 2-methylbutyrate (methyl 2-methylbutanoate)	0205	N	
Ethyl 2-methylbutyrate (ethyl 2-methylbutanoate)	0206	N	
n-Butyl 2-methylbutyrate (butyl 2-methylbutanoate)	0207	N	
Hexyl 2-methylbutanoate	0208	N	
Octyl 2-methylbutyrate (octyl 2-methylbutanoate)	0209	N	
Isopropyl 2-methylbutyrate (1-methylethyl 2-methylbutanoate)	0210	N, T	
3-Hexenyl 2-methylbutanoate	0211	N, T	
2-Methylbutyl 2-methylbutyrate (2-methylbutyl 2-methylbutanoate)	0212	N	
Methyl 2-methylpentanoate	0213	N, T	
Ethyl 2-methylpentanoate	0214	N	
Ethyl 3-methylpentanoate	0215	N, T	
Methyl 4-methylvalerate	0216	N	

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids			
Propyl formate	0117	N	No safety concern
Butyl formate	0118	N	
n-Amyl formate (pentyl formate)	0119	N	
Hexyl formate	0120	N	
Heptyl formate	0121	N, T	
Octyl formate	0122	N	
cis-3-Hexenyl formate (*cis*-3-hexenyl-1-yl formate)	0123	N	
Isobutyl formate (2-methylpropyl formate)	0124	N	
Methyl acetate	0125	N	
Propyl acetate	0126	N	
Butyl acetate	0127	R	
Hexyl acetate	0128	N	
Heptyl acetate	0129	N	
Octyl acetate	0130	N	
Nonyl acetate	0131	N	
Decyl acetate	0132	N	
Lauryl acetate (dodecyl acetate)	0133	N	
cis-3-Hexenyl acetate (*cis*-3-hexenyl-1-yl acetate)	0134	N	
trans-3-Heptenyl acetate (*trans*-3-heptenyl-1-yl acetate)	0135	N	
10-Undecen-1-yl acetate	0136	N	
Isobutyl acetate (2-methylpropyl acetate)	0137	N	
2-Methylbutyl acetate (2-methyl-1-butyl acetate)	0138	N	
2-Ethylbutyl acetate	0140	N, T	
Methyl propionate (methyl propanoate)	0141	N	
Propyl propionate (*n*-propyl propanoate)	0142	N	
Butyl propionate (butyl propanoate)	0143	N	
Hexyl propionate (*n*-hexyl propanoate)	0144	N	
Octyl propionate (octyl propanoate)	0145	N	
Decyl propionate (decyl propanoate)	0146	N	
cis-3- and *trans*-2-Hexenyl propionate (*cis*-3- and *trans*-2-hexenyl propanoate)	0147	N	Not evaluated[e]
Isobutyl propionate (2-methylpropyl propanoate)	0148	N	No safety concern
Methyl butyrate (methyl butanoate)	0149	N	
Propyl butyrate (*n*-propyl butanoate)	0150	N	
Butyl butyrate (*n*-butyl *n*-butanoate)	0151	N	
n-Amyl butyrate (pentyl butanoate)	0152	N	
Hexyl butyrate (hexyl butanoate)	0153	N	
Heptyl butyrate (heptyl butanoate)	0154	N, T	
Octyl butyrate (octyl butanoate)	0155	N, T	
Decyl butyrate (decyl butanoate)	0156	N, T	
cis-3-Hexenyl butyrate (*cis*-3-hexen-1-yl butanoate)	0157	N	
Isobutyl butyrate (2-methylpropyl butanoate)	0158	N	
Methyl valerate (methyl pentanoate)	0159	N	
Butyl valerate (butyl pentanoate)	0160	N	
Propyl hexanoate	0161	N	
Butyl hexanoate	0162	N	
n-Amyl hexanoate (pentyl hexanoate)	0163	N	
Hexyl hexanoate	0164	N	
cis-3-Hexenyl hexanoate (*cis*-3-hexen-1-yl hexanoate)	0165	N, T	

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
Isobutyl hexanoate (2-methylpropyl hexanoate)	0166	N	No safety concern
Methyl heptanoate	0167	N	
Propyl heptanoate	0168	N, T	
Butyl heptanoate	0169	N, T	
n-Amyl heptanoate (pentyl heptanoate)	0170	N	
Octyl heptanoate	0171	N, T	
Isobutyl heptanoate (2-methylpropyl heptanoate)	0172	N, T	
Methyl octanoate	0173	N	
n-Amyl octanoate (pentyl octanoate)	0174	N	
Hexyl octanoate	0175	N	
Heptyl octanoate	0176	N, T	
Octyl octanoate	0177	N, T	
Nonyl octanoate	0178	N, T	
Methyl nonanoate	0179	N	
Methyl laurate (methyl dodecanoate)	0180	N	
Butyl laurate (butyl dodecanoate)	0181	N	
Isoamyl laurate (3-methylbutyl dodecanoate)	0182	N, T	
Methyl myristate (methyl *n*-tetradecanoate)	0183	N	
Butyl stearate (butyl octadecanoate)	0184	N, T	
Esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids			
Citronellyl formate (3,7-dimethyl-6-octen 1-yl formate)	0053	N	No safety concern
Geranyl formate (*trans*-3,7-dimethyl-2,6-octadien-1-yl formate)	0054	N	
Neryl formate (*cis*-3,7-dimethyl-2,6-octadien-1-yl formate)	0055	N	
Rhodinyl formate (3,7-dimethyl-7-octen-1-yl formate)	0056	N	
Citronellyl acetate (3,7-dimethyl-6-octen-1-yl acetate)	0057	N	
Geranyl acetate[c] (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate)	0058	R	
Neryl acetate (*cis*-3,7-dimethyl-2,6-octadien-1-yl acetate)	0059	N	
Rhodinyl acetate (3,7-dimethyl-7-octen-1-yl acetate)	0060	N	
Citronellyl propionate (3,7-dimethyl-6-octen-1-yl propanoate)	0061	N	
Geranyl propionate (*trans*-3,7-dimethyl-2,6-octadien-1-yl propanoate)	0062	N	
Neryl propionate (*cis*-3,7-dimethyl-2,6-octadien-1-yl propanoate)	0063	N	
Rhodinyl propionate (3,7-dimethyl-7-octen-1-yl propanoate)	0064	N, T	
Citronellyl butyrate (3,7-dimethyl-6-octen-1-yl butanoate)	0065	N	
Geranyl butyrate (*trans*-3,7-dimethyl-2,6-octadien-1-yl butanoate)	0066	N	
Neryl butyrate (*cis*-3,7-dimethyl-2,6-octadien-1-yl butanoate)	0067	N	

Substance[a]	No.	Specifications[b]	Conclusion based on current levels of intake
Rhodinyl butyrate (3,7-dimethyl-7-octen-1-yl butanoate)	0068	N	No safety concern
Citronellyl valerate (3,7-dimethyl-6-octen-1-yl pentanoate)	0069	N, T	
Geranyl hexanoate (*trans*-3,7-dimethyl-2,6-octadien-1-yl hexanoate)	0070	N, T	
Citronellyl isobutyrate (3,7-dimethyl-6-octen-1-yl 2-methyl propanoate)	0071	N	
Geranyl isobutyrate (*trans*-3,7-dimethyl-2,6-octadien-1-yl 2-methyl propanoate)	0072	N, T	
Neryl isobutyrate (*cis*-3,7-dimethyl-2,6-octadien-1-yl 2-methyl propanoate)	0073	N	
Rhodinyl isobutyrate (3,7-dimethyl-7-octen-1-yl 2-methyl propanoate)	0074	N, T	
Geranyl isovalerate (*trans*-3,7-dimethyl-2,6-octadien-1-yl 3-methyl butanoate)	0075	N, T	
Neryl isovalerate (*cis*-3,7-dimethyl-2,6-octadien-1-yl 2-methyl butanoate)	0076	N	
Rhodinyl isovalerate (3,7-dimethyl-7-octen-1-yl 3-methylbutanoate)	0077	N, T	
Geranyl 2-ethylbutanoate (*trans*-3,7-dimethyl-2,6-octadien-1-yl 2-ethylbutanoate)	0078	N, T	

[a] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 5, 1997). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.
[b] N, new specifications prepared; NR, specifications not reviewed; R, existing specifications revised; S, specifications exist, revision not considered or not required; T, the existing, new or revised specifications are tentative and comments are invited.
[c] The ADI for this substance was maintained.
[d] Evaluation postponed, pending consideration of other α,β-unsaturated compounds.
[e] Evaluation postponed, pending consideration of other α,β-unsaturated carbonyl compounds.

Contaminant	Toxicological recommendations
Aflatoxins	Potencies were estimated

Substance[a] (considered for specifications only)	No.	Specifications[b]
Flavouring agents		
Allyl cyclohexane propionate (2-propenyl cyclohexane propanoate)	0013	S
Ethyl octanoate	0033	S
Ethyl nonanoate	0034	S
Isoamyl acetate (3-methylbutyl acetate)	0043	R
Isoamyl butyrate (3-methylbutyl butanoate)	0045	S
Isoamyl isobutyrate (3-methylbutyl 2-methylpropanoate)	0049	S
Isoamyl isovalerate (3-methylbutyl 3-methylbutanoate)	0050	S
Food additives		
Agar	—	R
Alginic acid	—	R
Aluminium powder	—	R
Ammonium alginate	—	R

Substance[a] (considered for specifications only)	No.	Specifications[b]
Anoxomer	—	W
Calcium alginate	—	R
Calcium propionate (calcium propanoate)	—	R
Carbon dioxide	—	R
Carthamus red	—	R, T[c]
Carthamus yellow	—	R
Citric acid	—	R
Diacetyltartaric and fatty acid esters of glycerol (DATEM)	—	R
Enzyme-hydrolysed sodium carboxymethyl cellulose	—	N, T[d]
Enzyme-treated starches	—	W
Ethyl hydroxyethyl cellulose	—	R
Gellan gum	—	R
Gum arabic	—	R
Microcrystalline wax	—	R
Mixed carotenoids	—	R
Modified starches	—	R
Petroleum jelly	—	R, T[e]
Potassium alginate	—	R
Potassium propionate (potassium propanoate)	—	R
Propionic acid	—	R, T[f]
Propylene glycol	—	R
Propylene glycol alginate	—	R
Propylene glycol esters of fatty acids	—	R
Sodium alginate	—	R
Sodium propionate (sodium propanoate)	—	R
Sulfur dioxide	—	R
Talc	—	R
Tartaric, acetic and fatty acid esters of glycerol, mixed	—	R, T[g]
Turmeric	—	W

[a] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 5, 1997). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.

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

[c] The existing tentative specifications for carthamus red were revised and the "tentative" designation was maintained. The Committee requested information on the content of carthamin and method of assay.

[d] New specifications for enzyme-hydrolysed sodium carboxymethyl cellulose were prepared and designated as "tentative". The Committee requested information on the physical state of the substance as manufactured, the nature and proportion of material of low relative molecular mass present, and tests that distinguish it from sodium carboxymethyl cellulose.

[e] The existing tentative specifications for petroleum jelly were revised and the "tentative" designation was maintained The Committee requested information on the method of analysis and levels of viscosity at 100°C, carbon number at 5% distillation point, average relative molecular mass and oil content. Unless this information was received by 31 March 1998, the specifications would be withdrawn.

[f] The specifications for propionic acid used as a preservative and an antimould and antirope agent were revised and designated as "tentative". The Committee requested information on the method of analysis and levels of readily oxidizable substances.

[g] The Committee compared the specifications for "diacetyltartaric and fatty acid esters of glycerol" (DATEM) with the existing tentative specifications for "tartaric, acetic and fatty acid esters of glycerol, mixed" and noted that the two substances appear very similar. The Committee has not received information which would allow these substances to be distinguished analytically. It therefore decided to maintain the tentative status of the existing specifications for "tartaric, acetic and fatty acid esters of glycerol, mixed" and requested data that would distinguish this substance from DATEM. Unless such data were provided by 31 March 1998, the Committee would consider combining the specifications for the two substances.