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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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



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Joint FAO/WHO Expert Committee on Food Additives

Geneva, 6–15 February 1996

Members

- Mrs J. Baines, Nutritionist, National Food Authority, Canberra, Australia (*Joint Rapporteur*)
- Dr Chen Junshi, Deputy Director, Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, China (*Joint Vice-Chairman*)
- Dr R. Clarke, Consultant in Food Science, Rome, Italy
- Dr S.M. Dagher, Chairman, Department of Biology, American University of Beirut, Beirut, Lebanon
- Dr C.E. Fisher, Head of Risk Assessment and Management Branch, Consumer and Nutrition Policy Division, Ministry of Agriculture, Fisheries and Food, London, England
- Professor C.L. Galli, Professor of Toxicology, Institute of Pharmacological Sciences, University of Milan, Milan, Italy
- Mr J. Gislason, Director, Office of Food and Hygiene, Environmental and Food Agency, Reykjavik, Iceland
- Dr D.L. Grant, Director, Health Evaluation Division, Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario, Canada
- Dr M.B. Grillo Rodriguez, Deputy Director of Food Hygiene, National Institute of Nutrition and Food Hygiene, Ministry of Public Health, Havana, Cuba
- Dr D.G. Hattan, Director, Division of Health Effects Evaluation, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA
- Dr A.G.A.C. Knaap, Toxicology Advisory Centre, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands
- Professor K. Kojima, Professor Emeritus, College of Environmental Health, Azabu University, Kanagawa-ken, Japan
- Dr P.M. Kuznesof, Chief, Chemistry Review Branch, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*Joint Vice-Chairman*)
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Dr P.A. Cadby, International Organization of the Flavor Industry (IOFI), Geneva, Switzerland (*WHO Temporary Adviser*)

Dr V.J. Feron, Toxicology Division, TNO Nutrition and Food Research Institute, Zeist, Netherlands (*WHO Temporary Adviser*)

Dr J. Gry, Institute of Toxicology, National Food Agency, Ministry of Health, Søborg, Denmark (*WHO Temporary Adviser*)

Dr Y. Hayashi, Kitasato University School of Pharmacy, Tokyo, Japan (*WHO Temporary Adviser*)

Dr S. Henry, Division of Programs and Enforcement Policy, Office of Plant and Dairy Foods and Beverages, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr J.L. Herrman, Scientist, International Programme on Chemical Safety, WHO, Geneva, Switzerland (*Joint Secretary*)

Mr H. van der Kooi, Chairman, Codex Committee on Food Additives and Contaminants and Senior Coordinator, Risks, Substances and Nutrition Division, Department of Environment, Quality and Health, Ministry of Agriculture, Nature Management and Fisheries, The Hague, Netherlands (*WHO Temporary Adviser*)

Dr A. Mattia, Division of Health Effects Evaluation, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr I.C. Munro, CanTox Inc., Mississauga, Ontario, Canada (*WHO Temporary Adviser*)

Dr J. Paakkanen, Nutrition Officer, Food Quality Liaison Group, Food and Nutrition Division, FAO, Rome, Italy (*Joint Secretary*)

Dr C.J. Portier, Acting Chief, Laboratory of Quantitative and Computational Biology, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA (*WHO Temporary Adviser*)

Dr A.G. Renwick, Head, Clinical Pharmacology Group, University of Southampton, Southampton, England (*WHO Temporary Adviser*)

Dr A. Rulis, Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr G. Semino, Institute of Pharmacological Sciences, University of Milan, Milan, Italy (*WHO Temporary Adviser*)

Professor P. Shubik, Senior Research Fellow, Green College, Oxford, England (*WHO Temporary Adviser*)

Professor A. Somogyi, Director, Federal Institute for Consumer Health Protection and Veterinary Medicine, Berlin, Germany (*WHO Temporary Adviser*)

Dr G.J.A. Speijers, Head, Section on Public Health, Toxicology Advisory Centre, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands (*WHO Temporary Adviser*)

Ms E. Vavasour, Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Health Canada, Ottawa, Ontario, Canada (*WHO Temporary Adviser*)

Mr P. Wagstaffe, Foodstuffs Division, Commission of the European Communities, Brussels, Belgium (*WHO Temporary Adviser*)

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

Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 37, 1996.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, Addendum 4. FAO Food and Nutrition Paper, No. 52, Add. 4, 1996.

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 Geneva from 6 to 15 February 1996. The meeting was opened by Dr J.L. Herrman, Scientist, International Programme on Chemical Safety, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Herrman noted that governments and the Codex Alimentarius Commission were increasingly relying on recommendations of the Committee relating to the safety of food additives and contaminants. Several substances on the agenda of the present meeting involved difficult issues of a general nature and would require new approaches if useful advice was to be provided.

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 forty-five previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendations made at the forty-fourth meeting (Annex 1, reference 116).

The tasks before the Committee were:

- (a) to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);
- (b) to undertake toxicological evaluations of certain food additives and contaminants (section 3 and Annex 2);
- (c) to review and prepare specifications for selected food additives (sections 3 and 4 and Annex 2); and
- (d) to assess dietary intake of aflatoxins and estimate the potential risks for different human populations (section 4).

2.1 Modification of the agenda

Salatrim, a fat substitute, was removed from the agenda at the request of the manufacturer.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants*

in food (Annex 1, reference 76), as well as principles elaborated subsequently at meetings of the Committee (Annex 1, references 77, 83, 88, 94, 101, 107 and 116), 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.

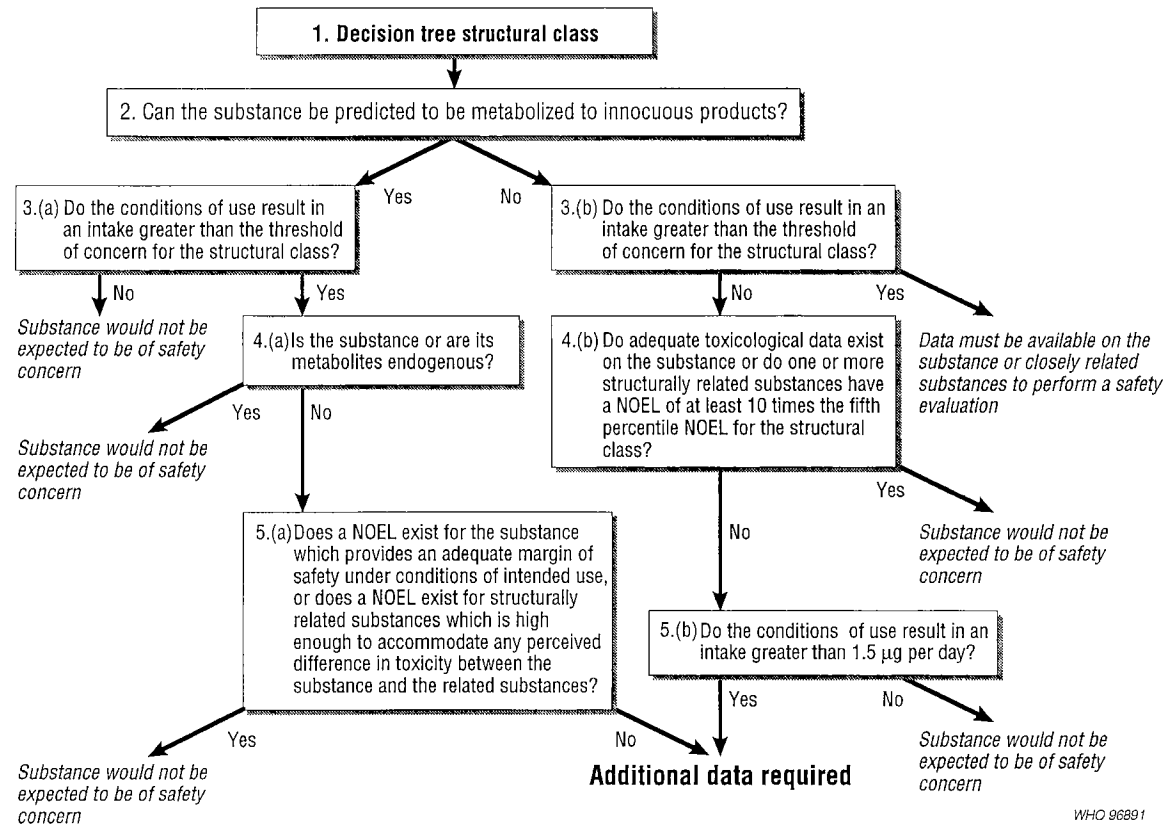
2.2.1 ***Procedure for the safety evaluation of flavouring agents***

The Committee evaluated three groups of flavouring agents. It used a procedure based on that reviewed at the forty-fourth meeting of the Committee (Fig. 1; Annex 1, reference 116, section 2.2.1). The approach incorporates a series of criteria designed to provide a means of evaluating such agents in a consistent and timely manner. The criteria, which were drawn up in the light of the principles for the safety evaluation of flavouring substances (Annex 1, reference 76), take account of available information on intake from current uses, structure-activity relationships, and metabolism and toxicity data. They incorporate procedures outlined in the report of the thirty-third meeting of the Committee (Annex 1, reference 83), which include a method for dividing flavouring substances up into three structural classes based on structural characteristics and metabolism. The use of these criteria provides a means of ranking flavouring substances in terms of concern over potential inherent toxicity and provides guidance on the nature and extent of the data required to perform a safety evaluation.

The criteria take advantage of the fact that some flavouring agents occur as normal constituents of mammalian tissues or are metabolized to form such constituents, and are then completely metabolized to innocuous end-products such as carbon dioxide and water. Flavouring agents with these characteristics are considered to be safe for consumption if human intake is low, but are evaluated on the basis of toxicity data if human intake is high. The safety evaluation may involve the use of toxicity data on the individual substance concerned or may rely, at least in part, on toxicity data on substances of closely related structure.

For flavouring agents that are not known to be metabolized to innocuous end-products, the safety evaluation must be based on toxicity data, even if intake is low. In such cases, there must be an adequate

Figure 1
Safety evaluation procedure reviewed at the forty-fourth meeting of the Committee^a



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^a Reproduced, with minor editorial changes and modification of the numbering, from Annex 1, reference 117.

margin of safety between human intake of the flavouring agent and the no-observed-effect level (NOEL) for the substance or the NOEL for a substance of closely related structure on which the safety evaluation relies.

For those flavouring agents currently in use for which no toxicity or metabolic data exist, but where intake is extremely low, it might be possible to specify a threshold below which intake is considered safe (human intake threshold).

The procedure described above involves the integration of data on intake, in relation to the human intake threshold, with information on structure–activity relationships, metabolism and toxicity. The data on intake used in the procedure at the present meeting were derived from figures for the total annual production of flavouring agents used in food in Europe and the USA. Estimates of intake were based on the assumption that only 60% of the total amount used is reported and that the total amount used is consumed by only 10% of the population. The Committee noted that the evaluations performed using the procedure were based on the intake estimates available at the meeting and that changes in intake might warrant re-evaluation of a flavouring agent. The Committee recommended that information on intake should be periodically updated to ensure the validity of safety evaluations.

The Committee noted that the procedure is intended for application to flavouring agents used in food and not to other uses of these agents. It also noted that many flavouring agents are members of structurally related groups and that, in conformity with past practice, consideration should be given to evaluating the safety of such groups as a whole.

The Committee noted that the safety evaluation procedure is not intended to be applied to flavouring agents with existing unresolved problems of toxicity. 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.

It was noted that a key element of the procedure involves determining whether a flavouring agent and the products of its metabolism are innocuous and/or endogenous substances. The Committee considered that these terms require definition. It recommended that “innocuous metabolic products” should be defined as products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent, while “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 noted that Acceptable Daily Intakes (ADIs) had previously been established for some flavouring agents or groups of flavouring agents, and recommended that these should be retained, since the information on which they are based is relevant to an evaluation of their safety and, in addition, they may have food additive uses other than as flavouring agents.

Application of the procedure

In applying the procedure to the groups of esters considered during the meeting, the Committee noted that consideration should be given to both the parent compound and its metabolic products, and that these should be evaluated separately when necessary.

The Committee used the procedure to evaluate three groups of esters, namely ethyl esters, isoamyl esters and allyl esters. First, the substance is assigned to a structural class according to the decision tree of Cramer et al. (2; see Figure 1).

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.

The approach then differs, depending on whether the flavouring agent is predicted to be metabolized to innocuous products (step 2). For flavouring agents with high intakes (step 3(a)) that are metabolized to innocuous but not endogenous products (step 4(a)), the procedure requires a NOEL for the substance or a structurally related substance which provides an adequate margin of safety in relation to the estimated intake (step 5(a)). In contrast, for flavouring agents not predicted to be metabolized to innocuous products (step 2) and with

low intakes (step 3(b)), the procedure requires adequate toxicological data on the substance or on a structurally related substance (step 4(b)). The Committee concluded that the procedure should be modified (see Fig. 2), so that step 4(b) in Fig. 1 would read “Does a NOEL exist for the substance which provides an adequate margin of safety under conditions of intended use [(3) (Annex 1, reference 76)], or does a NOEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?” The Committee did not fully discuss the application of step 5(b) of the original procedure (“Do the conditions of use result in an intake greater than 1.5 µg per day?”) to flavouring agents, and it was not considered at the present meeting.

The Committee found that the procedure provided a sound basis for evaluating the safety of the three groups of flavouring agents considered during the meeting and recommended that it should be used at future meetings to evaluate other groups of flavouring agents.

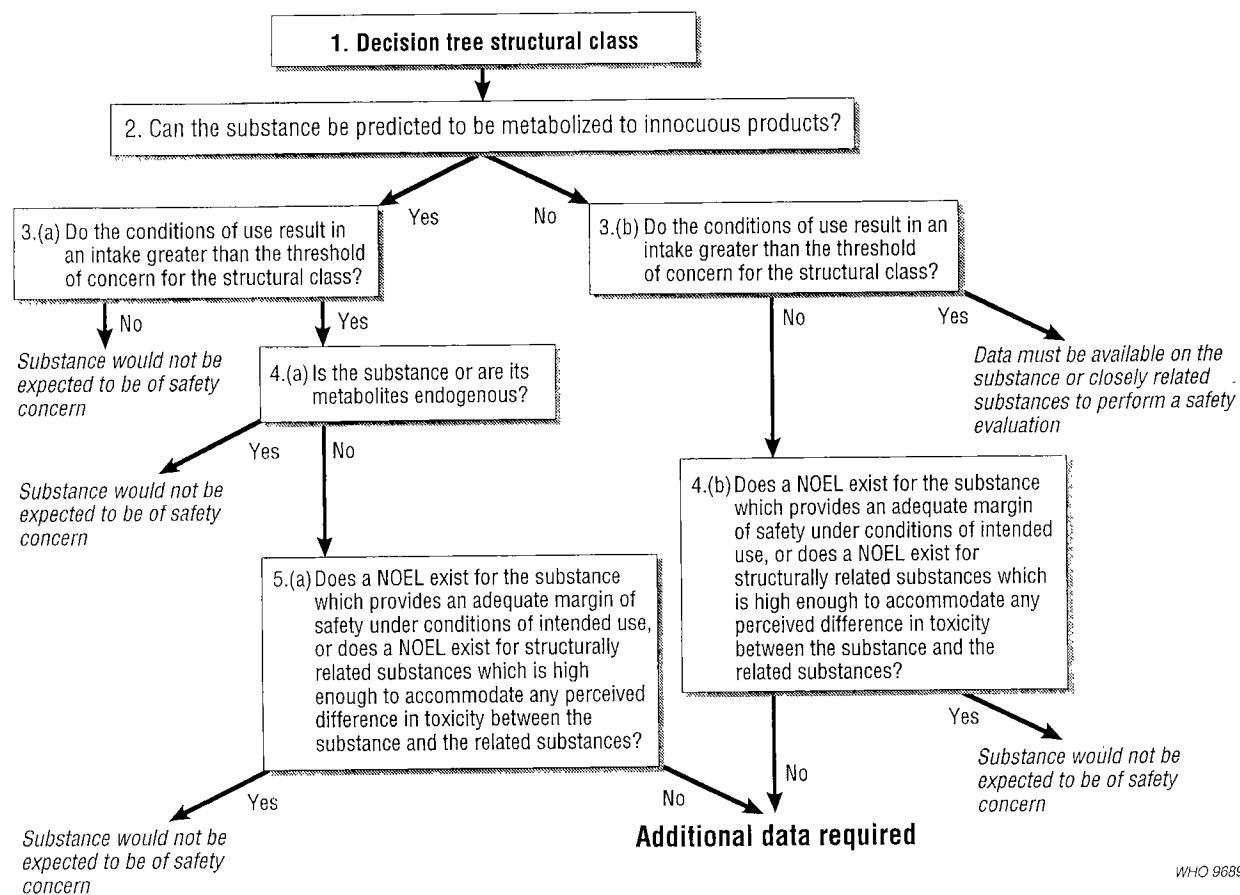
2.2.2 *Survival of rats in long-term studies*

The Committee discussed the general issue of survival in contemporary long-term studies in experimental animals in response to the problems encountered in assessing the adequacy of the data on alitame (section 3.4). It recognized that increasingly poor survival rates have been seen in rats in long-term studies over the past 5–10 years. Furthermore, the background incidence of some tumours has increased, and this has been related to an increase in the body weight of commonly used strains of rats, possibly due to selective breeding. These factors have tended to complicate and in some cases confound the interpretation of long-term studies, particularly in relation to carcinogenesis. They indicate that the traditional carcinogenesis protocol is becoming increasingly difficult to carry out, and that caution should be exercised in using data on historical controls. The Committee considered that these factors should be taken into account in interpreting the results of contemporary studies, but do not necessarily negate the value of such studies. Studies that do not satisfy arbitrarily imposed criteria for survival and/or duration may still provide useful data for assessing the carcinogenic potential of a substance.

2.2.3 *Deadlines for submission of data*

It has been customary for the Secretariat to specify a deadline for the submission of data in announcing forthcoming meetings of the Committee. In recent years, such deadlines have increasingly been ignored, making it difficult to produce adequately reviewed

Figure 2
Safety evaluation procedure, as modified by the Committee at the present meeting



monographs in time for the meeting. The Committee therefore agreed that data submitted after the specified deadline would normally be considered at a later meeting.

The Committee again emphasized that requests for the modification of specifications must be supported by data. It will make changes only if it considers that adequate justification has been provided.

2.2.4 *Toxicological significance of proliferative lesions of the adrenal medulla in rats fed polyols and other poorly digestible carbohydrates*

Polyols (sugar alcohols) are used mainly as bulk sweetening agents and particularly as replacements for sugar. They include the monosaccharide-derived polyols mannitol, sorbitol and xylitol, and the disaccharide-derived forms maltitol, isomalt and lactitol, as well as polyol mixtures such as maltitol syrup and sorbitol syrup, which contain hydrogenated polysaccharides.

The polyols have appeared on the agenda at many meetings of the Committee, starting with the seventh meeting in 1963, when sorbitol was reviewed, and most recently at the forty-first meeting in 1993 (Annex 1, references 7, 11, 13, 32, 47, 56, 59, 62, 70, 73, 83 and 107).

At its twenty-sixth meeting (Annex 1, reference 59), the Committee concluded that the adrenal medullary hyperplasia seen in rats fed 20% sorbitol in the diet was the physiological consequence of the gross dietary and metabolic imbalances produced by the high levels of this substance in ageing rats, and recommended that the influence of carbohydrate intake on mineral metabolism be taken into account in assessing the possible toxicological significance of this effect.

At its twenty-seventh meeting (Annex 1, reference 62), the Committee noted that the background incidence of these adrenal lesions in different strains of rat varied from 0% to 80%. It concluded that the high incidence of these lesions, their species-specificity, and their great variation within rat strains made it difficult to extrapolate the significance of the findings to humans in the absence of further information. At its forty-first meeting (Annex 1, reference 107), the Committee recommended that the information database on adrenal medullary hyperplasia and pheochromocytomas associated with polyols and other poorly absorbed carbohydrates be reviewed and that the mechanisms of appearance of these lesions and their toxicological significance be assessed at a future meeting.

At its present meeting, the Committee examined previously reviewed studies and those cited in a recent comprehensive review of all the relevant data (4).

Mutagenicity and genotoxicity studies. Mutagenicity and genotoxicity studies both *in vitro* and *in vivo* provided no evidence that any of the polyols has a mutagenic or genotoxic potential (Annex 1, references 72 and 74).

Long-term studies in animals. Long-term studies in different strains of rats demonstrated that adrenal medullary hyperplasia and neoplasia develop in response to long-term administration of diets containing high levels of polyols (over 5% of the diet). In contrast, such lesions were not observed after long-term feeding of polyols to mice or dogs. The effect on the adrenal medulla of the rat thus appeared to be species-specific. The finding was not unique to polyols; lactose, another poorly digested carbohydrate, also produced such adrenal lesions in rats, but not in mice.

The effects of individual polyols and lactose in long-term studies in rats are summarized in Table 1.

Studies in humans. A number of studies have been conducted on the safety, cariogenicity, caloric value and metabolism of polyols in humans. The consumption of these polyols by human volunteers in controlled studies and by the public at large has not been associated with any significant adverse effects other than laxation at high doses. These studies show that even relatively high doses of polyols (of the order of 100g per day), consumed for up to 5.3 years, have no effect on parameters that suggest adverse effects on energy metabolism, liver function or mineral homeostasis. For example, in two clinical studies designed to assess the overall safety of xylitol, in which male

Table 1
Main effects of polyols and lactose in long-term studies in rats

Substance	Effect ^a				
	Adrenal medullary hyperplasia or neoplasia	Caecal enlargement	Pelvic nephrocalcinosis	Hypercalciuria	Reduced weight gain
Mannitol	+	+	+	+	+
Sorbitol	+	+	+	+	+
Xylitol	+	+	+	+	+
Isomalt	—	+	+	ND	+
Lactitol	+	+	±	+	+
Maltitol	+	?	±	+	+
Maltitol syrup ^b	—	+	ND	ND	+
Lactose	+	+	+	+	+

^a + Positive effect, ? equivocal effect; — no effect; ND, no data.

^b Formerly referred to as hydrogenated glucose syrup; includes products containing 90–98% maltitol.

and female volunteers consumed 70–100 g of xylitol per day for 2.0–5.3 years, no effects on urinary concentrations of calcium, catecholamines, magnesium, phosphate, bilirubin, serum amyloid P component or amino acids, nor on biochemical or haematological parameters related to the metabolism of lipids or carbohydrates, or energy were observed. A 32-month clinical study of cariogenicity in 157 children also failed to demonstrate any effect on hepatobiliary function when xylitol was consumed at doses of up to 20 g per day.

Metabolic studies. Polyols are passively and poorly absorbed, and considerable amounts may reach the lower digestive tract, where they are fermented by gut microflora, mainly to short-chain volatile fatty acids, which are absorbed and utilized. However, there are large differences in the rates of digestion and absorption of the various polyols and major differences in the degree of hepatic metabolism once they are absorbed. As a result, no common metabolic pathway has been identified that could explain a direct action on the adrenal medulla.

Differences between the rat and the human adrenal medulla. Since the Committee last evaluated the relevance to humans of the adrenal medullary lesions in rats, several studies have been published which may explain the species specificity of these lesions. Despite the general similarities of the anatomy of the adrenal medulla in rats and humans, several potentially important differences exist: (i) the rat adrenal medulla has two distinct chromaffin cell populations, one producing predominantly epinephrine and the other norepinephrine, while in humans there is no clear distinction between chromaffin cell types; (ii) the rat adrenal medulla also has a third cell type, namely the small granule-containing cell, the functions of which are largely unknown and for which there is no clearly defined human counterpart; and (iii) the peptide and protein composition of the secretory granules in the chromaffin cells differs between rats and humans.

A series of studies has shown that rat chromaffin cells are much more susceptible to mitogenic stimuli than human chromaffin cells, suggesting that rat chromaffin cells are inappropriate as a model to assess the potential effects of chemicals on human chromaffin cells. The high susceptibility of rat chromaffin cells to mitogenic (proliferative) stimuli may account, at least in part, for the higher rate of spontaneous pheochromocytomas in rats (0.5% in Holtzman rats to 69% in Wistar rats) than in humans (0.005–0.1% reported in different studies). The chromaffin cells of mice, like those of humans, are resistant to mitogenic stimuli, and mice have a low spontaneous incidence of

adrenal medullary lesions (about 1%). Another important species difference is that, while many pharmacologically unrelated substances can induce phaeochromocytomas in rats, probably by enhancing the rate of spontaneous development, tumours of this type have not been reported to be associated with exposure to such substances in humans. A further difference between rats and humans is that the adrenal lesions reported in rats were not generally associated with increased catecholamine secretion or hypertension, whereas phaeochromocytomas in humans are often accompanied by hypertension.

A study was conducted in Wistar rats, which were fed diets containing 20% xylitol and either 0.4%, 0.2% or 0.05% calcium for up to 63 weeks. Controls received a diet containing 0.4% calcium, but no xylitol. Rats given 0.05% calcium in the diet showed lower urinary calcium levels and a significantly lower incidence of phaeochromocytomas than those in the groups given 0.4% and 0.2% calcium, although the total incidence of combined hyperplasia and neoplasia of the adrenal medulla was similar. In contrast, studies in humans conducted with sorbitol, lactitol, xylitol and maltitol syrup showed that these polyols either inhibited calcium absorption or did not affect urinary calcium levels.

Recent data support the hypothesis that altered calcium homeostasis is involved in the development of adrenal medullary proliferative lesions in long-term studies in rats. Administration of 20000 or 40000 IU of vitamin D₃ daily to groups of six male Sprague-Dawley rats for 4 weeks resulted in dramatic increases in serum calcium concentrations and concomitant increases in the percentage of labelled chromaffin cells as measured by incorporation of 5-bromo-2'-deoxyuridine (broxuridine). Vitamin D₃ was not responsible for the increased rates of cell proliferation since it had no mitogenic effects on rat chromaffin cells *in vitro*. In similar experiments on xylitol and lactose, a slight, but significant, increase in the percentage of labelled chromaffin cells was found in the treated rats. These results and the fact that consumption of polyols by rats leads to hypercalciuria indicate that disturbed calcium homeostasis is possibly involved in the genesis of the adrenal medullary proliferative lesions observed in long-term studies of certain polyols or lactose in rats.

Conclusions. The Committee reviewed some recent literature dealing with the potential mechanisms for the production of phaeochromocytomas in rats fed high levels of polyols or lactose. It noted that functional differences have been identified between the adrenal medulla of the rat and that of other species, including humans, and

that ingestion of polyols or lactose was associated with increased calcium absorption in rats but not in humans, as inferred from hypercalciuria. While a reasonably clear association could be demonstrated between calcium absorption and the incidence of the adrenal medullary lesions, the actual mechanism whereby the increased absorption of calcium produces phaeochromocytomas in rats is still unknown, despite extensive research.

As noted at previous meetings of the Committee, the development of proliferative lesions of the adrenal medulla in rats fed polyols or lactose is associated only with high doses of these substances. Those compounds that have been tested do not induce these lesions in mice or dogs. Moreover, there is no indication that any of the polyols or lactose is metabolized to reactive intermediates, nor is there any evidence to suggest that any of these substances or their metabolites are genotoxic.

After reviewing the data cited above and noting certain unique features of the rat adrenal medulla, the Committee confirmed the view expressed at previous meetings that the occurrence of proliferative lesions of the adrenal medulla in rats fed polyols and lactose is a species-specific phenomenon and is not relevant to the toxicological evaluation of these substances for humans. The previous evaluations of polyols were maintained. No toxicological monograph was prepared.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *International harmonization of specifications*

In recognition of its advisory role to the Codex Committee on Food Additives and Contaminants in facilitating international trade and assuring a wholesome global food supply, the Committee noted the desirability and importance of harmonizing its specifications with those of other internationally recognized bodies, when possible. Specifications developed at the current meeting were considered in this light.

2.3.2 *Limits for arsenic, lead and heavy metals*

The Committee reaffirmed the intention expressed at its forty-fourth meeting (Annex 1, reference 116) to consider lowering the existing general limits of 10mg/kg for lead and 40mg/kg for heavy metals for substances under consideration, unless data in support of these limits are provided. The Committee also reiterated its earlier recommendation that submissions on specifications should include actual

concentrations of lead and certain other heavy metals found in the substances under consideration. The Committee also agreed to continue, as decided at its forty-fourth meeting, to assess on a case-by-case basis the need for limits for arsenic in specifications for substances under review. Such limits would be reduced or withdrawn unless the information provided, the nature and source of the substance, or the levels of consumption indicate that limits for arsenic are necessary.

Finally, the Committee agreed that, for compounds with a limit of 10mg/kg for heavy metals, no separate limit for lead would be set unless the information provided indicated that such a limit was necessary.

2.3.3 *Harmful analytical solvents and reagents*

The Committee noted the need to find alternative chemicals or methods of analysis that will help to eliminate the use of solvents or reagents that are known or suspected carcinogens or have undesirable effects on the environment. This requirement should be addressed when analytical methods are reviewed in connection with specifications as well as when the *Guide to specifications* (FAO Food and Nutrition Paper No. 5, Rev. 2) (Annex 1, reference 100) is next revised.

2.3.4 *Cross-references*

The Committee agreed that specifications for methods for the identification and purity of compounds should not require cross-reference to other specifications. The Committee also re-emphasized that frequently used methods should be incorporated into FAO Food and Nutrition Paper No. 5, Rev. 2 (Annex 1, reference 100).

2.3.5 *Flavouring agents*

For the first time, the Committee was asked to consider systematically a long list of flavouring agents. In view of the large number of such substances expected to be evaluated in the future, the Committee decided to tabulate the specifications for flavouring agents and not to use the standard specifications format. Specifications for compounds used as flavouring agents but also having other functions are listed both in the standard specifications format and in tabular form. Special methods of analysis, spectra for use in identification, and structural formulae will be included as appendices to the table of flavouring agents. Reference is made to FAO Food and Nutrition Paper No. 5, Rev. 2 (Annex 1, reference 100), as appropriate.

Distillation ranges and limits for heavy metals, arsenic and non-volatile residues are not included in specifications for flavouring agents. For those which are also used in other ways, reference is made to the appropriate specifications monograph.

The Committee recognized that some of the common names used for commercial flavouring agents are ambiguous. In revising specifications for such agents, the Committee will employ, where it considers it appropriate, more systematic terminology. In order to avoid problems of communication, however, synonyms will be included in the specifications.

2.4 Principles governing intake assessments

The Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (5) recognized that intake assessments of food additives, contaminants, and residues of pesticides and veterinary drugs should be considered an integral part of the risk assessment procedure for these substances. FAO and WHO had therefore decided to appoint several experts on intake assessment to the Joint FAO/WHO Expert Committee on Food Additives.

The Committee identified a number of issues that would require attention in the future in developing accurate models for assessing intake:

- provision of guidance on the collection of more accurate data on food consumption in future surveys;
- provision of guidance on the subdivision of regional diets according to staple foods;
- provision of guidance on the collection of more accurate data on concentrations of contaminants in foods; and
- evaluation of the quality of the available models for assessing food intake, including high food consumption.

A report on the Committee's deliberations was prepared, and it was decided that it should serve as a working paper at the next meeting of the Committee when food additives and contaminants are considered.

3. Specific food additives

The Committee re-evaluated several food additives considered at previous meetings. In addition, the Committee evaluated a large number of flavouring agents using the approach reviewed at its forty-

fourth meeting (Annex 1, reference 116). Information on the evaluations and on specifications is summarized in Annex 2.

3.1 Antioxidants: gallates (dodecyl, octyl and propyl)

These substances were previously evaluated by the Committee at its third, sixth, eighth, tenth, fifteenth, sixteenth, seventeenth, twentieth, twenty-fourth, thirtieth and forty-first meetings (Annex 1, references 3, 6, 8, 13, 26, 30, 32, 41, 53, 73 and 107). At the twenty-fourth meeting, a group ADI of 0–0.2 mg per kg of body weight was established, based on the supposed similarity in biotransformation of these compounds. The gallates were again reviewed at the thirtieth meeting, when an ADI of 0–2.5 mg per kg of body weight was established for propyl gallate. However, the Committee was unable to establish an ADI for dodecyl and octyl gallate owing to lack of adequate data, and requested that studies be carried out on the metabolism of these substances, including identification of their metabolites in the milk of lactating animals and the toxicity of their known hydrolysis products.

At its forty-first meeting, the Committee reviewed new 4-week and 90-day toxicity studies in rats with propyl gallate and *in vitro* studies on the hydrolysis of the gallates in different tissues. The Committee allocated an ADI of 0–1.4 mg per kg of body weight for propyl gallate based on a NOEL of 1910 mg/kg in the feed (equal to 135 mg per kg of body weight per day) in a 90-day study in rats and a safety factor of 100. The Committee concluded that it was unlikely that either dodecyl or octyl gallate was carcinogenic or genotoxic; temporary ADIs were therefore allocated to both these substances, based on the NOELs observed in limited toxicological studies.

With octyl gallate, a slight hypochromic anaemia was observed at 100 mg per kg of body weight per day in a study in rats in which the substance was administered for two generations. A temporary ADI of 0–0.1 mg per kg of body weight was established for octyl gallate, based on a NOEL of 17.5 mg per kg of body weight per day in this study and a safety factor of 200.

With dodecyl gallate, a reduction in spleen weight and pathological changes in the liver, kidney and spleen were observed at 50 mg per kg of body weight per day in a 150-day study in rats in which the substance was administered by gavage. A temporary ADI of 0–0.05 mg per kg of body weight was established for dodecyl gallate, based on a NOEL of 10 mg per kg of body weight per day in this study and a safety factor of 200.

At its forty-first meeting, the Committee concluded that additional studies on the pharmacokinetics and metabolism of dodecyl, octyl and propyl gallate might help to explain the differences in toxicological potency of these compounds and requested data from such studies to be made available by 1996. If these studies did not satisfactorily resolve the issue with respect to the similarity of dodecyl and octyl gallate to propyl gallate, further toxicological studies (including long-term toxicity/carcinogenicity studies and genotoxicity studies) on dodecyl and octyl gallate might be required.

Since the forty-fourth meeting of the Committee, a few studies on gallates have been published; however, none of the data requested on the pharmacokinetics or metabolism of dodecyl, octyl and propyl gallate have been submitted.

The Committee therefore decided to retain the ADI for propyl gallate (0–1.4mg per kg of body weight) established at the forty-first meeting, but did not extend the temporary ADIs for dodecyl and octyl gallate.

Since no new data on dodecyl, octyl and propyl gallates were submitted at the present meeting, a toxicological monograph was not prepared. The existing specifications for dodecyl, octyl and propyl gallate were revised, with minor changes.

3.2 **Emulsifier: glycerol ester of wood rosin (ester gum)**

This substance, which is used as a food additive in beverages and chewing gum, is prepared from wood rosin derived from the stumps of the longleaf pine (*Pinus palustris*) and purified to meet food-grade specifications. Wood rosin differs from tall oils and gums, which are derived from other parts of the tree. The resin acids in wood rosin can vary considerably in composition; however, the main resin acids in glycerol ester of wood rosin are the abietic acids (including dehydroabietic acid and neoabietic acid), the pimaric acids (including isopimaric acid and sandaracopimaric acid) and palustric acid. The carboxylic acid group of the resin acids of wood rosin is attached to a sterically hindered tertiary carbon, which is responsible for the resistance of the resin acid ester linkage to hydrolysis. Glycerol ester of wood rosin was previously considered by the Committee at its eighteenth, twentieth, thirty-third, thirty-seventh and forty-fourth meetings (Annex 1, references 35, 41, 83, 94 and 116).

At its twentieth meeting, the Committee, in the light of the strong ester bond and anticipated stability of this material, expressed the view that long-term and reproductive studies should be performed on

this specific substance, as opposed to unmodified resin, before further evaluation.

Specifications for the food-grade material were adopted at the thirty-seventh meeting of the Committee (Annex 1, references 94 and 96). The specifications defined the material as a complex mixture of tri- and diglycerol esters of resin acids from wood rosin with a residual fraction of monoglycerol esters varying from 1% to 3%.

At its forty-fourth meeting, the Committee prepared a full toxicological monograph on glycerol ester of wood rosin (Annex 1, reference 117). In addition, the Committee reviewed several studies on this substance, including a metabolic study in rats given unlabelled glycerol ester of wood rosin (identified as “beverage-grade ester gum”) in the diet. The results of the metabolic study showed that glycerol ester of wood rosin was, for the most part, recovered unchanged from the faeces, which suggested that it was not hydrolysed in the gut to a significant extent and was largely unabsorbed. However, the lack of sensitivity of the analytical method used was such that a firm conclusion could not be reached as to the stability or non-bioavailability of this substance. The Committee was unable to establish an ADI and concluded that, as a minimum, studies demonstrating the metabolic stability and non-bioavailability of glycerol ester of wood rosin under conditions resembling those present in the human gastrointestinal tract would be required to permit further evaluation of this material.

At its present meeting, the Committee reviewed new studies with ¹⁴C-labelled glycerol ester of wood rosin in rats and *in vitro*, which indicated that the food-grade material is quite stable in the gastrointestinal tract and that only a minor fraction, most probably the monoglycerol ester fraction, will undergo partial hydrolysis. The Committee also reviewed the toxicological studies that were available at the forty-fourth meeting, including 13-week toxicity studies in rats given food-grade and non-food-grade glycerol ester of wood rosin and a 2-year toxicity/carcinogenicity study in Sprague–Dawley rats given wood rosin (Annex 1, reference 117). In the 13-week toxicity studies, the food-grade material was less toxic than the non-food-grade material. In the 2-year toxicity/carcinogenicity study, wood rosin did not induce any treatment-related histopathological effects when administered at dose levels of up to 434 mg per kg of body weight per day. The Committee concluded that glycerol ester of wood rosin is not genotoxic.

Although no long-term toxicity studies or reproductive toxicity studies were available for glycerol ester of wood rosin (as specified in

FAO Food and Nutrition Paper No. 52, Add. 3 (Annex 1, reference 118)), the Committee considered that the data from previously reviewed studies and the new studies confirming non-bioavailability were adequate to establish an ADI. The Committee therefore allocated an ADI of 0–25 mg per kg of body weight to glycerol ester of wood rosin, based on the NOEL of 2500 mg per kg of body weight per day in the 13-week toxicity studies in rats with the food-grade material and a safety factor of 100. The Committee did not round the ADI to one significant figure (Annex 1, reference 116, section 2.2.2), because this would have reduced the value by 20%.

An addendum to the toxicological monograph was prepared. The existing specifications were revised, with minor changes.

3.3 Flavouring agents

The Committee applied the modified safety evaluation procedure (see section 2.2.1) to the three groups of esters considered during the meeting. It first considered two components of the procedure that are common to all three structural classes of esters: the data on intake and hydrolysis.

Intake data

Intake estimates were derived from surveys in Europe and the USA. Estimates of the intake of flavouring agents by populations typically involve the acquisition of data on the amounts used in food. In the USA, a series of surveys was conducted between 1970 and 1987 by the National Academy of Sciences National Research Council (under contract to the Food and Drug Administration) in which information was obtained from ingredient manufacturers and food processors on the amount of each substance destined for addition to the food supply and on the usual and maximal levels at which each substance was added in a number of broad food categories (6–9). In Europe, a survey was conducted in 1995 by the International Organization of the Flavor Industry, in which flavour manufacturers reported the total amount of each flavouring agent incorporated into food sold in the European Union during the previous year (F. Grundschober, personal communication, 1996). Manufacturers were requested to exclude use of flavouring agents in pharmaceutical, tobacco or cosmetic products.

In using these survey data to estimate intakes of flavouring agents, it was assumed that only 60% of the total amount used is reported and that the total amount used in food is consumed by only 10% of the population.

$$\text{Intake} \begin{matrix} (\mu\text{g per person per day}) \end{matrix} = \frac{\text{Annual volume of production (kg)} \times 10^9 (\mu\text{g/kg})}{\text{Population of consumers} \times 0.6 \times 365 \text{ days}}$$

The population of consumers was assumed to be 32×10^6 in Europe and 24×10^6 in the USA.

Data on hydrolysis

The ethyl, isoamyl and allyl esters considered at the present meeting are mostly simple structures, and data on representative compounds *in vivo* and *in vitro* indicate that they would be rapidly and completely hydrolysed after their ingestion as flavours. A wide range of enzymes (carboxyesterases and carboxylic acid hydrolases) is capable of hydrolysing esters into their constituent alcohols and acids. Carboxyesterases are found in many tissues, and there is high esterase activity in the intestinal tract, blood, liver, kidney, lung, brain and pancreas (10–12). Studies of a series of esters with straight-chain acid or alcohol moieties, in the range C1–C8, showed that purified esterases from rat and pig liver had different chain length requirements for optimal activity, but showed a trend for increased V_{max} (maximal rate of reaction) and $\text{p}K_{\text{m}}$ (negative logarithm of Michaelis constant) values with an increase in the chain length of either the acid or the alcohol moiety (10, 12). The multiplicity of esterases in some tissues and their wide tissue distribution result in the rapid hydrolysis of esters *in vivo* (11).

Data on the hydrolysis of flavour esters and selected structural analogues *in vitro* are summarized in Table 2. Hydrolysis of all esters was slow in artificial gastric juice (1–37% after 2 hours). In contrast, nearly all simple straight-chain saturated carboxylic acid esters were completely hydrolysed by artificial pancreatic juice within 2 hours. Branched-chain carboxylic acid esters and acetate esters were hydrolysed more slowly. The time to 50% hydrolysis ($T_{1/2}$) by pancreatic juice of those esters considered at the present meeting ranged from 2 minutes to over 3 hours. The data did not indicate that there would be a marked difference in the rate of hydrolysis between the three groups of esters, although some discrepancies were apparent: e.g. isoamyl isovalerate was hydrolysed more rapidly than the corresponding ethyl ester, but the reverse was true for isoamyl hexanoate.

The rates of hydrolysis of the esters by liver and intestinal tissue were about 1000 times those by artificial pancreatic juice, and the half-lives of the flavour esters considered at the meeting were 4 seconds or less. Ethyl isovalerate (not a flavouring agent) was hydrolysed more slowly, which suggested that branched-chain carboxylic acid

Table 2
Hydrolysis of flavour esters and selected analogues

Ester	Artificial gastric juice		Artificial pancreatic juice		Liver homogenate		Intestinal homogenate	
	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$
Ethyl acetate	—	—	ND	—	—	—	100 (P) ^a	—
Ethyl butyrate	15 ^b	8 h 10 min ^c	100 ^b	6 min ^c	—	—	—	—
Ethyl isovalerate ^d	6 ^b	23 h 10 min ^c	34 ^b	3 h 18 min ^c	—	24 s (R) ^c	—	2 min 13 s (R) ^c
Ethyl hexanoate	—	4 h 53 min ^c	—	3 min ^c	—	0.1 s (R) ^c	—	0.5 s (R) ^c
Ethyl heptanoate	10 ^b	12 h 50 min ^c	100 ^b	10 min ^c	—	0.2 s (R) ^c	—	0.6 s (R) ^c
Ethyl nonanoate	37 ^b	2 h 57 min ^c	100 ^b	6 min ^c	—	—	—	—
Ethyl decanoate	—	—	80 ^a	—	—	—	—	—
Ethyl dodecanoate	12 ^b	10 h 40 min ^c	100 ^b	6 min ^c	—	—	—	—
Ethyl cyclohexylpropanoate ^d	—	—	100 ^a	—	—	—	—	—
Ethyl phenylacetate ^d	—	10 h 40 min ^c	—	1 h 50 min ^c	—	—	—	—
Ethyl furylpropanoate ^d	—	—	100 ^a	—	—	—	—	—
Isoamyl acetate	—	—	20 ^a	—	—	—	100 (P) ^a	—
Isoamyl butyrate	12 ^b	11 h ^c	100 ^b	11 min ^c	—	0.5 s (R) ^c	—	0.1 s (R) ^c
Isoamyl isovalerate	—	4 h 55 min ^c	—	10 min ^c	—	—	—	—
Isoamyl hexanoate	—	2 h 26 min ^c	—	38 min ^c	—	—	—	—
Isoamyl phenylacetate ^d	—	—	100 ^a	—	—	—	—	—
Allyl hexanoate	—	18 h 40 min ^c	100 ^a	2 min ^c	—	4 s (R) ^c	—	0.1 s (R) ^c
Allyl tiglate	—	—	ND ^a	—	—	—	100 (P) ^a	—
Allyl phenylacetate	—	—	100 ^a	—	—	—	—	—
Related esters								
Butyl acetate	23 ^b	5 h 18 min ^c	72 ^b	1 h 6 min ^c	—	8 min 11 s (R) ^c	—	1 min 48 s (R) ^c
1,3-Dimethylbutyl acetate	—	—	15 ^a	—	—	—	>99 (P) ^a	—
Benzyl acetate	—	—	50 ^a	—	—	—	—	—
Methylanthrinilate	1 ^b	99 h 10 min ^c	ND, ^a 2 ^b	69 h 10 min ^b	>99 (P) ^a	26 min 40 s (R) ^c	15 (P) ^a	2 min 28 s (R) ^c

$T_{1/2}$, time to 50% hydrolysis; P, pig tissue; R, rat tissue; ND, not detected.

^a Source: reference 13.

^b Source: reference 14.

^c Source: reference 15.

^d Close structural analogue of the flavouring agents considered at the meeting.

esters are hydrolysed more slowly than straight-chain carboxylic acid esters.

The data from the above-mentioned studies indicate that the ethyl, isoamyl and simpler allyl esters considered by the Committee would be completely metabolized on passage from the lumen of the gastrointestinal tract into the general circulation. The wide tissue distribution of esterase activity, which includes esterases in the blood, would ensure rapid hydrolysis of any intact ester that escaped first-pass metabolism in the intestine and liver. This conclusion was supported by data from an unpublished study in which isoamyl-3-(2'-furyl)propionate and allyl phenylacetate were not detected in the hepatic portal blood of guinea-pigs given an intraduodenal dose of these esters. Both esters underwent 98% hydrolysis in guinea-pig blood within 1 minute (16). Similarly, unhydrolysed ester was not detected in the blood of rats given benzyl acetate (see section 3.6.1). The data on hydrolysis indicate that allyl anthranilate may not undergo first-pass metabolism, and some of the intact ester may enter the general circulation. Measurable concentrations of methyl-*N*-methylantranilate were present in the portal blood of guinea-pigs given an intraintestinal dose of this ester (16); however, the absorption of intact allyl anthranilate would not be of toxicological concern since slow hydrolysis would reduce the hepatotoxicity due to allyl alcohol (17).

3.3.1 **Ethyl esters**

Fifteen ethyl esters used as flavouring agents in food were evaluated by the safety evaluation procedure considered at the forty-fourth meeting (Annex 1, reference 116) and modified at the present meeting (see Fig. 2). The esters evaluated were ethyl formate, ethyl acetate, ethyl propionate, ethyl butyrate, ethyl pentanoate (valerate), ethyl hexanoate (caproate), ethyl heptanoate (enanthate), ethyl octanoate (caprylate), ethyl nonanoate (pelargonate), ethyl decanoate (caprate), ethyl undecanoate, ethyl dodecanoate (laurate), ethyl tetradecanoate (myristate), ethyl hexadecanoate (palmitate), and ethyl octadecanoate (stearate). The ethyl esters considered are all straight-chain, saturated carboxylic acid esters and all occur as natural constituents of various foods. Ethyl formate, ethyl acetate, ethyl butyrate, ethyl heptanoate, ethyl nonanoate and ethyl dodecanoate have already been assigned ADIs, which are maintained.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, ethyl acetate, ethyl propionate and ethyl butyrate are the major ethyl esters to which humans are exposed, accounting for 91% and 97% respectively, of the

total annual volume of production of the 15 esters considered (9; F. Grundschober, unpublished data, 1996).

Application of the procedure to ethyl esters

In applying the modified procedure for flavouring substances (see Fig. 2) to an evaluation of the above-mentioned ethyl esters, the Committee assigned all 15 compounds to structural class I (step 1). These ethyl esters are considered to be completely hydrolysed in the human body to ethanol and their component carboxylic acids (see pp. 19–21), which are endogenous intermediates in human metabolism. Therefore, all the compounds were predicted to be metabolized to innocuous products (step 2), and the left-hand side of the decision tree was further considered. Apart from four compounds (ethyl acetate, ethyl propionate, ethyl butyrate and ethyl hexanoate), the intake estimates for all the ethyl esters were below the threshold for class I (1800 µg per day), so that they were considered not to be of safety concern, and no further information should be required (step 3(a)). For ethyl acetate, ethyl propionate, ethyl butyrate and ethyl hexanoate, it was then necessary to consider whether either the substance or any of its metabolites was endogenous (step 4(a)). In all four cases, the metabolites were known to occur endogenously, and therefore these compounds were considered to be of no safety concern at the estimated levels of current intake. Table 3 summarizes the evaluation of the 15 ethyl esters using the modified procedure.

Toxicity data

The ethyl esters evaluated were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. In consequence, no toxicity data were necessary for application of the procedure. Nevertheless, the Committee thought that it was useful to include the toxicity data on these substances (see Annex 3).

Group evaluation

In the unlikely event that all foods containing all of the 15 ethyl esters as flavouring substances were consumed simultaneously on a daily basis, the estimated daily intake for individuals in Europe and the USA would be 1000 and 870 µg per kg of body weight, respectively. The equivalent estimated daily per capita intakes of ethanol are 460 and 410 µg per kg of body weight, respectively. The endogenous synthesis of ethanol has been estimated to be approximately 40–80 mg per kg of body weight per day, which is of the order of 100–200 times

the estimated daily intake per kg of body weight derived from the ethyl esters.

Conclusion

The Committee concluded that the above-mentioned ethyl esters would not present safety concerns at the estimated levels of current intake. In all cases in which data on toxicity were available, they were compatible with this conclusion.

Toxicological monographs were not prepared. New specifications were prepared for ethyl propionate, ethyl pentanoate, ethyl hexanoate, ethyl octanoate, ethyl decanoate, ethyl undecanoate, ethyl tetradecanoate, ethyl hexadecanoate and ethyl octadecanoate. For ethyl undecanoate, the specifications were designated as “tentative”. The existing specifications for ethyl formate, ethyl acetate, ethyl butyrate, ethyl heptanoate, ethyl nonanoate and ethyl dodecanoate were revised.

3.3.2 *Isoamyl alcohol and related esters*

Isoamyl alcohol and 10 of its related esters used as flavouring agents in food were evaluated by the safety evaluation procedure considered at the forty-fourth meeting (Annex 1, reference 116) and modified at the present meeting (see Fig. 2). The esters evaluated were isoamyl formate, isoamyl acetate, isoamyl propionate, isoamyl butyrate, isoamyl hexanoate, isoamyl octanoate, isoamyl nonanoate, isoamyl isobutyrate, isoamyl isovalerate and 3-methylbutyl 2-methylbutyrate. Seven of these esters are linear saturated carboxylic acid esters and three are branched-chain carboxylic acid esters.

Isoamyl alcohol used for flavouring purposes is a mixture of 3-methyl-1-butanol (isoamyl alcohol) (about 80%) and 2-methyl-1-butanol (about 20%). Isoamyl acetate and isoamyl butyrate were evaluated by the Committee at its twenty-third meeting, when a group ADI for isoamyl butyrate of 0–3 mg per kg of body weight expressed as isoamyl alcohol was allocated (Annex 1, reference 50). Since studies on isoamyl acetate indicated that it would be hydrolysed *in vivo* similarly to isoamyl butyrate, the Committee decided to include it in the group ADI for isoamyl butyrate. At its present meeting, the Committee decided to maintain this ADI.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, isoamyl acetate is by far the most important isoamyl ester to which humans are exposed, accounting for 79% and 69%, respectively, of the total annual volume of

Table 3
Summary of the results of safety evaluations of 15 ethyl esters^a

Substance	<i>Step 3 (a)</i> Does intake exceed the threshold for human intake?	<i>Step 4 (a)</i> Metabolized to endogenous substances?	Products of hydrolysis	Metabolic fate	Conclusion based on current intake
Ethyl formate	No Europe: 1400 USA: 500	NR	Ethanol and formic acid	Metabolized in recognized biochemical pathways	No safety concern
Ethyl acetate	Yes Europe: 28000 USA: 28000	Yes	Ethanol and acetic acid	Endogenous in humans	
Ethyl propionate	Yes Europe: 3900 USA: 5900	Yes	Ethanol and propionic acid	Endogenous in humans	
Ethyl butyrate	Yes Europe: 24000 USA: 16000	Yes	Ethanol and butyric acid	Endogenous in humans	
Ethyl pentanoate	No Europe: 200 USA: 72	NR	Ethanol and valeric acid	Metabolized in recognized biochemical pathways	

Ethyl hexanoate	Yes Europe: 2200 USA: 600	Yes	Ethanol and hexanoic acid	Endogenous in humans	No safety concern
Ethyl heptanoate	No Europe: 220 USA: 190	NR	Ethanol and heptanoic acid	Metabolized in recognized biochemical pathways	
Ethyl octanoate	No Europe: 450 USA: 38	NR	Ethanol and octanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl nonanoate	No Europe: 140 USA: 47	NR	Ethanol and nonanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl decanoate	No Europe: 180 USA: 55	NR	Ethanol and decanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl undecanoate	No Europe: 30 USA: 0.17	NR	Ethanol and undecanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl dodecanoate	No Europe: 240 USA: 45	NR	Ethanol and lauric acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl tetradecanoate	No Europe: 250 USA: 180	NR	Ethanol and myristic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl hexadecanoate	No Europe: 88 USA: 1.3	NR	Ethanol and palmitic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl octadecanoate	No Europe: 2.6 USA: 0.38	NR	Ethanol and octadecanoic acid	Metabolized in glycolytic and fatty acid pathways	

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

^a Step 1: All of the esters in this group are in structural class I, the human intake threshold of which is 1800 µg per day.

Step 2: All of the esters in this group are hydrolysed to their component alcohol, ethanol, and their corresponding carboxylic acids, all of which are innocuous products. Intake values are expressed in µg per day.

production of the 10 esters considered (9; F. Grundschober, personal communication, 1996). The intake of isoamyl butyrate, isoamyl alcohol and isoamyl isovalerate is approximately 20% of that of isoamyl acetate. The other esters are produced in much smaller quantities. With the exception of isoamyl nonanoate, isoamyl alcohol and all of the above-mentioned esters have been detected as natural constituents of various foods and alcoholic beverages.

Application of the procedure to isoamyl alcohol and related esters

In applying the modified procedure for flavouring agents (Fig. 2) to an evaluation of isoamyl alcohol and its related esters, the Committee assigned all 11 compounds to class I of the three structural classes (step 1). These esters are considered to be completely hydrolysed in the human body to isoamyl alcohol and its component carboxylic acids (see pp. 19–21), and the hydrolysis products either occur as, or are rapidly metabolized to, normal endogenous intermediates in human metabolism of amino acids and fatty acids. Since all 11 compounds were predicted to be metabolized to innocuous products (step 2), the left-hand side of the decision tree was further considered. Apart from two compounds (isoamyl acetate and isoamyl butyrate), the intake estimates for isoamyl alcohol and its related esters were below the threshold for class I (1800 µg per day), so that they were considered not to be of safety concern, and no further information should be required (step 3(a)). For isoamyl acetate and isoamyl butyrate, it was then necessary to consider whether the substance or any of its metabolites was endogenous (step 4(a)). In both cases, the metabolites were known to occur endogenously, and therefore these compounds were considered to be of no safety concern at the estimated levels of current intake.

2-Methyl-1-butanol, one of the components of isoamyl alcohol, was also evaluated using the modified procedure. This compound belongs to class I of the three structural classes. It is metabolized to innocuous products, and its intake does not exceed the threshold for class I. The Committee therefore considered this substance not to be of safety concern, and did not require any additional information.

Table 4 summarizes the evaluation of isoamyl alcohol and its related esters by the modified procedure.

Toxicity data

The isoamyl esters evaluated were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. In consequence, no toxicity data were necessary for application of the

Table 4
Summary of the results of safety evaluations of isoamyl alcohol and 10 isoamyl esters^a

Substance	Step 3 (a) Does intake exceed the threshold for human intake?	Step 4 (a) Metabolized to endogenous substances?	Products of hydrolysis and primary alcohol oxidation	Metabolic fate	Conclusion based on current intake
Isoamyl alcohol	No Europe: ND USA: 1600	NR	Isovaleric acid	Oxidation product. Metabolized in amino acid and fatty acid pathways	No safety concern
Isoamyl formate	No Europe: 50 USA: 30	NR	Isovaleric acid and formic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl acetate	Yes Europe: 23000 USA: 10000	Yes	Isovaleric acid and acetic acid	Endogenous in humans	
Isoamyl propionate	No Europe: 300 USA: 120	NR	Isovaleric acid and propionic acid	Metabolized in amino acid, fatty acid and tetrahydrofolate pathways	
Isoamyl butyrate	Yes Europe: 4000 USA: 1900	Yes	Isovaleric acid and butyric acid	Endogenous in humans	
Isoamyl hexanoate	No Europe: 90 USA: 30	NR	Isovaleric acid and hexanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl octanoate	No Europe: 20 USA: 0.6	NR	Isovaleric acid and octanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl nonanoate	No Europe: 2 USA: 0.001	NR	Isovaleric acid and nonanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl isobutyrate	No Europe: 12 USA: 7	NR	Isovaleric acid and isobutyric acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl isovalerate	No Europe: 1400 USA: 800	NR	Isovaleric acid	Primary component of hydrolysis. Metabolized in amino acid and fatty acid pathways	
Isoamyl 2-methylbutyrate	No Europe: 6.5 USA: 2.1	NR	Isovaleric acid and 2-methylbutyric acid	Metabolized in amino acid and fatty acid pathways	

NR, not required for evaluation because consumption of the substance was determined to be of no safety concern at an earlier step of the procedure; ND, no intake data reported.

^a Step 1: All of the esters in this group are in structural class I, the human intake threshold of which is 1800 µg per day.

Step 2: All of the esters in this group are hydrolysed to their component alcohols and the corresponding carboxylic acids, all of which are innocuous products. Intake values are expressed in µg per day.

procedure. Nevertheless, the Committee thought that it was useful to include the toxicity data on these substances (see Annex 3).

Group evaluation

In the unlikely event that all foods containing isoamyl alcohol and its 10 related esters as flavouring agents were consumed simultaneously on a daily basis, the estimated daily per capita consumption in Europe and the USA would be 670 and 240 µg per kg of body weight, respectively. The equivalent estimated daily per capita intakes of isoamyl alcohol would be 340 and 170 µg per kg of body weight, respectively, well below the ADI of 0–3 mg per kg of body weight established for isoamyl alcohol as a component of isoamyl acetate and isoamyl butyrate.

Conclusion

The Committee concluded that isoamyl alcohol and the above-mentioned related esters do not present safety concerns at the estimated current levels of intake. In all cases in which toxicity data were available, they were compatible with this conclusion.

Toxicological monographs were not prepared. New specifications were prepared for isoamyl alcohol, isoamyl formate, isoamyl propionate, isoamyl hexanoate, isoamyl octanoate, isoamyl nonanoate, isoamyl isobutyrate, isoamyl isovalerate and isoamyl 2-methylbutyrate. For isoamyl octanoate, isoamyl nonanoate and isoamyl 2-methylbutyrate, the specifications were designated as “tentative”. The existing specifications for isoamyl acetate and isoamyl butyrate were revised.

3.3.3 Allyl esters

Twenty-one allyl esters used as flavouring agents in food were evaluated by the procedure considered at the forty-fourth meeting (Annex 1, reference *II6*) and modified at the present meeting of the Committee (see Fig. 2). As a consequence of the Committee’s decision not to consider step 7 of the original proposed procedure (Fig. 1) at this meeting, allyl 2-furoate could not be evaluated beyond step 6. The esters evaluated were allyl propionate, allyl butyrate, allyl hexanoate, allyl heptanoate, allyl octanoate, allyl nonanoate, allyl isovalerate, allyl sorbate, allyl 10-undecenoate, allyl tiglate, allyl 2-ethylbutyrate, allyl cyclohexaneacetate, allyl cyclohexanepropionate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate, allyl cyclohexanehexanoate, allyl phenylacetate, allyl phenoxyacetate, allyl cinnamate, allyl anthranilate and allyl 2-furoate. These esters are formed from

allyl alcohol and carboxylic acids. Of the 21 allyl esters, only allyl hexanoate and allyl 2-furoate have been reported as natural components of food.

Allyl hexanoate, allyl heptanoate and allyl isovalerate were evaluated by the Committee at its thirty-seventh meeting (Annex 1, reference 94). In view of evidence that these esters are all rapidly hydrolysed to allyl alcohol, the Committee concluded that they should be evaluated for a group ADI on the basis of the allyl alcohol moiety. The Committee allocated an ADI of 0–0.05 mg per kg of body weight for allyl hexanoate, allyl heptanoate and allyl isovalerate as allyl alcohol equivalent. This corresponds to 0–0.13 mg per kg of body weight for allyl hexanoate, 0–0.15 mg per kg of body weight for allyl heptanoate, or 0–0.12 mg per kg of body weight for allyl isovalerate, or *pro rata* combinations of these substances. These ADIs were maintained at the present meeting.

The Committee concluded, on the basis of the toxicological data available, that there were no existing unresolved toxicity problems in relation to allyl alcohol. Thus, in agreement with the general considerations dealing with the application of the procedure, it could be applied to the allyl esters. None of the other allyl esters have previously been evaluated by the Committee.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, allyl hexanoate, allyl heptanoate and allyl cyclohexanepropionate are the major allyl esters to which humans are exposed (9; F. Grundschober, personal communication, 1996). These three esters account for over 96% (approximately 85%, 4% and 7%, respectively) of the total annual volume of production in Europe of the 21 allyl esters considered and for over 99% (approximately 85%, 3% and 12%, respectively) of the total annual volume of production in the USA. The other esters are produced in much smaller quantities. The estimated daily per capita intake of allyl hexanoate, the allyl ester produced in by far the greatest annual volume, is 43 µg per kg of body weight per day in Europe and 14 µg per kg of body weight per day in the USA.

Application of the procedure to allyl esters

In applying the modified procedure for flavouring agents (see Fig. 2) to an evaluation of the 21 allyl esters considered at the present meeting, the Committee assigned all except three of the compounds to class II of the three structural classes (step 1). Allyl phenoxacetate, allyl anthranilate and allyl 2-furoate were assigned to class III.

Generally, allyl esters would be expected to be hydrolysed in the human body to allyl alcohol and their corresponding carboxylic acids (see pp. 19–21). However, none of the allyl esters considered could be predicted to be metabolized to innocuous products (step 2), since all 21 would be hydrolysed to allyl alcohol. Accordingly, the right-hand side of the decision tree was considered. For all 21 allyl esters except allyl hexanoate, the intake estimate was below the threshold for the structural class for the substance (540 µg per day for class II and 90 µg per day for class III). For allyl hexanoate, the intake estimates in Europe (2600 µg per day) and the USA (820 µg per day) both exceeded the threshold for class II. Accordingly, additional data on this substance or a closely related substance were required in order to proceed with the safety evaluation (step 3(b)). For the remaining 20 substances, it was then necessary to determine whether adequate data were available on the substance or on a structurally related substance that provide an adequate margin of safety at current estimated levels of intake (step 4(b)). This condition was met for all the 20 esters evaluated, except allyl 2-furoate.

Table 5 summarizes the evaluation of the 21 allyl esters using the modified procedure.

Toxicity data

Allyl alcohol. Results of dietary studies in animals indicate that allyl alcohol and allyl esters may cause liver damage. The mechanism of hepatotoxicity involves acrolein, an oxidation product of allyl alcohol, which is known to damage the periportal region of the liver lobule (29).

The current intake of allyl alcohol from the hydrolysis of all of the allyl esters was evaluated in relation to the ADI for allyl alcohol of 0–0.05 mg per kg of body weight allocated by the Committee at its thirty-seventh meeting (Annex 1, reference 94). This ADI is based on a NOEL of 4.8–6.2 mg per kg of body weight per day from a 15-week study in rats given allyl alcohol in drinking-water (30). In addition, the Committee considered another study which had not previously been evaluated in which drinking-water containing 300 mg/l of allyl alcohol was administered to rats for 106 weeks. The results did not raise any additional concerns (31).

Allyl propionate. The results of a 13-week study in which allyl propionate was fed to rats in the diet at a dose level of 18 mg per kg of body weight per day did not reveal any evidence of hepatotoxicity (18).

Allyl butyrate. No signs of liver toxicity were noted when allyl butyrate was administered by gavage to rats at a dose of 50 mg per kg of

body weight per day for 17 weeks. However, there was slight to marked peribronchial lymphocytic infiltration of the lungs, which was also observed in control animals but to a lesser degree (20). Peribronchial lymphocytic infiltration of the lungs was the only effect reported in a second 17-week study in which rats were given allyl butyrate by gavage at a dose of 50 mg per kg of body weight per day (19).

Allyl hexanoate. In short-term studies in rats, administration of allyl hexanoate at a dose of 50 mg per kg of body weight per day was not associated with any evidence of hepatotoxicity (19, 20).

No adverse effects were reported when allyl hexanoate was incorporated into the diet of rats at a dose of 125 mg per kg of body weight per day for 1 year (20). Adjustment of the dose to take into account the loss of allyl hexanoate from the diet due to evaporation (approximately 31 % per week) resulted in an estimated intake of 86 mg per kg of body weight per day.

Allyl heptanoate. In dietary studies of 13 weeks' duration in rats and of 18 months' duration in dogs, no adverse effects were observed at doses of up to 500 and 25 mg per kg of body weight per day, respectively (18, 21).

Allyl octanoate. No short-term studies were available on allyl octanoate. However, the structure of this compound is closely related to that of allyl hexanoate.

Allyl nonanoate. No short-term studies were available on allyl nonanoate. However, the structure of this compound is closely related to that of allyl heptanoate.

Allyl isovalerate. No evidence of hepatotoxicity was observed at daily intake levels of 62 mg per kg of body weight in short- and long-term studies in mice and rats (22).

Allyl sorbate. No short-term studies were available on allyl sorbate. However, this compound is structurally related to allyl hexanoate. Sorbic acid was evaluated by the Committee at its seventeenth meeting (Annex 1, reference 32), when an ADI of 0–25 mg per kg of body weight was established. No adverse effects were reported when rats and mice were maintained on diets containing 1.5% sorbic acid for 2 years and 80 weeks, respectively (23, 24).

Allyl 10-undecenoate. No short-term studies were available on allyl 10-undecenoate. However, this compound is structurally related to allyl heptanoate. No adverse effects were reported in adult rats or their offspring when the hydrolysis product, 10-undecenoic acid, was administered by gavage at 100, 200 or 400 mg per kg of body weight

Table 5
Summary of the results of safety evaluations of 21 allyl esters

Substance	Step 1 Structural class	Step 2 ^a Metabolized to innocuous products?	Step 3 (b) ^b Does intake exceed the threshold for human intake?	Step 4 (b) Adequate NOEL for substance or related substance?	Toxicological data	Conclusion based on current intake
Allyl propionate	II	No	No Europe: 7.9 USA: <0.01	Yes	NOELs for allyl alcohol and propionic acid provide an adequate margin of safety for allyl alcohol and propionic acid from the hydrolysis of allyl propionate (Annex 1, reference 94) (18)	No safety concern
Allyl butyrate	II	No	No Europe: 11 USA: <0.01	Yes	NOELs for allyl alcohol and allyl butyrate provide an adequate margin of safety for allyl butyrate (Annex 1, reference 94) (19)	
Allyl hexanoate ^c	II	No	Yes Europe: 2600 USA: 820	—	NOELs for allyl alcohol and allyl hexanoate provide an adequate margin of safety for allyl hexanoate; ADI for allyl hexanoate, 0–0.13 mg per kg of body weight (Annex 1, reference 94) (20)	
Allyl heptanoate	II	No	No Europe: 130 USA: 28	Yes	NOELs for allyl alcohol and allyl heptanoate provide an adequate margin of safety for allyl heptanoate; ADI for allyl heptanoate, 0–0.15 mg per kg of body weight (Annex 1, reference 94) (18, 21)	
Allyl octanoate	II	No	No Europe: 45 USA: 1.3	Yes	NOELs for allyl alcohol and allyl hexanoate provide an adequate margin of safety for allyl octanoate (Annex 1, reference 94) (21)	

Allyl nonanoate	II	No	No Europe: 2.4 USA: <0.01	Yes	NOELs for allyl alcohol and allyl heptanoate provide an adequate margin of safety for allyl nonanoate (Annex 1, reference 94) (21)	No safety concern
Allyl isovalerate	II	No	No Europe: <0.01 USA: 0.19	Yes	NOELs for allyl alcohol and allyl isovalerate provide an adequate margin of safety for allyl isovalerate; ADI for allyl isovalerate, 0–0.12mg per kg of body weight (Annex 1, reference 94) (22)	
Allyl sorbate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol, sorbic acid and allyl hexanoate provide an adequate margin of safety for the hydrolysis products of allyl sorbate; ADI for sorbic acid, 0–25mg per kg of body weight (Annex 1, reference 32) (23, 24)	
Allyl 10-undecenoate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and 10-undecenoic acid provide an adequate margin of safety for the hydrolysis products of allyl 10-undecenoate (Annex 1, reference 94) (25)	
Allyl tiglate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and for a structurally related analogue, 3-methyl-2-butenic acid, provide an adequate margin of safety for the hydrolysis products of allyl tiglate (Annex 1, reference 94) (26)	
Allyl 2-ethylbutyrate	II	No	No Europe: <0.01 USA: 0.02	Yes	NOELs for allyl alcohol and 2-ethylbutyric acid provide an adequate margin of safety for the hydrolysis products of allyl 2-ethylbutyrate (Annex 1, reference 94) (27)	

Table 5 (continued)

Substance	Step 1 Structural class	Step 2 ^a Metabolized to innocuous products?	Step 3 (b) ^p Does intake exceed the threshold for human intake?	Step 4 (b) Adequate NOEL for substance or related substance?	Toxicological data	Conclusion based on current intake
Allyl cyclohexaneacetate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester, allyl cyclohexanepropionate, provide an adequate margin of safety for allyl cyclohexaneacetate (Annex 1, reference 94) (19, 20)	No safety concern
Allyl cyclohexanepropionate	II	No	No Europe: 220 USA: 110	Yes	NOELs for allyl alcohol and allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanepropionate (Annex 1, reference 94) (19, 20; H.A. Shelanski, personal communication, 1953; H. Paynter, personal communication, 1957)	
Allyl cyclohexanebutyrate	II	No	No Europe: 0.14 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanebutyrate (Annex 1, reference 94) (19, 20)	
Allyl cyclohexanevalerate	II	No	No Europe: 0.14 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanevalerate (Annex 1, reference 94) (19, 20)	
Allyl cyclohexanehexanoate	II	No	No Europe: 0.36 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanehexanoate (Annex 1, reference 94) (19, 20)	

Allyl phenylacetate	II	No	No Europe: 7.5 USA: <0.01	Yes	NOELs for allyl alcohol and for the phenylethyl ester of the hydrolysis product phenylacetic acid provide an adequate margin of safety for the hydrolysis products of allyl phenylacetate (Annex 1, reference 94) (20)	No safety concern
Allyl phenoxyacetate	III	No	No Europe: 35 USA: 2.5	Yes	NOELs for allyl alcohol and for the structurally related ethyl ester of <i>p</i> -methylphenoxyacetic acid provide an adequate margin of safety for the hydrolysis products of allyl phenoxyacetate (Annex 1, reference 94) (28)	
Allyl cinnamate	II	No	No Europe: 5.4 USA: 0.28	Yes	NOELs for allyl alcohol and for cinnamaldehyde, the aldehyde precursor of cinnamic acid, provide an adequate margin of safety for the hydrolysis products of allyl cinnamate (Annex 1, reference 94) (Trubeck Laboratories, unpublished data, 1958)	
Allyl anthranilate	III	No	No Europe: 0.14 USA: 0.09	Yes	NOELs for allyl alcohol and for methylantranilate, a simple ester of anthranilic acid, provide an adequate margin of safety for the hydrolysis products of allyl anthranilate (Annex 1, reference 94) (20)	
Allyl 2-furoate ^d	III	No	No Europe: 0.14 USA: <0.01	No	—	—

^a All allyl esters are metabolized to allyl alcohol and their respective carboxylic acids.

^b The thresholds for human intake for classes II and III are 540 µg per day and 90 µg per day, respectively. All intake values are expressed in µg per day.

^c As evaluation of allyl hexanoate resulted in a positive response to the question in step 3(b) of Fig. 2, this flavouring agent was evaluated individually, on the basis of the available toxicity data.

^d Evaluation of allyl 2-furoate was postponed, pending consideration of step 4(b) of the original proposed procedure (Annex 1, reference 116) by the Committee (see Fig. 1).

per day for up to 9 months (25). Similarly, no adverse effects were reported in mice given this compound by gavage at 100, 200 or 400 mg per kg of body weight per day for 6 months (25).

Allyl tiglate. No short-term studies were available on allyl tiglate. However, this compound is structurally related to allyl isovalerate. In a limited study of the hepatotoxicity of the metabolites of isoprene derivatives, groups of rats were given the isomeric acid, 3-methyl-2-butenic acid, by gavage at doses of 400–2500 mg per kg of body weight per day for 1–2 months (26). The study, which was limited to cytological examination of the liver, revealed no abnormalities.

Allyl 2-ethylbutyrate. No short-term studies were available on allyl 2-ethylbutyrate. In a limited study, no effects were reported when a diet containing 0.6% 2-ethylbutyric acid (equivalent to 300 mg per kg of body weight per day) was fed to rats for 90 days (27).

Allyl cyclohexanepropionate. No adverse effects were reported in rats given diets containing allyl cyclohexanepropionate at a dose equivalent to 50 or 125 mg per kg of body weight per day for 27–28 weeks or 1 year, respectively (19, 20). Similarly, no adverse effects were observed when rats were given 2, 20 or 100 mg per kg of body weight of allyl cyclohexanepropionate in sesame oil by stomach tube daily, 5 days per week, for 3 months (H.A. Shelanski, personal communication, 1953) or were maintained on diets containing 0.1% or 0.25% allyl cyclohexanepropionate for 13 weeks (H. Paynter, personal communication, 1957).

Allyl cyclohexaneacetate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate and allyl cyclohexanehexanoate. No short-term studies on these esters were available. However, they are all structurally related to allyl cyclohexanepropionate.

Allyl phenylacetate. No short-term studies were available. No adverse effects were observed when rats were maintained on diets providing 500 mg per kg of body weight per day of the structurally related phenyl ester of phenylacetic acid, phenylethyl phenylacetate, for 17 weeks (20).

Allyl phenoxyacetate. No short-term studies were available. No adverse effects were observed when rats were maintained on diets providing 15 mg per kg of body weight per day of the structurally related ethyl ester of *p*-methylphenoxyacetic acid for 90 days (28).

Allyl cinnamate. No short-term studies were available. Cinnamaldehyde, the aldehyde precursor of cinnamic acid, was studied in rats, which were maintained on diets providing 50, 125 or 500 mg of

cinnamaldehyde per kg of body weight per day for 16 weeks. At 500 mg per kg of body weight per day, slight hepatocellular swelling and hyperkeratosis of the gastric squamous epithelium were reported (20). No adverse effects were reported when cinnamaldehyde was added to the diet of rats to provide an average daily intake of up to 227 mg per kg of body weight for 12 weeks (Trubeck Laboratories, unpublished data, 1958).

Allyl anthranilate. No short-term studies were available. No adverse effects were reported when rats were maintained for 90 days on diets providing 50 or 500 mg per kg of body weight per day of methyl anthranilate, a simple ester of anthranilic acid (20).

Allyl 2-furoate. No data on the ester or on a closely related substance were available to enable the Committee to conclude that there was an adequate margin of safety for this flavouring substance (see Fig. 2, step 4(b)). In addition, no data on the hydrolysis of allyl-2-furoate were available. The Committee therefore requested additional toxicity data on this substance.

Group evaluation

Neither the estimated daily per capita intake of allyl hexanoate in Europe (43 µg per kg of body weight per day) nor that in the USA (14 µg per kg of body weight per day) exceeds the ADI allocated by the Committee. Similarly, the estimated current intakes of allyl heptanoate and allyl isovalerate are below the individual ADIs previously allocated by the Committee. For the other allyl esters considered at the meeting (except allyl 2-furoate), a NOEL exists for the substance itself or for a structurally related substance that provides an adequate margin of safety at the estimated current levels of intake. In addition, the estimated current intake of allyl alcohol from the consumption of all 21 allyl esters is 18 µg per kg of body weight per day in Europe and 5.8 µg per kg of body weight per day in the USA. These estimates are below the ADI of 0–0.05 mg per kg of body weight previously established for allyl alcohol.

Conclusions

Evaluation of this group of esters demonstrated that the safety evaluation procedure is capable of identifying flavouring substances of possible safety concern at the estimated current levels of intake, such as allyl hexanoate. The Committee noted that this concern was met by its previous evaluation of allyl hexanoate (together with allyl heptanoate and allyl isovalerate) (Annex 1, reference 94). The Committee concluded that these allyl ester flavouring agents do not

present safety concerns at the estimated current levels of intake. Whenever data on toxicity were available, they were compatible with this conclusion.

Evaluation of allyl 2-furoate was postponed, pending consideration of either additional toxicity data or step 5(b) of the original procedure (Fig. 1) by the Committee at a future meeting.

Toxicological monographs were not prepared. New tentative specifications were prepared for allyl propionate, allyl sorbate, allyl cyclohexaneacetate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate, allyl cyclohexanehexanoate, allyl phenylacetate, allyl cinnamate, allyl anthranilate and allyl 2-furoate. New specifications were also prepared for allyl butyrate, allyl octanoate, allyl nonanoate, allyl 10-undecanoate, allyl 2-ethylbutyrate and allyl phenoxyacetate. The existing specifications for allyl hexanoate, allyl heptanoate, allyl isovalerate, allyl tiglate and allyl cyclohexanepropionate were revised.

3.4 Sweetening agent: alitame

Alitame was last considered at the forty-fourth meeting of the Committee (Annex 1, reference 116), but no ADI was allocated because of significant concerns about deficiencies in the carcinogenicity studies in rats. Specifically, in a study in Long–Evans rats, poor survival rates at 24 months and an increased incidence of hepatocellular adenomas in females at the highest dose were noted. While it was considered unlikely that these adenomas would progress to hepatocellular carcinomas, the data were considered inconclusive in this regard. The second study, in Sprague–Dawley rats, showed lower survival rates at both 22 and 24 months than those found in the Long–Evans rats, and hence was considered inadequate to provide further information regarding the potential carcinogenicity of alitame.

At its present meeting, the Committee reconsidered the question of the adequacy of the carcinogenicity studies in the light of the survival rates of animals in contemporary long-term studies (see section 2.2.2) and a further statistical analysis of the data from the two studies, which specifically assessed the adequacy of the study in Sprague–Dawley rats to detect liver lesions.

The Committee noted that, while the survival rate of Long–Evans rats at 24 months was low, it was comparable to that observed in contemporary studies in rats of this strain. No hepatocellular carcinomas were observed in the study in Long–Evans rats. It also noted that the survival rate of Sprague–Dawley rats was comparable to that in contemporary studies in rats of this strain and that because there were

more animals per group initially than in the study using Long–Evans rats, the number of surviving animals was comparable between the two strains. On the basis of a logistical regression model developed using data from the study with Long–Evans rats, an increased probability of developing hepatocellular adenomas and eosinophilic foci would have been expected in the Sprague–Dawley rats, given the dose levels and the duration of the study, but no such increase was observed. On the basis of these considerations, the two studies were considered adequate to assess the potential carcinogenicity of alitame.

The Committee concluded that there was no evidence that alitame was carcinogenic, and therefore allocated an ADI of 0–1 mg per kg of body weight, based on the NOEL of 100 mg per kg of body weight identified at the forty-fourth meeting in the 18-month study in dogs and a safety factor of 100.

Although the Committee had not specifically requested a further study of tolerance to repeated doses of alitame in diabetic subjects, it was aware that such a study is under way, and requested that the results be submitted for evaluation when available.

An addendum to the toxicological monograph was prepared. The existing specifications were revised, with minor changes.

3.5 **Thickening agent: konjac flour**

Konjac flour was previously considered by the Committee at its forty-first meeting (Annex 1, reference 107). At that meeting, the Committee allocated a temporary ADI “not specified” on the basis of the available toxicological data, particularly data from human studies, the long history of use of konjac flour as a food in China and Japan, and estimates of consumption from traditional and anticipated food additive uses. The results of additional short-term toxicity studies, which the Committee was informed had been conducted in rats and dogs, together with adequate data on the fate of konjac flour in the gut and information on its influence on the bioavailability of fat-soluble vitamins, were requested for review by 1996.

No information on the short-term toxicity studies referred to in the forty-first report could be located by the Committee at its present meeting. The Committee reviewed data from additional short-term studies and a long-term study, all conducted in rats. The short-term studies were a 28-day study on the effect of konjac flour on protein digestion and absorption, and a 12-week study on the hypocholesterolaemic effect of konjac flour. The long-term study was on the effect of konjac flour on calcium and phosphorus metabolism

and tissue pathology. While these studies were not specifically designed to assess the potential toxicity of konjac flour, no evidence of toxicity was reported at a dose of 10% in the diet for up to 12 weeks, or at 1% in the diet for 18 months. Two additional studies on genotoxicity provided no evidence of potential to induce forward mutations at the thymidine kinase locus in lymphoma cells in culture or in micronuclei in mouse bone marrow.

The Committee also considered some additional data on the fate of konjac flour in the large intestine, including the results of a recent study using human faecal flora *in vitro*, which showed that extensive hydrolysis of konjac flour occurs in the large intestine. Konjac flour underwent less fermentation than D-glucose, D-galactose, soluble starch, pectin and guar gum, but more than xanthan gum, L-glucose, carboxymethylcellulose and sodium alginate. Although only indirect evidence was provided, the Committee concluded that konjac flour, like other polysaccharide gums, undergoes fermentation in the large intestine to fatty acids (primarily acetate, propionate and butyrate).

The Committee reviewed data from animal and human studies on the effect of konjac flour and other polysaccharide gums on the absorption of fat-soluble vitamins and cholesterol and the reabsorption of bile acids. The available data indicate that konjac flour affects the absorption of vitamin E and cholesterol only at high doses (possibly through interference with bile acid micelle formation and subsequent interference with transport mechanisms). The Committee noted that definitive studies to establish the threshold dose of konjac flour that affects vitamin E absorption had still not been carried out, but considered that it was likely to be much higher than the levels of intake of konjac flour when used as a food additive.

The Committee stressed that this evaluation applies only to the use of konjac flour as a food additive, and concluded that the additional studies provided no evidence of adverse effects in experimental animals. The metabolic fate of konjac flour in the intestine is similar to that of other polysaccharide gums. On the basis of this reassessment and the anticipated food additive uses of konjac flour (as a thickener, emulsifier, stabilizer, gelling agent, texturizer and glazing agent), the Committee established an ADI "not specified" for konjac flour.

A monograph addendum was prepared. The existing specifications were revised, with minor changes.

3.6 Miscellaneous substances

3.6.1 *Benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts*

All of these substances have been evaluated previously by the Committee, as the individual substances. Because of their structural similarity and common metabolic fate, however, a group ADI has been established for these substances. With the exception of benzoic acid and the benzoate salts, which are used as food preservatives, all of these substances are used as flavouring agents. Benzyl alcohol is also used as a carrier solvent.

At its forty-first meeting (Annex 1, reference 107), the Committee recommended that a full review of benzyl acetate, benzoic acid, the benzoate salts, benzaldehyde and benzyl alcohol be performed in 1995 to determine whether reproductive toxicity/teratogenicity studies or other studies would be required.

At its present meeting, the Committee reviewed data from studies on disposition and metabolism, short-term and long-term toxicity, genotoxicity, reproductive toxicity, teratogenicity and observations in humans. On the basis of this review, a number of issues were identified which are important in the safety evaluation of these compounds. Since they are all metabolized to benzoic acid, it was considered reasonable to assume that the results of studies on one member of the group would apply to all the others.

The results of a number of studies in humans and experimental animals indicated that the formation of hippuric acid from benzoic acid is a saturable process in which the availability of glycine is the rate-limiting step. This observation is particularly relevant to the interpretation of the toxic effects of these compounds in experimental animals, since supplementation of the diet with glycine was shown to alleviate the toxic effects of high doses of benzyl acetate and benzoic acid, including reductions in body-weight gain and neurotoxicity. However, even with saturation of hippuric acid formation, clearance of compounds in the benzyl group is relatively rapid in both experimental animals and humans. An extensive review of the toxicity of benzoate showed that at high doses it interferes with intermediary metabolism, including the urea cycle, gluconeogenesis, fatty acid metabolism, and the tricarboxylic acid cycle, probably by sequestering coenzyme A prior to its conjugation with glycine. This is consistent with the observation of effects such as metabolic acidosis, convulsions, and hyperpnoea in experimental animals and humans given very high doses of this substance.

Administration of benzyl acetate to rats by gavage was shown to result in higher peak plasma levels of benzoic acid in comparison with ingestion of a similar daily dose in the diet, while plasma levels of hippuric acid were similar regardless of the route of administration. The toxicity of benzyl acetate was also higher when it was administered by gavage than when it was given in the diet. Since depletion of glycine may be a major factor in the toxic effects observed at the high doses used in animal studies, the Committee considered that it would be inappropriate to extrapolate the results of gavage studies to humans. It also considered that depletion of glycine might be of concern with respect to the developing fetus and neonate. It was noted that benzoic acid and hippuric acid are generated as a result of phenylalanine and tyrosine metabolism.

Long-term studies in which benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and sodium benzoate were administered in the feed or by gavage to mice and rats were available for review by the Committee. No definitive conclusions could be drawn from carcinogenicity studies of sodium benzoate in mice and rats, as the information provided was insufficient for this purpose, and survival rates in the study in rats were too low to allow it to be considered as conclusive. The Committee reviewed the studies evaluated in the previous monographs and an additional study in which benzaldehyde was administered in corn oil by gavage to rats at 200 or 400 mg per kg of body weight per day for 103 weeks and to mice at 200 or 400 mg per kg of body weight per day (males), or 300 or 600 mg per kg of body weight per day (females) for 103 weeks. On the basis of these studies, the Committee concluded that neither benzyl acetate nor benzyl alcohol is carcinogenic. As in the studies in mice and rats given benzyl acetate in corn oil by gavage, increased incidences of pancreatic acinar cell adenomas in rats and of papillomas of the forestomach in mice were noted after administration of benzaldehyde. However, as in its previous review of benzyl acetate, the Committee concluded that the results of studies in which the compound was administered in the diet were more relevant to its safety assessment as a food additive than those in which it was given in corn oil by gavage.

The Committee also reviewed data from genotoxicity studies. None of the four compounds was mutagenic in the Ames test, either with or without metabolic activation. The compounds all induced gene mutations in the mouse lymphoma assay at the thymidine kinase locus (benzoic acid was not tested), although the requirement for metabolic activation varied. Some weak clastogenic activity was noted in *in vitro* assays, but not in *in vivo* assays.

Several studies addressing aspects of the potential teratogenicity and reproductive toxicity of benzyl acetate, benzyl alcohol, benzaldehyde and sodium benzoate were reviewed. Delayed development and reduced fetal and postnatal pup body weights were observed in developmental toxicity studies in rats, mice, hamsters and rabbits, but only at doses that were toxic to the mother. In a teratogenicity study with sodium benzoate, doses that induced severe maternal toxicity were associated with embryotoxic and fetotoxic effects and fetal malformations. A 4-generation study in rats showed no effect on growth, fertility, lactation or survival.

The Committee was aware of reports of idiosyncratic human intolerance to benzoate, but these were not considered relevant to the establishment of an ADI for this group of compounds. The Committee endorsed the view expressed in the report of its twenty-seventh meeting (Annex 1, reference 62) that appropriate labelling is a feasible means of offering protection to susceptible individuals.

The Committee was satisfied that the data reviewed for compounds in this group were sufficient to demonstrate the lack of teratogenic, reproductive or carcinogenic potential. Consequently, the Committee concluded that further studies were not required, and the group ADI of 0–5 mg per kg of body weight as benzoic acid equivalents was maintained.

A toxicological monograph was prepared. The existing specifications for benzoic acid, the benzoate salts (calcium, potassium and sodium), benzaldehyde, benzyl acetate, benzyl alcohol and benzyl benzoate were revised, with minor changes.

Benzyl alcohol is used as both a flavouring agent and a carrier solvent. The specifications for this compound were therefore retained in the form of a monograph, in addition to being incorporated in the table on specifications for flavouring agents (see section 2.3.5).

3.6.2 ***Sucrose acetate isobutyrate***

Sucrose acetate isobutyrate was evaluated previously by the Committee at its nineteenth, twenty-first, twenty-sixth and forty-first meetings (Annex 1, references 38, 44, 59 and 107). At the forty-first meeting, a temporary ADI of 0–10 mg per kg of body weight was allocated, pending the submission of information that would clarify the disparate effects of sucrose acetate isobutyrate on hepatobiliary function in the dog compared with other species, in particular, humans.

In the dog, doses as low as 0.5% of the diet (equivalent to 125 mg per kg of body weight per day) were associated with the development of

increased serum alkaline phosphatase activity, impairment of biliary excretion as indicated by decreased bromosulfophthalein clearance, a marked increase in the activity of several enzymes in the bile canaliculi, increased liver weights, and microscopic changes in hepatocellular morphology after 12 weeks. All of the effects noted in these short-term studies were reversible within 3–6 weeks after withdrawal of sucrose acetate isobutyrate from the diet. The effect of oral administration of sucrose acetate isobutyrate on biliary excretion in the dog was further investigated in a series of liver function tests. A single oral dose of 25 mg per kg of body weight was shown to reduce clearance of bromosulfophthalein and a very slight effect was still apparent at 5 mg per kg of body weight, although this was considered to be the NOEL by the Committee at its forty-first meeting (Annex 1, reference 107).

None of these hepatic effects was observed in the rat or monkey in studies lasting up to 1 year at dose levels of up to 2000 and 2400 mg per kg of body weight per day, respectively, nor did tests of liver function indicate impairment of biliary excretion. In humans, sucrose acetate isobutyrate given orally at a dose of 20 mg per kg of body weight per day for 14 days did not result in changes in the activities of serum enzymes that are markers for liver damage nor in the clearance of bromosulfophthalein.

The existing data on sucrose acetate isobutyrate were re-evaluated at the present meeting. Data on the disposition of sucrose acetate isobutyrate in rats, dogs and humans indicate differences between these species, humans resembling the rat rather than the dog. Dogs excrete more highly acylated sucrose molecules in the urine and bile than do rats and humans (data only for urinary excretion) and (at least for the form of sucrose acetate isobutyrate of highest relative molecular mass, sucrose octaisobutyrate), excrete a higher proportion of the dose in the bile than does the rat. In addition, in humans there was no effect on indices of hepatobiliary function at a dose of 20 mg per kg of body weight per day, a dose which exceeds the NOEL of 5 mg per kg of body weight for impairment of bromosulfophthalein clearance in the dog.

The Committee concluded that the effects of sucrose acetate isobutyrate on hepatobiliary excretion in the dog were not relevant for humans. Therefore, an ADI of 0–20 mg per kg of body weight was allocated, based on the NOEL in the long-term study in rats of 2000 mg per kg of body weight per day and a safety factor of 100.

A toxicological monograph was not prepared. The existing specifications were revised, with minor changes.

4. **Contaminants: aflatoxins**

Aflatoxins B₁, B₂, G₁ and G₂ are produced in plants and plant products contaminated by three *Aspergillus* species: *A. flavus*, *A. parasiticus* and the rare species, *A. nomius*. Aflatoxins M₁ and M₂, the hydroxylated metabolites of aflatoxins B₁ and B₂, occur predominantly in the milk of cows fed rations containing aflatoxins B₁ and B₂. However, aflatoxin B₁ is usually found in the greatest concentration in the food supply, and most of the available toxicological data relate to this compound.

The aflatoxins were previously evaluated at the thirty-first meeting of the Committee (Annex 1, reference 77). At that time, the Committee considered aflatoxin to be a potential human carcinogen, and urged that the intake of dietary aflatoxin 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 (32).

At its present meeting, the Committee reviewed a wide range of toxicity studies in animals that provided both qualitative and quantitative information on the above-mentioned aflatoxins. These studies showed that aflatoxins produce primary liver cancer in animals, the carcinogenic potency varying widely from species to species and among the various toxins.

Most of the epidemiological studies show a correlation between exposure to aflatoxin B₁ and primary liver cancer, although there are some conflicting results. However, other factors are also associated with an increased risk of primary liver cancer in humans, most notably carriage of hepatitis B virus. The risk associated with exposure to aflatoxins appears to be enhanced by simultaneous exposure to hepatitis B virus or possibly hepatitis C virus. This interaction affects the potency and possibly also the biochemistry of the aflatoxins. Many other etiological agents for primary liver cancer may also interact with exposure to aflatoxins, making it difficult to interpret the epidemiological studies in the context of aflatoxins alone.

The Committee was requested to estimate the carcinogenic potency of aflatoxins and to derive estimates of the potential risks for different human populations. Therefore, despite the difficulties in interpreting the results of the available epidemiological studies on aflatoxins, it seemed appropriate to use these data on humans for this purpose.

If the potential risks of exposure to aflatoxins are to be assessed, potency estimates derived from human studies must be combined

with estimates of aflatoxin intake derived from data on the consumption of affected commodities and levels of aflatoxins in those commodities. The level of aflatoxin contamination of foodstuffs, however, varies widely both temporally and geographically, and is affected by a variety of factors, as discussed at the thirty-first meeting (Annex 1, reference 77). The intake of aflatoxins also varies widely with diet. Further development of biochemical markers may help to clarify the level of intake. A major current source of uncertainty in the data on aflatoxin levels is local assessment of the level of aflatoxin contamination in food produced and used locally.

Thus, although potency and intake can be estimated for aflatoxins, and these estimates can be used for calculating the risks for various human populations, such calculations involve considerable uncertainty.

The Committee considered all of these factors in estimating the potential risks of exposure to the aflatoxins; however, the task could not be completed at the present meeting. In view of the value of such estimates, the Committee recommended that assessment of the carcinogenic potency of aflatoxins and the potential risks associated with their intake be continued at its next meeting and that a monograph be published summarizing the data and analyses. The Committee also recommended that the refined models for assessing intake of aflatoxins be included in the risk assessment as they become available. In the meantime, the Committee reiterated its previous recommendation that exposure to aflatoxins should be reduced to the lowest practicable levels, so as to reduce, as far as possible, the potential risk. In this regard, the Committee considered that the measures for minimizing aflatoxin contamination of food that were described in the report of its thirty-first meeting (Annex 1, reference 77) were still highly relevant.

5. Revision of certain specifications

A total of 34 substances were examined for specifications only (see Annex 2), and the specifications for 29 were revised. The existing specifications for the polyols were revised as a group, taking into account the availability of more comprehensive analytical methods. This review was undertaken in conjunction with the evaluation of the toxicological significance of the proliferative lesions of the adrenal medulla observed in rats given these substances (section 2.2.4). The specifications for isomalt were revised to include products obtained by an alternative purification step. For lactitol, the “tentative” designa-

tion for the specifications was deleted, as the required information was forthcoming.

The specifications for citric acid, lactic acid, propylene glycol, calcium stearoyl-2-lactylate, sodium stearoyl-2-lactylate and triacetin were revised, with minor corrections.

The specifications for acesulfame potassium were revised and criteria for organic impurities were included.

The Committee agreed that the existing specifications for annatto extracts were in need of revision with a view to covering oil- and alkali-extracted products separately from solvent-extracted products. Therefore, the existing specifications for annatto extracts were revised to cover oil- and alkali-extracted products only, and new specifications were prepared to cover solvent-extracted products.

The existing specifications for ammonium hydroxide were revised and the title changed to ammonia solution.

The existing tentative specifications for calcium dihydrogen phosphate were revised and the “tentative” designation was deleted.

The specifications for cyclohexylsulfamic acid (cyclamic acid) and its calcium and sodium salts were reviewed and the limits for cyclohexylamine and dicyclohexylamine were decreased. A request for the addition of a limit for aniline was rejected as no test for this substance was forthcoming.

The tentative specifications for enzyme-treated starches were on the agenda for revision. However, as no new information was received, the Committee decided to maintain the “tentative” qualification, and requested new information for evaluation in 1997. Unless this information is received, the specifications will be withdrawn.

The Committee agreed that hydrochloric acid produced during the manufacture of chlorinated hydrocarbon pesticides was not to be considered to be of food-grade quality. A purity criterion limiting the occurrence of total organic compounds was added to the specifications for this substance.

The existing specifications for microcrystalline cellulose were revised in order to limit the product to materials with a particle size of not less than 5 μm . Some other minor changes were also made.

The existing specifications for propylene glycol esters of fatty acids were revised and designated as “tentative”. The Committee requested a method of assay for the total ester content for evaluation in 1997.

The existing specifications for sodium polyphosphates, glassy, were revised in order to define the soluble product specifically. New specifications were prepared for sodium metaphosphate, insoluble.

The existing specifications for stearyl tartrate were revised in order to describe the material more accurately. The “tentative” designation was deleted.

The Committee noted that the existing specifications for tartaric, acetic and fatty acid esters of glycerol, mixed (Annex 1, reference 12), were out of date and incomplete. New specifications were therefore prepared and designated as “tentative”. The Committee decided to request information on methods of manufacture for evaluation in 1997 in order to distinguish this material from diacetyltartaric and fatty acid esters of glycerol (DATEM). When this information is available the two related substances will be evaluated together to decide whether the ADIs of the two materials should be different or the same.

The Committee considered a request to prepare specifications for carboxymethyl cellulose, enzyme-hydrolysed. However, the Committee understood that this product was not yet on the market and decided to defer the establishment of specifications until such time as it is known to be commercially available.

6. Recommendations

1. In view of the large number of food additives 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. In view of the importance of identity and purity specifications in defining the products being considered in safety assessments, and their significance for the national food legislation of many FAO/WHO Member States, the Committee emphasized the need for the regular updating and compilation of the *Compendium of food additive specifications* (Annex 1, reference 96) and the *Guide to specifications* (Annex 1, reference 100).
3. In view of the usefulness of the safety evaluation procedure used at the present meeting for evaluating the three groups of flavouring

agents, the Committee recommended that the procedure be applied to groups of flavouring agents to be evaluated at future meetings. It also recommended that step 5(b) of the original procedure be considered as soon as possible.

4. The Committee recommended that FAO and WHO continue to develop searchable databases on substances that have been evaluated by the Committee (e.g. on CD-ROM). Such databases would be of considerable use to regulatory authorities, industry and other interested parties worldwide. It was noted that the International Programme on Chemical Safety is producing a CD-ROM that includes recent information on the evaluations performed by the Committee, and the FAO and WHO homepages on the World-Wide Web will soon include summaries of the evaluations made by the Committee. Use of these homepages will provide timely information to interested parties and offer a rapid means of obtaining information on food additives and contaminants evaluated by the Committee.
5. The Committee recommended that the Codex Alimentarius Commission distinguish between substances when including them in the International Numbering System (INS) list. This would avoid confusion between substances that are assigned the same number, such as sorbitol and sorbitol syrup.

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Annex 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. *General principles governing the use of food additives* (First report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of intentional food additives to establish their safety for use* (Second report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants)* (Third report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. I. *Antimicrobial preservatives and antioxidants*. Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
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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 per kg of body weight and other toxicological recommendations
Antioxidants		
Dodecyl gallate	R	No ADI allocated ^b
Octyl gallate	R	
Propyl gallate	R	0–1.4
Emulsifier		
Glycerol ester of wood rosin	R	0–25
Flavouring agents		
Ethyl esters		
Ethyl formate	R	No safety concern at current levels of intake ^c
Ethyl acetate	R	No safety concern at current levels of intake ^d
Ethyl propionate	N	
Ethyl butyrate	R	No safety concern at current levels of intake ^c
Ethyl pentanoate	N	No safety concern at current levels of intake ^c
Ethyl hexanoate	N	No safety concern at current levels of intake ^d
Ethyl heptanoate	R	No safety concern at current levels of intake ^c
Ethyl octanoate	N	
Ethyl nonanoate	R	
Ethyl decanoate	N	
Ethyl undecanoate	N, T	
Ethyl dodecanoate	R	
Ethyl tetradecanoate	N	
Ethyl hexadecanoate	N	
Ethyl octadecanoate	N	
Isoamyl alcohol and related esters		
Isoamyl alcohol	N	No safety concern at current levels of intake ^c
Isoamyl formate	N	
Isoamyl acetate	R	No safety concern at current levels of intake ^d
Isoamyl propionate	N	No safety concern at current levels of intake ^c
Isoamyl butyrate	R	No safety concern at current levels of intake ^d
Isoamyl hexanoate	N	No safety concern at current levels of intake ^c
Isoamyl octanoate	N, T	
Isoamyl nonanoate	N, T	

Substance	Specifications ^a	Acceptable Daily Intake (ADI) in mg per kg of body weight and other toxicological recommendations
Isoamyl isobutyrate	N	No safety concern at current levels of intake ^c
Isoamyl isovalerate	N	
Isoamyl 2-methylbutyrate	N, T	
Allyl esters		
Allyl propionate	N, T	No safety concern at current levels of intake ^e
Allyl butyrate	N	
Allyl hexanoate	R	No safety concern at current levels of intake ^f
Allyl heptanoate	R	No safety concern at current levels of intake ^g
Allyl octanoate	N	
Allyl nonanoate	N	
Allyl isovalerate	R	
Allyl sorbate	N, T	
Allyl 10-undecanoate	N	
Allyl tiglate	R	
Allyl 2-ethylbutyrate	N	
Allyl cyclohexaneacetate	N, T	
Allyl cyclohexane-propionate	R	
Allyl cyclohexanebutyrate	N, T	
Allyl cyclohexanevalerate	N, T	
Allyl cyclohexane-hexanoate	N, T	
Allyl phenylacetate	N, T	No safety concern at current levels of intake ^g
Allyl phenoxyacetate	N	
Allyl cinnamate	N, T	No safety concern at current levels of intake ^g
Allyl anthranilate	N, T	No safety concern at current levels of intake ^g
Allyl 2-furoate	N, T	Evaluation not completed ^h
Sweetening agent		
Alitame	R	0–1 ⁱ
Thickening agent		
Konjac flour	R	ADI “not specified” for food additive uses ^j
Miscellaneous substances		
Benzyl acetate	R	0–5 (group ADI)
Benzyl alcohol	R	
Benzaldehyde	R	
Benzoic acid and its salts	R	
Sucrose acetate isobutyrate	R	0–20

Contaminant	Toxicological recommendations
Aflatoxins	Evaluation not completed ^k

Substance (considered for specifications only)	Specifications ^a
Polyols	
Mannitol	R
Sorbitol	R
Xylitol	R
Isomalt	R
Lactitol	R
Maltitol	R
Maltitol syrup	R
Sorbitol syrup	R
Cyclohexylsulfamic acid and its salts	
Cyclohexylsulfamic acid	R
Calcium cyclamate	R
Sodium cyclamate	R
Miscellaneous substances	
Acesulfame potassium	R
Ammonia solution	R
Annatto extracts (oil- and alkali-extracted)	R
Annatto extracts (solvent-extracted)	N
Benzyl benzoate	R
Calcium dihydrogen phosphate	R
Calcium stearoyl-2-lactylate	R
Citric acid	R
Enzyme-hydrolysed carboxymethyl cellulose	O ^l
Enzyme-treated starches	S, T ^m
Ethanol	R
Gellan gum	R
Hydrochloric acid	R
Lactic acid	R
Microcrystalline cellulose	R
Propylene glycol	R
Propylene glycol esters of fatty acids	R, T ⁿ
Sodium metaphosphate, insoluble	N
Sodium polyphosphates, glassy	R
Sodium stearoyl-2-lactylate	R
Stearyl tartrate	R
Tartaric, acetic and fatty acid esters of glycerol, mixed	N, T ^o
Triacetin	R

Notes to Annex 2

- (a) N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; and T, the existing, new or revised specifications are tentative and comments are invited.
- (b) *Dodecyl and octyl gallate*. The temporary ADI was not extended because the additional studies on the pharmacokinetics and metabolism of dodecyl and octyl gallate requested at the forty-first meeting of the Committee (WHO Technical Report Series, No. 837) were not available.
- (c) This flavouring agent is in structural class I; the conclusions are based on a “yes” answer at step 2 and a “no” answer at step 3(a) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report).
- (d) This flavouring agent is in structural class I; the conclusions are based on “yes” answers at steps 2, 3(a) and 4(a) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report).
- (e) This flavouring agent is in structural class II; the conclusions are based on “no” answers at steps 2 and 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). When step 4(b) of the modified approach was applied (see Fig. 2), the Committee concluded that an adequate margin of safety existed between the NOEL and current levels of intake.
- (f) This flavouring agent is in structural class II; the conclusions are based on a “no” answer at step 2 and a “yes” answer at step 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). It was evaluated on the basis of the available toxicity data.
- (g) This flavouring agent is in structural class III; the conclusions are based on “no” answers at steps 2 and 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). When step 4(b) of the modified approach was applied (see Fig. 2), the Committee concluded that an adequate

margin of safety existed between the NOEL and current levels of intake.

- (h) *Allyl 2-furoate*. The evaluation was postponed, pending consideration of step 5(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996, at a future meeting of the Committee at which food additives and contaminants are evaluated. The Committee requested additional toxicity data on this substance.
- (i) *Alitame*. The results of an ongoing study of tolerance to repeated doses of alitame in diabetic subjects should be submitted for assessment when available.
- (j) *Konjac flour*. Includes uses as a thickener, emulsifier, stabilizer, and gelling, texturizing and glazing agent.
- (k) *Aflatoxins*. The evaluation could not be completed at the present meeting. The Committee recommended that assessment of the carcinogenic potential of aflatoxins and the potential risks associated with intake be continued at the next meeting of the Committee at which food additives and contaminants are evaluated.
- (l) *Enzyme-hydrolysed carboxymethyl cellulose*. The Committee considered a request to prepare specifications for this substance. However, the Committee understood that this product was not yet on the market, and decided to defer the establishment of specifications until such time as it is known to be commercially available.
- (m) *Enzyme-treated starches*. The tentative specifications for enzyme-treated starches were on the agenda for revision. However, as no new information was received, the Committee decided to maintain the “tentative” qualification, and requested new information for evaluation in 1997. Unless this information is received, the specifications will be withdrawn.
- (n) *Propylene glycol esters of fatty acids*. The existing specifications for propylene glycol esters of fatty acids were revised and designated as “tentative”. The Committee requested a method of assay for the total ester content for evaluation in 1997.
- (o) *Tartaric, acetic and fatty acid esters of glycerol, mixed*. The Committee noted that the specifications for tartaric, acetic and fatty acid esters of glycerol, mixed, in FAO Nutrition Meetings Report Series, No. 40A, B, C, 1967, were out of date and incomplete. New specifications were therefore prepared and

designated as “tentative”. The Committee requested information on methods of manufacture for evaluation in 1997 in order to distinguish this material from diacetyltartaric and fatty acid esters of glycerol (DATEM).

Annex 3

Toxicological data on ethyl and isoamyl esters

The ethyl and isoamyl esters evaluated at the present meeting of the Committee were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. Consequently, no toxicity data were necessary for application of the modified procedure for flavouring agents discussed in section 2.2.1 of the main report. Nevertheless, the Committee believed that it was useful to include the toxicity data on these substances as an annex to the report.

Ethyl esters

The component alcohol, ethanol, was evaluated by the Committee at its fourteenth meeting, when an ADI limited by Good Manufacturing Practice was established for ethanol for use as an extraction solvent (Annex 1, reference 26). It is absorbed rapidly and completely oxidized via well-known metabolic pathways. There is endogenous synthesis of ethanol, since it is present in the serum of subjects who have abstained from alcohol ingestion. Low concentrations of ethanol are metabolized rapidly, and the endogenous concentrations detected in serum correspond to the formation of about 2.5–5 g per day (1, 2). The estimated per capita intake of ethanol derived from the ethyl esters is about 25–30 mg per day (3, F. Grundschober, personal communication, 1996).

Short-term studies on ethyl formate, ethyl hexanoate, ethyl heptanoate, ethyl octanoate and ethyl nonanoate in rats showed no adverse effects at daily doses of up to 500 mg per kg of body weight in the diet for 13–17 weeks (4). Ethyl acetate given in drinking-water to rats for 56 weeks did not produce adverse effects at a dose corresponding to 4 mg per kg of body weight per day (5). The Committee was aware of studies in which high doses of a number of carboxylic acids had been given to rats and had resulted in forestomach lesions (6–8). However, the studies were considered not to be relevant to the ingestion of esters as flavouring agents.

Ethyl formate

Ethyl formate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference 50). At that meeting, the Committee concluded that ethyl formate could be included in the group ADI with

formic acid of 0–3 mg per kg of body weight (expressed as formic acid) on the basis of the available short-term studies, metabolic studies, and toxicological data on formic acid and formic acid esters.

Formic acid was reported not to produce adverse effects in long-term experiments in rats at daily doses of up to the equivalent of 500 mg per kg of body weight for up to 3 years (9).

Ethyl acetate

Ethyl acetate was evaluated by the Committee at its eleventh meeting (Annex 1, reference 14). At that time, an ADI of 0–25 mg per kg of body weight was established for this compound on the basis of its known metabolic fate. No toxicological data were available for evaluation. In a more recent study, no adverse effects were reported when rats were given a drinking-water–fusel oil mixture containing ethyl acetate at a dose corresponding to 4 mg per kg of body weight per day for 56 weeks (5).

Acetic acid was last evaluated by the Committee at its seventeenth meeting (Annex 1, reference 32), when an ADI “not limited” was established for this compound on the basis of its known metabolic pathway and its consumption as a normal constituent of the human diet.

Ethyl propionate

Ethyl propionate has not been previously evaluated by the Committee. Propionic acid was last evaluated by the Committee at its seventeenth meeting (Annex 1, reference 32), when an ADI “not limited” was established for this compound on the basis of available biochemical and toxicological studies and knowledge of its role in normal metabolism.

Ethyl butyrate

Ethyl butyrate was evaluated by the Committee at its eleventh meeting (Annex 1, reference 14). At that meeting, an ADI of 0–15 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and information on its hydrolysis into normal constituents of food. Butyric acid has not been previously evaluated by the Committee.

Ethyl pentanoate (valerate)

Neither ethyl pentanoate nor pentanoic acid has been previously evaluated by the Committee.

Ethyl hexanoate (caproate)

Neither ethyl hexanoate nor hexanoic acid has been previously evaluated by the Committee.

Ethyl heptanoate (enanthate)

Ethyl heptanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference 50). At that time, an ADI of 0–2.5 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and data on its metabolic fate.

Ethyl octanoate (caprylate)

Ethyl octanoate has not been previously evaluated by the Committee. No adverse effects were observed when rats were fed ethyl octanoate at dose levels of up to 1% in the diet (equivalent to 500 mg per kg of body weight per day) for 17 weeks (4).

Salts of octanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70), when an ADI “not specified” was established on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway.

Ethyl nonanoate (pelargonate)

Ethyl nonanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference 50), when an ADI of 0–2.5 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and data on its metabolic fate.

Ethyl decanoate (caprate)

Ethyl decanoate has not been previously evaluated by the Committee.

Salts of decanoic acid were evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70). At that meeting, an ADI “not specified” was established for these compounds on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway.

Ethyl undecanoate

Ethyl undecanoate has not been previously evaluated by the Committee.

Ethyl dodecanoate (laurate)

Ethyl dodecanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference 50). At that meeting, the Committee established an ADI of 0–1 mg per kg of body weight for this substance on the basis of information on its hydrolysis into dodecanoic acid and ethanol, the known toxicity of ethanol and the ready metabolism of dodecanoic acid, a naturally occurring fatty acid.

Salts of dodecanoic acid were evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70), when an ADI “not specified” was established on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway. No adverse effects were reported when dodecanoic acid was given to rats at a dose level of approximately 5000 mg per kg of body weight per day for 18 months (10).

Ethyl tetradecanoate (myristate)

Ethyl tetradecanoate has not been previously evaluated by the Committee.

Salts of tetradecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70), when an ADI “not specified” was established. Tetradecanoic acid is common in the triglyceride part of fats and oils used for human consumption.

Ethyl hexadecanoate (palmitate)

Ethyl hexadecanoate has not been previously evaluated by the Committee.

Salts of hexadecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70), when an ADI “not specified” was established. Hexadecanoic acid is one of the major saturated fatty acids in the triglyceride part of fats and oils used for human consumption.

Ethyl octadecanoate (stearate)

Ethyl octadecanoate has not been previously evaluated by the Committee.

Salts of octadecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference 70), when an ADI “not specified” was established. Octadecanoic acid is one of the major saturated fatty acids in the triglyceride part of fats and oils used for human consumption.

Isoamyl esters

Short-term studies on the parent alcohol, isoamyl alcohol, in rats showed no adverse effects at daily doses of 1000 mg per kg of body weight by gavage for 17 weeks (11) or 2000 mg per kg of body weight in drinking-water for 53–56 weeks (5). The only ester for which a similar adequate study was available was isoamyl isovalerate. No adverse effects were observed in rats given isoamyl isovalerate in the diet at 22, 70 or 220 mg per kg of body weight per day for 13 weeks, as indicated by the results of biochemical analyses of blood and urine, organ weights, and histopathological examination (12).

Toxicity data from studies on the carboxylic acid components of isoamyl esters gave no evidence of systemic toxicity at daily doses of at least 400 mg per kg of body weight (8, 9, 13).

Further information on formic, acetic, propionic and butyric acids is given under ethyl esters (see above).

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