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

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Geneva, 4–13 June 2002

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

Toxicological evaluation of certain food additives. WHO Food Additives Series No. 50, in press

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, Addendum 10. FAO Food and Nutrition Paper, No. 52, Add. 10, 2002

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 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 (JECFA) met in Geneva from 4 to 13 June 2002. The meeting was opened by Mr D.G. Aitken, Chef de Cabinet, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Mr Aitken noted that a number of general issues were on the agenda, including consideration of papers on risk analysis and intake that had been referred by the Codex Committee on Food Additives and Contaminants (*1*) to the present Committee for comment. These two papers outline the specific roles of the Expert and Codex Committees in the development of Codex standards. The iterative process by which the two committees consider these and other issues highlights the importance of communication between them and for ensuring that the Expert Committee adequately responds to the needs of the Codex and that the roles of the two committees are properly defined.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*2*), there have been fifty-eight previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the fifty-seventh meeting (Annex 1, reference *154*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);

— to evaluate certain food additives and flavouring agents (sections 3 and 4 and Annex 2); and

— to review and prepare specifications for selected food additives and flavouring agents (sections 3 and 4 and Annex 2).

2.1 Modification of the agenda

Annatto extracts, ethyl carbamate, methylmercury and sodium dichloroisocyanurate were removed from the agenda because data necessary for their evaluation were not available. The evaluation of curcumin was deferred until 2003 because the Committee its fifty-seventh meeting extended the temporary acceptable daily intake (ADI) to that time. Gum arabic was removed from the agenda because new information was not provided on differences in the

origin, manufacture, quality and use patterns of gum arabic from *Acacia senegal* and from *Acacia seyal*.

Nitrite was added to the agenda because the pivotal observed toxic effects of nitrate, which was evaluated at the present meeting, are consequent on its conversion to nitrite in vivo.

The Committee also considered the safety of the secondary components of a large number of flavouring agents for which the minimum assay values were below 95% and confirmation of use as flavours of a number of flavouring agents.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of the food additives on the agenda, the Committee took into consideration the principles established and contained in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated at subsequent meetings of the Committee (Annex 1, references *77, 83, 88, 94, 101, 107, 116, 122, 131, 137, 143, 149, 152* and *154*), including the present one. Environmental Health Criteria, No. 70 (Annex 1, reference *76*) embraces the major observations, comments and recommendations contained, up to the time of its publication, in the reports of the Committee and other associated bodies. The Committee noted that the publication 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 technical advances.

2.2.1 *Safety evaluation of flavouring agents*

Flavouring agents with other functional uses

The Committee noted that a small number of the chemicals submitted for evaluation as flavouring agents have other uses in foods, for example as solvents, acidity regulators or preservatives, and that the Committee has previously evaluated them for these uses under the normal procedures for food additives. The Committee re-affirmed its position that the safety evaluation of these chemicals should include consideration of existing safety evaluations for other uses and that their evaluation as flavouring agents should make reference to the previous evaluations.

Flavouring agents that undergo chemical change in food

The Committee noted that some flavouring agents are added to food in the expectation that they will undergo chemical conversion during food processing or storage to form the compounds that provide the flavouring

effect in the food as consumed. Such agents can be evaluated by the Procedure for the Safety Evaluation of Flavouring Agents only if the breakdown and reaction products can be chemically identified. The Committee therefore stressed that information on breakdown and transformation products should be made available in submissions of data on flavouring agents for evaluation.

2.3 Project to update principles and methods of risk assessment of chemicals in food

The Committee was informed of progress being made on the Project, which was initiated by FAO and WHO. General principles and methods for the assessment of food additives, contaminants, residues of veterinary drugs and pesticides and food ingredients that have been developed over the years and published in Environmental Health Criteria, Nos 70 (Annex 1, reference *76*) and 104 (*3*) and in reports of JECFA and the Joint FAO/WHO Meeting on Pesticide Residues will be updated and consolidated, and the utility of new assessment procedures will be considered.

The final product will contain a historical background, and the activity will be placed in the context of risk analysis. A framework for incorporation of new principles and methods will be developed. The Project will focus on:

— chemical characterization (including contaminants and natural constituents) and development of specifications for food additives, pesticides and veterinary drugs;

— maximum residue levels for pesticides and veterinary drugs;

— exposure assessment (including short- and long-term intake, deterministic and probabilistic approaches and cumulative and aggregate exposure);

— toxicological test procedures and evaluation (including general issues and specific toxicological end-points);

— human data (clinical studies, epidemiological studies including biomarkers, potentially susceptible populations, allergenicity, intolerance and interactions with the diet);

— evaluations (including such issues as thresholds of toxicological concern, potency estimates, margins of safety, benchmark doses, acute reference doses, special considerations for contaminants, uncertainty and variability, scientific criteria for re-evaluation);

— principles related to specific substances (e.g. flavouring agents and substances consumed in large amounts); and

— a glossary (nomenclature and terminology).

The Committee emphasized the importance of this activity to its work, and encouraged FAO and WHO to proceed with it in a timely manner. It recommended that:

— the approach not be prescriptive, in order to maintain maximum flexibility in evaluating chemicals and in incorporating new methods of assessment;

— the intended audience, including risk managers and potential submitters of data, be clearly defined and kept in mind during all stages of the Project;

— new testing procedures and methods of assessment be validated before they are used; and

— harmonization and cooperation with risk assessment activities of other international and national organizations be considered, as appropriate.

2.3.1 *Specifications of identity and purity of food additives*

The *Project to Update Principles and Methods for Risk Assessment of Chemical in Foods* will include the definition of substances considered for safety by JECFA and the Joint FAO/WHO Meeting on Pesticide Residues. The Committee has a defined process for drafting specifications for food additives; as part of its input to the Project, the Committee considered a paper on the development of food additive specifications that had been prepared for the Project.

In general, the guidance given in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) for drafting food additive specifications remains valid. However, this document was written before the role of the Committee in risk analysis had been defined, and it does not discuss how formulation of specifications fits into the Committee's work on risk assessment.

In considering this issue, the Committee recommended that:

— The updated principles should explicitly recognize that development of specifications is an integral part of the risk assessment of food additives.

— Risk assessment requires data on the manufacture and composition of an additive at all steps in its development and safety testing. In addition, information is needed on technological function and current and intended uses.

— Risk assessments should include specifications for the material evaluated and the product to be marketed.

— The updated principles should require continuous review of specifications in the light of possible changes in the manufacture, use and consumption of the additive.

2.4 Procedure for evaluating flavouring agents that are members of groups that have been evaluated previously by the Committee

The Committee has evaluated a large number of flavouring agents with the Procedure for the Safety Evaluation of Flavouring Agents. To facilitate the evaluations, the substances have been grouped according to their chemical structure. A number of flavouring agents in development and additional ones in commerce fit into the groups of flavouring agents that have already been evaluated, and the Committee concluded that these flavouring agents should be evaluated and the evaluations documented in a manner consistent with the previous practices and procedures of the Committee. Past evaluations should serve as the basis for evaluating new or additional flavouring agents and, if a substantial body of new data became available, the previous evaluation might need to be reconsidered. The Committee recommended that the *Guidelines for the preparation of working papers (monographs) on flavouring agents*[1] be updated accordingly.

2.5 Risk analysis principles and exposure assessment

The Codex Committee on Food Additives and Contaminants at its Thirty-fourth Session (*1*) asked JECFA to review and comment on papers that it had prepared, entitled *Application of risk analysis principles for food additives and contaminants* and *Draft principles for exposure assessment of contaminants and toxins in food.* The Expert Committee reviewed these papers and provided comments to the Codex Committee in the form of letters from the Chairman and Vice-Chairman of the present Committee to the Chairman of the Codex Committee.

2.6 Risk analysis terms related to food safety

In considering the definitions of 'hazard' and 'risk' adopted by the Codex Alimentarius Commission for risk assessment, the Committee noted that different definitions have been used by other bodies involved in chemical risk assessment. This could cause problems in communication and interpretation of risk assessments made by different organizations. For example, in the Codex definition, 'hazard' is considered to be *a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect,* whereas some other bodies (e.g. the

[1] Available at http://www.who.int/pcs

International Union of Pure and Applied Chemistry) consider hazards to be intrinsic chemical and biological properties (potentially adverse effects) of a chemical. JECFA has implicitly tended to the latter interpretation of 'hazard'. Similarly, 'risk' is defined in purely probabilistic terms by some organizations, whereas the Codex definition of 'risk' includes not only the probability of an adverse effect but also its 'severity'. The word 'severity' has been used variously to describe either the magnitude of response or the qualitative nature of the effect of a substance; this difference could also lead to confusion. The term 'severity' is used by the Committee to refer to the magnitude of a response and not to its qualitative nature.

The Committee noted the ongoing Joint IPCS/OECD project to harmonize the terminology used in chemical hazard or risk assessment[1], in which these issues are being addressed, and recommended that the harmonized terminology agreed upon in that project be adopted by the Committee and by the Codex Alimentarius Commission.

2.7 Consideration of guidelines

The Committee confirmed that detailed guidelines for the preparation of working papers were required and should be revised regularly on the basis of comments provided by members of the Committee. At its present meeting, the Committee considered guidelines that had been prepared by the Joint Secretariat and made comments and suggestions for improvement.

Comprehensive assessments of the intake of food additives are a recent task of the Committee. Therefore, at the present meeting, specific attention was paid to the *Guidelines for the preparation of working papers on the intake of food additives*. The Committee suggested that intake from dietary sources other than food additives and exposure to non-dietary sources might also be of relevance. The terms for intake assessment used in working papers should be standardized within the Committee and harmonized with those developed by OECD/IPCS (as summarized in the *Glossary of exposure assessment-related terms*[2]).

A draft guideline for working procedures to be followed by the Committee in elaborating specifications for food additives was considered, and substantial changes and amendments were suggested to the Secretariat.

2.8 Specifications for flavouring agents

The Committee concluded that it was not desirable to develop separate specifications for flavouring agents (e.g. benzoic acid) that it has evaluated for other uses. In such cases, the material used for flavouring purposes should comply with the specifications for its use for other technological purposes,

[1] Available at http://www.ipcsharmonize.org/index.html

and the list of specifications for flavouring agents should simply make reference to the full specifications monograph.

The Committee recognized that information on secondary components of flavouring agents should be incorporated into specifications when relevant to the safety evaluation. As necessary, this information would include upper limits on the content of such components. The Committee agreed that this information should appear as a distinct item under the heading 'Other requirements'. At the same time, the Committee decided to adjust the format for other items included under 'Other requirements' in the specifications tables to distinguish more clearly between genuine requirements and items included for information. The preamble to the table of specifications published in Food and Nutrition Paper 52 was expanded to explain how the information listed under 'Other requirements' is to be used.

3. Specific food additives (other than flavouring agents)

The Committee evaluated several food additives for the first time and re-evaluated others. The evaluations and specifications are summarized in Annex 2. Details of further toxicological studies and other information required for certain substances are given in Annex 3.

3.1 Safety evaluations

3.1.1 *Alitame*

Alitame is an intense sweetener, with a sweetness potency 2000 times greater than that of sucrose. It is a dipeptide of L-aspartic acid and D-alanine, with a terminal *N*-substituted tetramethylthietanylamine moiety. Alitame is prepared by a multistep synthesis involving the reaction between two intermediates, (*S*)-[2,5-dioxo-(4-thiazolidine)] acetic acid and (*R*)-2-amino-*N*-(2,2,4,4-tetramethyl-3-thietanyl)propanamide. The final product is isolated and purified by crystallization of an alitame-4-methylbenzenesulfonic acid adduct, followed by additional purification steps, and finally recrystallization from water.

Alitame was considered by the Committee at its forty-fourth and forty-sixth meetings (Annex 1, references *116* and *122*). Most of the toxicological studies were examined at the forty-fourth meeting, and specifications and a toxicological monograph were prepared; however, an ADI could not be allocated because of concern about deficiencies in the studies of carcinogenicity. At its forty-sixth meeting, the Committee reconsidered this issue in the light of a general discussion of the survival rates of animals in contemporary long-term studies and a further statistical analysis of the data from the two available

studies. At that meeting, the Committee concluded that there was no evidence that alitame is carcinogenic. An ADI of 0–1 mg/kg bw was allocated on the basis of the NOEL of 100 mg/kg bw per day in an 18-month study in dogs. The Committee noted that, although not specifically requested, a further study of tolerance to repeated doses of alitame in persons with diabetes was under way and that, as is customary, the results should be forwarded to the Committee when available.

While consideration of the 90-day study of tolerance in diabetic subjects was on the agenda of the present meeting, it was postponed pending receipt of a final report. The ADI of 0–1 mg/kg bw allocated by the Committee at its forty-sixth meeting was retained.

No data on the dietary intake of alitame were available at the previous meetings of the Committee. At its present meeting, the Committee compared the maximum levels of alitame listed in the Codex draft General Standard on Food Additives (GSFA) with the theoretical maximum level calculated by the budget method (see Annex 1, reference *137*). On the assumption that alitame is used in all foods, the theoretical maximum level of alitame, based on the current ADI, was calculated to be 40 mg/kg. The maximum levels in the GSFA are up to 300 mg/kg in a wide range of foods and beverages, with no limit in 'other sugars and syrups' or in table-top sweeteners. Detailed assessments of the intake of alitame when used in foods were therefore required.

National assessments of intake based on recent individual dietary records and GSFA maximum levels were provided by Australia and by New Zealand. These data showed that the ADI might be exceeded by some consumers, at levels representing 148% of the ADI in Australia and 140% of the ADI in New Zealand for consumption at the 95th percentile. These are likely to be overestimates, as the surveys were of short duration (24 h) and because it was assumed that alitame was systematically present in some major food categories. The intake of alitame from 'other sugars and syrups' was not assessed since no manufacturer's use levels were available. In both Australia and New Zealand, the main contributor to the mean estimated intake was sweet bakery wares, which was responsible for 89% of the overall estimated intake from all food categories in Australia and 88% in New Zealand. These estimates are based on data from only two countries, and further work is required to refine the intake estimates with recent data from other countries.

The Committee identified GSFA food category 7 (bakery wares, including bread) as a food group that might contribute to a high intake of alitame, as this group includes foods that are staples in many countries. The Committee therefore suggested that the Codex Committee on Food Additives and Contaminants consider reviewing the standards for alitame.

An addendum to the monograph summarizing the available data on intake was prepared. The specifications for alitame were revised. The addresses of suppliers of some of the chemicals needed for the purity tests were updated. In addition, in line with the decision made by the Committee at its fifty-seventh meeting (Annex 1, reference *154*), a brief description of the method of manufacture of alitame was included. The revised specifications also incorporate the heavy metals limits established by the Committee at its fifty-seventh meeting.

3.1.2 *Cross-linked sodium carboxymethyl cellulose*

Cross-linked sodium carboxymethyl cellulose is manufactured by acidifying an aqueous suspension of sodium carboxymethyl cellulose and heating the suspension to achieve cross-linking. The product is then washed and dried. It is also produced during the manufacture of sodium carboxymethyl cellulose by lowering the pH and heating to cause cross-linking. Cross-linked sodium carboxymethyl cellulose is used in tablets of table-top sweeteners and dietary food supplements, as it facilitates disintegration in aqueous solutions, with a maximum level of use of 30 g/kg. It is also widely used as an excipient in pharmaceutical applications.

Cross-linked sodium carboxymethyl cellulose has not been evaluated previously by the Committee. The parent compound, sodium carboxymethyl cellulose, was considered by the Committee in its evaluations of modified celluloses at its fifth, seventh, tenth, thirteenth, seventeenth, twenty-sixth, twenty-seventh, thirtieth and thirty-fifth meetings (Annex 1, references *5*, *7*, *13*, *19*, *32*, *59*, *62*, *73* and *88*) and of ethyl cellulose and ethylhydroxyethyl cellulose at the twenty-sixth and twenty-seventh meetings (Annex 1, references *59* and *62*). At its thirty-fifth meeting, the Committee reviewed new data on seven modified celluloses (Annex 1, reference *89*), including sodium carboxy-methyl cellulose. The data consisted of the results of studies in rats on caecal enlargement, effects on caecal flora and developmental toxicity and studies of mutagenicity in vitro. New data were also available from studies in humans, indicating that some individuals may experience laxative effects at a dose as low as 5 g per person per day. The Committee concluded that modified celluloses are of low toxicity and allocated a group ADI 'not specified'[1] to seven modified celluloses: methyl cellulose, ethyl

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

cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxy-methyl cellulose, ethyl cellulose and ethylhydroxyethyl cellulose. The Committee pointed out that the laxative properties of these celluloses should be taken into account when they are used as food additives.

Enzymatically hydrolysed sodium carboxymethyl cellulose was evaluated by the Committee at its fifty-first meeting (Annex 1, reference *137*). The Committee compared the toxicity and absorption, distribution and metabolism of enzymatically hydrolysed carboxymethyl cellulose with that of the parent compound and concluded that the similarities in the results were consistent with the absence of any toxicologically significant difference between the two. Therefore, the enzymatically hydrolysed form was included in the group ADI 'not specified' with the other seven modified celluloses.

At its present meeting, the Committee reviewed two studies on cross-linked sodium carboxymethyl cellulose and considered its properties in the light of previous evaluations of modified celluloses. Like other modified celluloses, cross-linked sodium carboxymethyl cellulose is considered to be of low toxicity. Because cross-linking renders it insoluble in water, it is less likely to be absorbed than the parent compound.

In a 90-day dietary study in rats, the only treatment-related observations were increased food consumption, decreased body-weight gain and effects on the kidneys of animals receiving cross-linked sodium carboxymethyl cellulose at 50 000 mg/kg of diet, equivalent to 3900–4700 mg/kg bw per day averaged over the study period. The changes in food consumption or body-weight gain were consistent with a 5% reduction in the nutritional content of the diet, as compared with the basal diet fed to control animals, due to addition of the test substance. In contrast to the effects of some other non-digestible substances evaluated previously by the Committee, caecal enlargement was not observed. Mineralization at the corticomedullary junction was observed in the kidneys of some female rats, with a higher incidence in treated groups than in controls. The report equated the renal mineralization to nephrocalcinosis and noted that, although this is a spontaneous change in control female rats, it was related to treatment in female rats fed cross-linked sodium carboxymethyl cellulose at 50 000 mg/kg of diet, but not at 10 000 mg/kg of diet.

Pelvic nephrocalcinosis and corticomedullary nephrocalcinosis were observed in rats given sodium carboxymethyl cellulose or enzymatically hydrolysed carboxymethyl cellulose in a study evaluated by the Committee at its fifty-first meeting (Annex 1, reference *137*). In that study, it was also reported that corticomedullary nephrocalcinosis was observed more frequently in females than in males. Because of the inconsistency of the dose–response relationship, however, the Committee at its fifty-first meeting

had not been convinced that these changes were of toxicological concern. The changes observed in the study evaluated at the current meeting appeared to represent a minimal increase in the incidence and severity of a spontaneous lesion, which may be within normal variation. As discussed in the report of the twenty-sixth meeting (Annex 1, reference *59*), nephrocalcinosis is a common finding in laboratory rodents. No implications for human hazard have been established. Therefore, the NOEL for cross-linked sodium carboxymethyl cellulose in the above study was 3900 mg/kg bw per day.

A study of developmental toxicity in rats showed no evidence of maternal toxicity or teratogenicity at the highest possible dose of cross-linked sodium carboxymethyl cellulose of 50 000 mg/kg of diet. The NOEL was 4500 mg/kg bw per day.

The Committee noted that evaluation of the results of the 90-day toxicity study was not straightforward, because of nutritional differences between the basal diet given to control animals and the diets supplemented with cross-linked sodium carboxymethyl cellulose. However, taking into account evaluations of other modified celluloses, the Committee concluded that the effects of cross-linked sodium carboxymethyl cellulose were consistent with dietary overloading with a poorly absorbed substance of low toxicity. The Committee included cross-linked sodium carboxymethyl cellulose in the group ADI 'not specified' with the other modified celluloses.

A toxicological monograph and new specifications were prepared.

3.1.3 *Mineral oils (low- and medium-viscosity)*

Explanation

Mineral oils (medium- and low-viscosity) comprise a subgroup of the family of mineral oils and waxes. They are manufactured from crude mineral oils in various refining steps, such as distillation, extraction and crystallization, and are subsequently purified by acid treatment (oleum method) and/or hydrotreatment (catalytic hydrogenation). Mineral oils (medium- and low-viscosity) are mixtures of highly refined paraffinic and naphthenic liquid hydrocarbons with boiling-points greater than 200 °C.

In order to define the materials more clearly, the Committee at its forty-fourth meeting (Annex 1, reference *116*) prepared individual specifications for microcrystalline wax and for two groups of mineral oils: mineral oils (high-viscosity) and mineral oils (medium- and low-viscosity). The latter group was furthermore divided into three classes. For the purpose of characterization of the different types of oils and waxes, the criteria viscosity, average relative molecular mass and carbon number at 5% distillation-point were used in the specifications (see Table 1).

Food-grade mineral oils were last evaluated by the Committee at its forty-fourth meeting (Annex 1, reference *116*), when four 90-day studies conducted in Fischer 344 rats with a range of mineral oils and waxes representative of materials in commercial use were reviewed. The materials tested included low-, medium- and high-viscosity mineral oils (N10(A), N15(H), P15(H), N70(A), N70(H), P70(H) and P100(H)); paraffin waxes (low-melting-point wax and intermediate-melting-point wax); and microcrystalline waxes (high-melting-point wax and high-sulfur wax). All the substances, with the exception of the microcrystalline waxes, appeared to accumulate in the tissues of the animals to varying degrees, depending on the material and dose. Except for P70(H) and P100(H) oils, there was evidence of accumulation of the mineral hydrocarbons and effects indicative of a reaction to a foreign body at one or more doses. The types of effects seen were similar and included

Table 1

Classification of mineral hydrocarbons

Name	ADI (mg/kg bw)[a]	Viscosity at 100 °C (mm^2/s)	Average relative relative molecular mass	Carbon number at 5% distillation-point
Microcrystalline wax	0–20[a,b]	≥ 11	≥ 500	≥ 25
High-melting-point wax		Not included in the present studies		
Low-melting-point wax	Withdrawn[c]	No specification		
Low-melting-point wax		3.3	380	22
Mineral oil (high viscosity)	0–20[a]	> 11	> 500	≥ 28
P100		11	520	29
Mineral oil (medium and low viscosity) class I	0–10[d]	8.5–11	480–500	≥ 25
P70		9.0	480	27
Medium-viscosity liquid petroleum		8.7	480	25
P70(H)		8.6	480	27
Mineral oil (medium and low viscosity) class II	0–0.01[e,f]	7.0–8.5	400–480	≥ 22
N70(H)		7.7	420	23
Mineral oil (medium and low viscosity) class III	0–0.01[e,f]	3.0–7.0	300–400	≥ 17
P15(H)		3.5	350	17
N15(H)		3.5	330	17

P100 oil, crude: paraffinic, viscosity (40 °C): 100 mm^2/s; P70 oil, crude: paraffinic, viscosity (40 °C): 70 mm^2/s; P70(H) oil, crude: paraffinic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation); N70(H) oil, crude: naphthenic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation; P15(H) oil, crude: paraffinic, viscosity (40 °C): 15 mm^2/s, hydrotreated (catalytic hydrogenation; N15(H) oil, crude: naphthenic, viscosity (40 °C): 15 mm^2/s, hydrotreated (catalytic hydrogenation)

[a] Established by the Committee at its forty-fourth meeting
[b] Group ADI
[c] Previous ADI 'not specified'
[d] Established at the present meeting
[e] Temporary group ADI
[f] Extended at the present meeting

focal histiocytosis, increased weights of liver, lymph nodes, spleen and kidneys, granulomas or microgranulomas of the liver, haematological changes typical of a mild, chronic inflammatory reaction and biochemical changes indicative of mild hepatic damage.

The ADI of 0–20 mg/kg bw established at the forty-fourth meeting (Annex 1, reference *116*) for mineral oils with the specifications of high-viscosity oils and of high-melting-point and high-sulfur waxes was based on NOELs at the highest dose tested (2% in the diet) in 90-day studies in Fischer 344 rats. The NOELs for all the other materials except P70(H) oil (i.e. class II and III medium- and low-viscosity oils and low-melting-point wax) were based on an increased incidence of histiocytosis in the lymph nodes at the next highest dose. For P70(H) oil, the NOEL was based on an increased incidence of pigmented macrophages in male rats at a dietary concentration of 2%, a minor effect considered of doubtful biological significance. Accordingly, because effects were observed at all doses, the ADIs for low-melting-point and intermediate-melting-point waxes were withdrawn. A group temporary ADI of 0–0.01mg/kg bw was allocated for class II and III medium- and low-viscosity mineral oils, the temporary nature of the ADI being due to uncertainty about the long-term significance of the inflammatory response to accumulated dietary mineral hydrocarbons. A temporary ADI of 0–1 mg/kg bw was allocated for P70(H) oil. These temporary ADIs were extended at the fifty-first meeting (Annex 1, reference *137*).

At its forty-fourth meeting, the Committee considered that, although the types of effects seen were essentially reactions to a foreign body, it was possible that a prolonged inflammatory response of the type observed could result in functional changes in the immune system and that this aspect required further investigation. It also noted that the oils and waxes for which high NOELs were observed contained a greater proportion of hydrocarbon components of high relative molecular mass (high carbon number) and had higher viscosities than those materials with a low NOEL, which contained a greater proportion of hydrocarbon components of lower relative molecular mass (low carbon number). The Committee required information about the compositional factors in mineral oils that influence their absorption and toxicity. It also required a study of at least 1 year's duration on one of these materials in Fischer 344 rats, including an assessment of immune function at appropriate times and an investigation of the kinetics of accumulation of the material, to determine whether a plateau is reached. It recommended that a reversal period of 1 year be included, in order to determine whether the granulomatous hepatic lesions observed in rats in the 90-day studies were fully reversible.

At its present meeting, the Committee reviewed a number of new studies, including the results of a combined 2-year study of toxicity and carcino-

genicity and a 1-year study of toxicity with a 1-year recovery period with P70(H) and P100(H) oils (with the specifications of class-I medium- and low-viscosity mineral oils and of high-viscosity mineral oil, respectively) conducted in parallel. In addition, the Committee received and reviewed a number of studies conducted with low- and medium-viscosity mineral oils, including: a 2-year study of the carcinogenicity of a medium-viscosity liquid petroleum (class I medium- and low-viscosity mineral oil); studies of pharmacokinetics and studies of humoral immune function after administration to P15(H) mineral oil (class III medium- and low-viscosity mineral oil) in Fischer 344 and Sprague-Dawley rats; and a 90-day study of histopathological responses and compositional analysis of absorbed hydrocarbons with N15(H), N70(H) and P70(H) oils (classes III, II and I medium- and low-viscosity mineral oils, respectively). Several studies of low-melting-point paraffin wax were also reviewed by the Committee, as they were considered to provide information relevant for the evaluation of low- and medium-viscosity mineral oils relating to the difference in response to mineral hydrocarbons in Fischer 344 and Sprague-Dawley rats.

Toxicological data

In the long-term studies of toxicity, Fischer 344 rats were given a diet containing P70(H) or P100(H) oil, at concentrations that were varied to provide constant doses ranging from 60 to 1200 mg/kg bw per day, for up to 24 months. At 24 months, treatment with either test material was associated with mild treatment-related effects, which included: dose-related increases in the absolute and relative weights of the mesenteric lymph nodes; an increase in the severity of reticuloendothelial-cell hyperplasia (previously described as focal histiocytosis) of the mesenteric lymph nodes; increases in the incidence and/or severity of vacuolation of periportal hepatocytes; and an increased incidence of sinusoidal dilatation in the liver of male rats only, which was not dose-related. These effects were observed even at the lowest dose tested, 60 mg/kg bw per day. There were no treatment-related effects on survival with either material. Neither P70(H) nor P100(H)was carcinogenic in this study.

The effects observed at 12 months were marginal and included a slight increase in the severity of reticuloendothelial-cell hyperplasia of the mesenteric lymph nodes in male and female rats treated with P70(H) at the highest dose, the only dose for which histopathological data were available, as well as statistically significantly increased absolute and relative weights of mesenteric lymph nodes in males at this dose. Because of the marginal nature of these changes at 12 months, the reversibility of the lesions at the end of the recovery period could not be assessed; however, the results did indicate lack of progression of tissue alterations after dietary exposure to mineral hydrocarbons for 12 months.

No special indicators of immune function were measured in the long-term studies, although standard end-points of haematology, clinical chemistry, organ weight and histopathology, indicative of immune function, were evaluated. The only alteration in these end-points was exacerbation of mild cellular infiltration of the mesenteric lymph nodes, which had not been observed previously after administration for 90 days.

Aside from the earlier onset and increased severity of reticuloendothelial-cell hyperplasia of the mesenteric lymph nodes and the greater increase in the weights of mesenteric lymph nodes in response to dietary administration of P70(H), there was little difference in response to the two oils. None of the effects at 24 months was reported in 90-day studies at concentrations up to 2% of the diet (equivalent or equal to 2000 mg/kg bw per day) of either material. The pigmented macrophages observed with P70(H) oil at 2% in the diet (equivalent to 2000 mg/kg bw per day) in the 90-day study reviewed at the forty-fourth meeting, on which the ADI was based, were not observed after 24 months' intake at doses up to 1200 mg/kg bw per day.

Accumulated hydrocarbon was detected in the liver, mesenteric lymph nodes and spleen; the amounts of hydrocarbon could be quantified only in the liver. In the liver, a steady-state level of hydrocarbon accumulation appeared to have been reached in rats treated with the highest dose (1200 mg/kg bw per day) by 3 months, the only dose for which data on the complete time course were available. The concentration of P70(H) reached in the liver at any given time was about twice that of P100(H). The concentrations of mineral hydrocarbons in the liver returned to control levels within 12 months of cessation of treatment.

Medium-viscosity liquid petroleum (corresponding to class I medium- and low-viscosity mineral oils, including P70(H) oil) was not carcinogenic when fed to Fischer 344 rats at a concentration of 2.5% or 5% in the diet (equivalent to 1250 and 2500 mg/kg bw per day). Increased incidence or severity of reticuloendothelial-cell hyperplasia of the mesenteric lymph nodes was also observed in rats of each sex in this study at both dietary concentrations.

The pharmacokinetics of single doses of P15(H) oil given by gavage at a dose of 34 or 340 mg/kg bw over 96 h was studied in female Fischer 344 and Sprague-Dawley rats, with [^{14}C]1-eicosanylcyclohexane as the tracer. In one of the studies, the animals received a 2-week dietary pretreatment with low-viscosity mineral oil. The faeces were the major route of elimination, and urinary excretion was a minor route. Elimination of radiolabel by either route was more rapid in Sprague-Dawley than in Fischer 344 rats. Estimates of the area under the curve for serum concentrations of mineral hydrocarbons indicated that the bioavailability of mineral hydrocarbon was greater in Fischer 344 rats. Rats of this strain also accumulated and retained a larger

proportion of the administered dose in the liver (2% vs 0.1–0.5%) and, to a much lesser extent (about 100-fold), in the mesenteric lymph nodes. While a longer delay in faecal excretion of radiolabel was seen in Fischer 344 rats than in Sprague-Dawley rats in one study, suggesting a strain-related difference in intestinal absorption of mineral hydrocarbons, this difference was not observed in two similar studies. Rather, the results suggested that Sprague-Dawley rats metabolized and excreted radiolabelled mineral hydrocarbon tracer more efficiently than Fischer 344 rats, which exhibited deposition and retention in the liver. Dietary pretreatment with mineral oil did not affect the extent to which hydrocarbon accumulated in the liver of either strain of rats. In another study, the rate of metabolism of *n*-heptadecane by liver microsomes in vitro differed by rat strain, but not sex, in the order Wistar > Sprague-Dawley > Fischer 344. Metabolism of *n*-octadecane was negligible in all strains, consistent with the findings for hydrocarbons with more than 17 carbons in microsomal systems in vitro.

New short-term studies in which the responses of female Fischer 344 and Sprague-Dawley rats to dietary administration of P15(H) oil (for 120 and 90 days, respectively) at concentrations of up to 2% were compared indicated a more severe response in the Fischer 344 strain. The effects seen in these rats were: increased weights of the liver, mesenteric lymph nodes and spleen; granulomatous inflammation of the liver; and reticuloendothelial-cell hyperplasia of the mesenteric lymph nodes. In Sprague-Dawley rats, only statistically significant increases in liver weight and reticuloendothelial-cell hyperplasia of the lymph nodes, mostly of minimal severity, were observed. The increased liver weights in Fischer 344 rats receded during a 30-day recovery period. Reversibility was not assessed in Sprague-Dawley rats.

The results of the new 90-day study in female Fischer 344 rats with low-melting-point wax and with N15(H), N70(H) and P70(H) oils at a dietary concentration of 2% (equal to approximately 2000 mg/kg bw per day at 90 days) confirmed the previous findings in lymph nodes, liver and spleen, with an additional finding of inflammation of the cardiac mitral valve, which had not been seen previously with this material. This effect occurred at a lower incidence than with low-melting-point wax in this study.

The Committee reviewed the results of a study of T-dependent humoral immune function in response to 90 days' administration of P15(H) oil in female Fischer 344 and Sprague-Dawley rats. No effects were observed in the Sprague-Dawley rats. Interpretation of the results in the Fischer 344 rats was complicated by the increase in spleen weight that resulted from treatment. No data were provided to determine whether the increased spleen weight was associated with a change in the proportion of spleen cell types, which could alter interpretation of the results.

The responses of female Fischer 344 and Sprague-Dawley rats to mineral hydrocarbons were also compared in a 90-day toxicity study with low-melting-point wax at a dietary concentration of 0.2% or 2.0%. This substance had induced the most severe effects in similar studies in Fischer 344 rats with a range of food-grade mineral hydrocarbons, in which, in general, female rats had a stronger response to these materials. The results for Fischer 344 rats in the new study confirmed the findings of the previously evaluated 90-day studies with low-melting-point wax: altered haematological and hepatic clinical chemical parameters, increased weights of the liver, mesenteric lymph nodes and spleen; hepatic vacuolation (affecting both hepatocytes and Kupffer cells) and granulomatous inflammation; reticuloendothelial-cell hyperplasia of mesenteric and cervical lymph nodes; and focal inflammation of the cardiac mitral valve. In addition, increased severity of extramedullary haematopoiesis of the spleen, differential effects on serum immunoglobin concentrations and lipid-like material in crystalline form in hepatocytes and Kupffer cells were observed in this strain. In contrast, the only effects observed in female Sprague-Dawley rats were increased liver weights and slightly increased reticulo-endothelial-cell hyperplasia of the mesenteric lymph nodes and severity of hepatocellular and Kupffer-cell vacuolation. The crystalloid structures and inflammatory response in the liver were absent in this strain.

Tissue accumulation of mineral hydrocarbon after administration of low-melting-point wax also showed a clear strain difference in terms of degree, onset and the tissues affected. Quantifiable amounts of hydrocarbon were detected in the liver and mesenteric lymph nodes of Fischer 344 rats in a time- and dose-related manner, starting at 30 days in the livers of animals at the higher dose and occurring in both tissues in animals at both doses by 90 days. However, only the mesenteric lymph nodes of Sprague-Dawley rats had quantifiable amounts of hydrocarbon, and only at 90 days in animals at the higher dose. This observation was confirmed in a qualitative investigation of the accumulation of low-melting-point wax in the liver and Kupffer cells of female Fischer 344 and Sprague-Dawley rats after administration of a diet containing 2% wax for 14, 30 or 60 days. Detectable amounts were found in liver cells of Fischer 344 rats by 14 days, but none was found at any time in Sprague-Dawley rats.

In a separate study of low-melting-point wax, feeding a diet containing 2% resulted in alterations in Kupffer-cell function and morphology after 60 days in female Fischer 344, but not Sprague-Dawley, rats. Effects were also seen on selected parameters (i.e. leukocytes, serum liver enzyme activities and hepatic histopathology) that have been associated with administration of low-melting-point wax in this strain, and these were accompanied by accumulation of mineral hydrocarbon in the liver.

No new information was available on the compositional elements of mineral oils that affect their absorption or toxicity.

As the materials tested in the long-term studies reviewed at the present meeting, P70(H) and P100(H) oils, were not associated with induction of liver granulomas in Fischer 344 rats, the studies did not help the Committee to determine the long-term consequences or reversibility of the liver granulomas that had been seen in previous studies in response to consumption of low- and medium-viscosity mineral oils and low-melting-point waxes by Fischer 344 rats. In addition, the Committee was unable to interpret the effects in the study of humoral immune function in response to dietary administration of P15(H) oil.

The results of the studies on the effects of P15(H) oil and low-melting-point wax in Fischer 344 and Sprague-Dawley strains indicated that the more extensive response of Fischer 344 rats, in particular that of females, is associated with greatly enhanced retention of mineral hydrocarbons in the tissues, which is probably due to a reduced ability to metabolize absorbed hydrocarbons. The Committee concluded that additional studies are needed in order to determine whether the Fischer 344 rat is an appropriate model of human response to dietary intake of food-grade mineral hydrocarbons. In particular, elucidation of the metabolic differences between Fischer 344 rats and other strains and species, including humans, would be useful.

Neither P70(H) nor P100(H) oil was carcinogenic in the combined study of toxicity and carcinogenicity reviewed by the Committee at its present meeting. The effects observed even at the lowest dose, i.e. enhanced reticuloendothelial-cell hyperplasia, increased weights of mesenteric lymph nodes and increased incidence and grade of vacuolation of hepatocytes, were shown not to progress to more severe effects, and there was no indication that accumulated test material contributed to suppression or activation of an inflammatory response. Consequently, these effects were considered to be indicators of exposure to mineral hydrocarbon rather than adverse effects. At the present meeting, the NOEL for P70(H) oil was identified as the highest dose tested in the combined study of toxicity and carcinogenicity in rats, 1200 mg/kg bw per day, to which a safety factor of 100 was applied. An ADI of 0-10 mg/kg bw was allocated for class I medium- and low-viscosity mineral oils, which include P70(H) oil. An ADI of 0–20 mg/kg bw for P100(H) oil already exists (see Table 1).

No data were available that would permit allocation of a full ADI for medium- and low-viscosity mineral oils in classes II and III. The Committee noted that the new information reviewed at the present meeting indicated that the observed effects of these mineral oils, on which the temporary ADI is based, may be strain- and sex-specific. The Committee therefore extended the

temporary group ADI of 0–0.01 mg/kg bw for class II and III medium- and low-viscosity mineral oils until 2006, pending information on the relevance to humans of the response of Fischer 344 and Sprague-Dawley rats to these materials. In order for the data to be applicable to as wide a range of mineral oils as possible, the Committee suggested that commercial mineral oils of the lowest viscosity be used in such studies. Additional studies might be required, depending on the outcome of these studies.

Intake

The major food uses of mineral oils are in vegetable and fruit coatings and in packaging, bakery and confectionery manufacture and grain and seed dust control, and these uses are also the major sources of dietary intake of mineral oils in some countries. Dietary intake was assessed from data on the levels of use in foods and on migration from coatings and packaging materials into foods, combined with national data on food consumption in the 1990s. In both the United Kingdom and the USA, the average total intake of mineral hydrocarbons (excluding petroleum jelly) from food use was estimated to be 0.47 mg/kg bw per day; the intake at the 90th percentile of consumption by the population of the United Kingdom was 0.80 mg/kg bw per day. Class III medium- and low-viscosity mineral oils (including P15(H) oil) accounted for 0.21 mg/kg bw per day in the United Kingdom and 0.25 mg/kg bw per day in the USA; these values are 21 and 25 times the temporary ADI of 0–0.01 mg/kg bw, respectively, whereas class I and II medium- and low-viscosity mineral oils and high-viscosity mineral oil (including P70(H) and N70(H) oils, respectively) accounted for 0.18 and 0.19 mg/kg bw per day, respectively. As these different categories of mineral oil have different ADIs, but data on intake are not available for separate categories, the intake of each category cannot be compared with the corresponding ADI. Use of solid hydrocarbons (e.g. microcrystalline wax (high-melting-point wax) and paraffin wax (low-melting-point wax)) accounted for the remainder of the total intake.

The intake of high-viscosity and class I, II and III medium- and low-viscosity mineral oils that have migrated into food from coating and packaging materials was estimated to be 0.001 mg/kg bw per day in both the United Kingdom and the USA, while the combined intake of paraffin wax and microcrystalline wax from this source was estimated to be 0.005 and 0.006 mg/kg bw per day, respectively.

Naturally occurring hydrocarbons are widely distributed in many edible plants and animals, and they contribute significantly to the overall dietary intake of hydrocarbons. For example, the dietary intake of naturally occurring hydrocarbons was estimated to be 0.47, 0.25 and 0.19 mg/kg bw per day in the populations of the European Union, the United Kingdom and the USA,

respectively. It is clear, therefore, that account should be taken of intakes from naturally occurring hydrocarbons when evaluating the safety of mineral oils.

Mineral oil is included in the Codex draft GSFA in numerous food categories, with maximum use levels of 200–3000 mg/kg and, in some categories, in accordance with good manufacturing practice. The Committee suggested that the Codex Committee on Food Additives and Contaminants consider reviewing the standards for mineral oil, particularly in view of the fact that the intake of class III medium- and low-viscosity mineral oil is more than 20 times higher than its temporary ADI of 0–0.01 mg/kg bw.

An addendum to the toxicological monograph, including data on intake, was prepared. The existing specifications for mineral oils (medium- and low-viscosity) were revised, with minor editorial changes.

3.1.4 *Nitrate and nitrite*

Nitrite

Explanation

Nitrite occurs in the environment, in food and water, and is produced endogenously. It is also used as a food additive, mainly as a preservative, antimicrobial agent and colour fixative. It is used in foods such as cheese and cheese products, raw and processed meats, edible casings, processed fish and fish products and roe.

Nitrite was reviewed by the Committee at its sixth, eighth, seventeenth, twentieth and forty-fourth meetings (Annex 1, references *6, 8, 32, 41* and *116*). At its sixth meeting, the Committee allocated an ADI of 0–0.4 mg/kg bw to this substance, expressed as sodium nitrite. This ADI was based on a marginal reduction in body-weight gain at a dose of 100 mg/kg bw per day in a long-term study in rats. At its seventeenth meeting, the Committee lowered the ADI for sodium nitrite to 0–0.2 mg/kg bw and made it temporary At that time, the Committee used a safety factor higher than normal (500) because the ADI was based on a marginal effect and there is a possibility of endogenous formation of *N*-nitroso compounds from nitrite and *N*-nitrosatable compounds present in food and the gastrointestinal tract. At its twentieth meeting, the Committee considered the reports of a WHO task group and of a working group of the International Agency for Research on Cancer on *N*-nitroso compounds but concluded that they did not provide sufficient evidence to revise the temporary status of the ADI.

After that meeting, numerous toxicological and epidemiological data became available, which the Committee considered at its forty-fourth meeting. Nitrite both with and without nitrosatable precursors was found to be genotoxic in vitro in several tests, but, with the exception of a test in *Drosophila*

melanogaster, the results obtained in vivo were negative. The results of carcinogenicity studies with nitrite were negative, except those in which extremely high doses of both nitrite and nitrosatable precursors were administered simultaneously or premixed in the diet. In addition, the epidemiological data provided no evidence for an association between exposure of humans to nitrite and nitrate and the risk for cancer.

At its forty-fourth meeting, the Committee noted that several controlled laboratory studies had shown that *N*-nitroso compounds are formed endogenously when both nitrite and *N*-nitrosatable compounds are present at high concentrations; it observed, however, that quantitative data were available only on those *N*-nitroso compounds that are readily formed endogenously, such as *N*-nitrosoproline, which is not carcinogenic. As there was no quantitative evidence of the endogenous formation of carcinogenic *N*-nitroso compounds at the levels of intake of nitrite and nitrosatable precursors achievable in the diet, a quantitative risk assessment of nitrite on the basis of endogenously formed *N*-nitroso compounds was considered to be inappropriate. The Committee at its forty-fourth meeting therefore based its safety evaluation on studies of toxicity with nitrite. The NOELs in these studies were 5.4 mg/kg bw per day (expressed as nitrite ion) in a 90-day toxicity study in rats, in which hypertrophy of the zona glomerulosa was observed, and 6.7 mg/kg bw per day (expressed as nitrite ion) in a 2-year study in rats in which effects on the heart and lungs were observed. On this basis, the Committee allocated an ADI of 0–0.06 mg/kg bw, expressed as nitrite ion, by applying a safety factor of 100.

At its present meeting, the Committee reviewed the data that had become available on nitrite since its forty-fourth meeting, including data on the relevance and adverse nature of certain effects, with new information on the mode of action of effects on the adrenals and on toxicokinetics.

Toxicological and epidemiological data

The Committee considered a new study of toxicokinetics in human volunteers given sodium nitrite in their drinking-water. The maximum plasma nitrite concentrations were observed 15–30 min after dosing, and nitrite disappeared rapidly from plasma, with a half-life of approximately 30 min. The bioavailability of sodium nitrite was similar and virtually total after low and high oral doses. An intravenous dose of sodium nitrite of 290–380 mg per person induced methaemoglobinaemia, with maximum percentages of 8.4–12%. After oral administration, the maximum concentration of methaemoglobin was reached 0.70 h after dosing.

Several new studies were available on the acute and short-term toxicity of nitrite in humans, in which the severity of methaemoglobinaemia was reported after accidental, high intake of nitrite. Most were case reports of poisoning

incidents. None of these studies added data that could be used for the safety evaluation.

The Committee considered studies recently completed within the National Toxicology Program in the USA. In 14-week studies of the toxicity of sodium nitrite administered in drinking-water to mice at doses equal to 0, 90, 190, 340, 750 or 990 mg/kg bw per day and to rats at doses equal to 0, 30, 55, 120, 200 or 310 mg/kg bw per day, elevated levels of methaemoglobinaemia were observed in rats in all treatment groups, but not in mice. The Committee considered a level of methaemoglobin formation of up to 5% not to be adverse. The lowest NOEL value was observed in a study in male rats and was equal to 55 mg/kg bw per day (37 mg/kg bw per day expressed as nitrite ion) on the basis of reduced sperm motility at higher doses. Reduced sperm motility was also seen in mice at higher doses. The results of 2-year carcinogenicity studies with sodium nitrite added to drinking-water of mice and rats at a concentration of 750, 1500 or 3000 mg/l (equal to 45, 90 and 160 mg/kg bw per day in mice and to 35, 70 and 130 mg/kg bw per day in rats) led to the conclusion that nitrite is not carcinogenic in rats or male mice. The authors noted that there was equivocal evidence of carcinogenic activity of sodium nitrite in female mice, in view of the positive trend in the incidence of squamous-cell papilloma and carcinoma (combined) in the forestomach. As no evidence of genotoxicity in vivo or of cytotoxicity in the forestomach was found, the mode of action of sodium nitrite in inducing forestomach neoplasia is unclear.

A study of reproductive toxicity in mice given drinking-water containing sodium nitrite at concentrations up to 0.24% w/w (equivalent to 240 mg/kg bw per day) did not reveal adverse effects on reproductive performance or on end-points examined at necropsy.

New studies on genotoxicity were available. Sodium nitrite was mutagenic in a test for reverse mutation but did not induce micronucleus formation in the bone marrow or peripheral erythrocytes of mice treated in vivo, consistent with previous results.

A few studies on the endogenous formation of *N*-nitroso compounds after intake of nitrite or nitrate and of nitrosatable compounds (amines and amides) and the possible association with cancer were available. In addition, one long-term study of toxicity and carcinogenicity was reviewed, in which rats were fed fishmeal at various concentrations concomitantly with sodium nitrite. Dose-dependent increases in the incidences and multiplicity of atypical renal tubules, adenomas and renal-cell carcinomas were found. The concentration of *N*-nitrosodimethylamine in the stomach contents after 4 weeks of treatment with 64% fishmeal plus 0.12% sodium nitrite was twice that measured after administration of 8% fishmeal plus 0.12% sodium nitrite.

However, the diets used in this study were considered to be nutritionally inappropriate for the rat: they had a high protein content, resulting in abnormally high renal nitrogen clearance. These studies did not provide additional insight for the safety evaluation of nitrite.

A number of epidemiological studies of the relationship between the intake of nitrite and cancer risk have been published since the forty-fourth meeting. At its present meeting, the Committee ranked the study designs according to their capacity to provide evidence of a relationship. In the descriptions below, relative risk estimates are given for those studies in which levels of intake of nitrite were provided. Four of the studies were cross-sectional, involving measurement of nitrite in, e.g., salivary or gastric juice in cancer patients and healthy subjects. Because cross-sectional studies do not take into account the time between exposure and disease, any observed differences in biomarkers of exposure might also be a consequence of the disease; therefore, these studies cannot contribute to a causal interpretation of the results of studies of nitrite and cancer risk.

Nine (longitudinal) case–control studies on previous nitrite intake and various cancer types were reviewed. For oral and laryngeal cancer, no association was found with nitrite intake. One study conducted in the USA reported a positive association with oesophageal cancer, with odds ratios of 1.0 (reference category), 1.2 and 1.6 for persons with a daily nitrite intake of < 1.1 mg, 1.1–1.6 mg and > 1.6 mg, respectively. The odds ratios and the trend across odds ratios were not statistically significant, however. The association between nitrite intake and oesophageal cancer was stronger, and it was significant for persons with a history of canker sores. Another study in the USA, however, found no association between nitrite intake and oesophageal cancer, nor with the subtypes adenocarcinoma and squamous-cell carcinoma; a positive association was found only with gastric cancer other than of the cardia. A positive association with gastric cancer was also reported in an Italian case–control study (average consumption, 2.4 mg/day), while no association was found in a French study (average consumption, 1.9 mg/day).

An association of borderline significance was found between nitrite intake and urinary bladder cancer in men but not women of Japanese descent, nor in whites of either sex, in Hawaii, USA. Although a positive association was reported from a study in the USA between brain tumours in children and their mothers' consumption of processed meat, no association was found with nitrite intake during gestation or in childhood in a recent case–control study from Israel. One study on nasopharyngeal cancer among Taiwanese reported no association with nitrite intake in adulthood (as reported by cases and controls), but a positive association was found with childhood nitrite

intake as recalled by the mothers of the cases and controls. The validity of recall of remote dietary intake is questionable, however.

Two prospective cohort studies have been conducted on nitrite intake and cancer risk. A cohort study from the Netherlands, with 6 years of follow-up, on dietary nitrite and gastric cancer risk reported relative risks of 1.0 (reference category), 1.2, 1.2, 0.9 and 1.4 for increasing mean quintiles of nitrite intake of 0.01, 0.04, 0.09, 0.16 and 0.35 mg/day, respectively. Neither the relative risks nor the trend was significant. A Finnish cohort study, with 24 years of follow-up, reported no association with the incidence of stomach, colorectal, or head-and-neck tumours. The average nitrite intake by this cohort was reported to be 5.3 mg/day.

Thus, some studies indicated increased risks for oesophageal and gastric cancer; however, other studies — particularly prospective cohort studies — revealed no such association. The results for brain tumours in children and for urinary bladder cancer in adults were equivocal. Wide variation between the studied populations in the recorded intake of nitrite was noted. In none of these studies was a possible interaction between nitrite and nitrosatable amines evaluated in respect of cancer risk. The results of these studies and those of the epidemiological studies considered by the Committee at its forty-fourth meeting do not provide evidence that nitrite is carcinogenic to humans. In addition, studies on nitrate intake and cancer risk (of relevance because of the conversion of nitrate to nitrite) also did not provide evidence of a positive association.

A 6-week study was performed in young adult and old rats to determine whether older animals are more sensitive to the toxic effects of nitrite, particularly with regard to the known effects on the kidney and on the functions of some hormones (insulin, thyroxine). No age-related differences were found. The hypertrophy of the zona glomerulosa in the adrenals of rats of this strain was seen only at an intake equivalent to 50 mg/kg bw per day, expressed as nitrite ion.

Several studies were available on the mechanism of action of nitrite on the vascular system, blood pressure and the adrenals in rats. Doses of 50 mg/kg bw or higher, expressed as nitrite ion, are known to lower blood pressure by causing vasodilatation. The Committee calculated that an oral dose equivalent to 160 mg/kg bw of nitrate ion induced a reduction in blood pressure of 15–20 mm Hg.

Administration of nitrite to rats resulted in minimal hypertrophy of the zona glomerulosa of the adrenal gland and secretion of aldosterone, which was reversible after 60 days. Inhibition of angiotensin-converting enzyme indicated that the effect was produced indirectly via stimulation of the renin–angiotensin axis.

The Committee concluded that the minimal hypertrophy reflected physiological adaptation to small fluctuations in blood pressure and should not be considered a direct toxic action on the adrenals. This conclusion implies that the safety evaluation should not be based on the NOEL for minimal hypertrophy of the adrenal zona glomerulosa, used by the Committee at its forty-fourth meeting, but on NOELs for other end-points. The NOEL of 5.4 mg/kg bw per day (expressed as nitrite ion) was therefore considered to be no longer relevant, as it was based on the indirect effect on the adrenals described above. The Committee established an ADI of 0–0.07 mg/kg bw, expressed as nitrite ion, on the basis of the NOEL of 6.7 mg/kg bw per day for effects on the heart and lung in a 2-year study in rats and a safety factor of 100.

Nitrite causes methaemoglobinaemia. As this might occur after a single dose, it would be appropriate to establish an acute reference dose for nitrite. The data available for review at the present meeting related primarily to its long-term toxicity and were not relevant for establishing an acute reference dose. The Committee recommended that the acute toxicity of nitrite be reviewed at a future meeting.

Intake

Ideally, all sources of nitrite should be included in an intake assessment; however, only food and water were included in the assessments made at this meeting. The intake of nitrite from non-food additive sources, on the basis of the concentrations in food derived from European studies and the GEMS/Food regional diets and with an addition for water was below the ADI (40–50% of the ADI for the various diets). Major contributors to the estimated intake from sources other than food additives are cereals (35–60% of the estimated intake) and water (20–40% of the estimated intake).

The estimated intakes from use of nitrite as a food additive derived from national assessments were above the ADI, assuming maximum levels in the Codex draft GSFA. The intake of nitrite by consumers at the mean represented 460–500% of the ADI, while that of consumers at the 95th percentile represented 1300–1400% of the ADI. The intakes of nitrite from food additive use based on maximum permitted levels in national standards also exceeded the ADI (consumers at the mean, 100–130% of the ADI; consumers at the 95th percentile, 320–360% of the ADI). The estimated intakes based on the GSFA do not reflect reality, as the calculations include the GSFA maximum levels, which often are significantly higher than the typical levels of addition to foods by manufacturers. The calculations also do not take into consideration degradation of nitrite over time and do not reflect the concentrations in foods as consumed. The intakes are based on 24-h food consumption data, which tend to result in overestimates of intake by consumers at high percentiles.

More realistic estimates of the intake of nitrite from all dietary sources, submitted in total diet and duplicate diet studies, showed mean intakes representing 5–15% of the ADI, although the intakes by consumers at higher percentiles approached the ADI and exceeded it in one study, representing 55–330% of the ADI. A major contributor to the total intake estimated from these studies was beverages (specific types not stated), which accounted for 30–35% of the total estimated intake, owing more to the high volumes consumed than to high concentrations of nitrite. Analysed concentrations in foods as consumed were used in these studies. These results confirm that the estimates of intake from use of nitrite as a food additive at the listed maximum levels in the GSFA or national maximum permitted levels are overestimates.

The Committee recommended that assessments of the intake of nitrite should also include sources other than food additives, such as vegetables and drinking-water. Studies with more accurate methods of assessment should be conducted, based on analysed concentrations of nitrite in foods. Furthermore, foods that are 'ready to consume' should be included to account for losses of the chemicals over time and during food storage, preparation and cooking, as occurs for nitrite.

The Committee recommended that the Codex Committee on Food Additives and Contaminants reconsider the list of maximum levels of nitrite in the GSFA, as the estimated intakes might exceed the ADI.

An addendum to the toxicological monograph, including an assessment of intake, was prepared.

Nitrate

Explanation

Nitrate occurs in the environment, in air, food (particularly in vegetables and fruits) and water, and is produced endogenously. It is also used as a food additive, mainly as a preservative and anti-microbial agent. It is used in foods such as cheese and cheese products, raw and processed meats, edible casings, processed fish and fish products and spirits and liqueurs.

Nitrate was reviewed by the Committee at its sixth, eighth, seventeenth and forty-fourth meetings (Annex 1, references *6, 8, 32* and *116*). At its sixth meeting, the Committee allocated an ADI of 0–5 mg/kg bw, expressed as sodium nitrate. This ADI was based on a NOEL of 500 mg/kg bw per day for body-weight gain at a higher dose in a long-term study in rats and a short-term study of toxicity in dogs, with a safety factor of 100. This ADI was retained by the Committee at its eighth and seventeenth meetings. After the latter meeting, numerous toxicological and epidemiological data became

available, which were considered by the Committee at its forty-fourth meeting.

At that meeting, the Committee concluded that nitrite should also be considered, because nitrate is readily converted in humans to nitrite. The rat was considered an unsuitable animal model for assessing the toxicity of nitrate, as it does not convert nitrate to nitrite in a quantitatively similar way to humans. Nevertheless, as the data on the toxicity of nitrate in other animal species were considered limited, the toxicity of nitrite in rats and the conversion rate of nitrate to nitrite were also evaluated.

The Committee at its forty-fourth meeting concluded that nitrate itself was not genotoxic, and the results of studies of carcinogenicity with nitrate were negative except when extremely high doses of both nitrate and nitrosatable precursors were administered. The available epidemiological data were considered to provide no evidence for an association between exposure of humans to nitrite and the risk for cancer. On the basis of this information, the NOEL of 370 mg/kg bw per day, expressed as nitrate ion, in a long-term study in rats was considered to be the most appropriate for the safety evaluation. When the proportion of nitrate converted to nitrite in humans was taken as 5% for the average individual and 20% for those with a high level of conversion, and when the NOEL for nitrite (6 mg/kg bw per day, expressed as nitrite ion) was used to calculate the 'transposed' NOEL for nitrate, expressed as nitrate ion, these values were estimated to be 160 and 40 mg/kg bw per day for average and high responders, respectively. As these figures were derived in part from data on human pharmacokinetics, use of a safety factor of less than 100 was considered to be justified.

On the basis of the NOEL of 370 mg/kg bw per day, expressed as nitrate ion, and a safety factor of 100, an ADI of 0–5 mg/kg bw expressed as sodium nitrate or 0–3.7 mg/kg bw expressed as nitrate ion was allocated. On the basis of the 'transposed' NOEL for nitrate of 160 mg/kg bw per day for normally responding persons (5% rate of conversion) and a safety factor of 50, an ADI of 0–3.2 mg/kg bw, expressed as nitrate ion, could be allocated. These two methods of deriving the ADI for nitrate thus resulted in similar figures, and the Committee at its forty-fourth meeting therefore retained the previously established ADI of 0–3.7 mg/kg bw, expressed as nitrate ion.

The Committee at its present meeting reviewed data relevant to the evaluation of nitrate which had become available since its forty-fourth meeting. Studies illustrating the relevance and severity of certain effects and other supporting data were also considered. New information on metabolism and toxicokinetics were included. Data on the putative health benefits of nitrate were not assessed, as this is not a safety issue and is therefore not within the purview of the Committee.

The few new studies on the toxicokinetics and metabolism of nitrate in animals that have become available since the forty-fourth meeting of the Committee confirm that the rat is not a good surrogate species for humans in this respect, as it does not show salivary transport of nitrate and therefore has limited conversion of nitrate to nitrite .

In a study of the conversion of nitrate to nitrite in humans, in which sodium nitrate was administered in drinking-water at a single dose of 7.3 mg/kg bw, expressed as nitrate ion, neither blood pressure nor methaemoglobin concentration was affected. The nitrite concentration of the gastric juice was approximately six times higher after administration of nitrate in combination with pretreatment with omeprazole at 40 mg/day (which increased the gastric pH) than after nitrate alone. Nitrate was absorbed rapidly, the concentration in plasma increasing within 10 min, and the half-life of nitrate in plasma was about 6.5 h; about 70% of the dose was excreted in urine within 10 h of dosing. The plasma concentration of nitrite did not change after nitrate administration. About 8% of the total nitrate administered was converted to nitrite in saliva, as found in other studies. The Committee at its forty-fourth meeting concluded that the range of nitrate conversion is 5–7% for normal individuals and 20% for individuals with a high rate of conversion.

The results of studies in humans that considered the potential of high intake of nitrate to cause methaemoglobinaemia were equivocal. Some of the studies showed an association between a high nitrate concentration in drinking-water and methaemoglobinaemia, and others indicated that gastrointestinal infections, inflammation and the ensuing overproduction of nitric oxide are major factors in infantile methaemoglobinaemia. No increase in methaemoglobin concentration was seen in volunteers after a single administration of sodium nitrate in drinking-water providing a dose of 7.3 mg/kg bw, expressed as nitrate ion.

A study in humans showed that nitrate in vegetable matrices and from other sources, such as drinking-water, is almost totally bioavailable.

As nitrate shares a common transport mechanism with iodide, studies were conducted to determine whether nitrate affects thyroid function. A 28-day study with volunteers given sodium nitrate in drinking-water at a concentration equivalent to 15 mg/kg bw per day (11 mg/kg bw per day expressed as nitrate ion) showed no effects on thyroid function and no increase in the per cent of methaemoglobinaemia. A 90-day study of toxicity in rats showed that sodium nitrate at a dose of 50 mg/kg bw per day did not affect the thyroid or the zona glomerulosa of the adrenals.

In studies in humans, consumption of drinking-water containing sodium nitrate at a concentration of 2800 mg/l concomitantly with volatile *N*-nitro-

satable amines in the diet (in cod, salmon or shrimp) led to a two- to threefold increase in urinary excretion of *N*-nitrosodimethylamine and *N*-nitrosopiperidine.

Several studies were reviewed on the effect of administration of nitrate on the release of nitric oxide at the junction of the oesophagus and the stomach in humans, which, it was speculated, might be associated with an increased incidence of cancer at this site. However, no such association has been observed in epidemiological studies.

A number of epidemiological studies have been published since the forty-fourth meeting of the Committee on the relationship between nitrate intake and cancer risk. At its present meeting, the Committee ranked the study designs according to their capacity to provide evidence of a relationship. In the descriptions below, relative risk estimates are given for those studies in which levels of intake of nitrate were provided.

Six ecological (correlation) studies were reported on nitrate in drinking-water and mortality from or incidence of cancer. Elevated risks were found for prostate cancer and for brain tumours (each in one study), but the results of six studies on gastric cancer were conflicting. The results of ecological studies (in which populations are the units of measurement) cannot be extrapolated to the individual level. Furthermore, most of the ecological studies were based on limited data on nitrate concentrations and on cancer mortality rates (rather than incidence rates), and none took an induction period for cancer into account.

Three of the studies were cross-sectional, involving measurement of, e.g., salivary nitrate in cancer patients and healthy subjects. Because cross-sectional studies do not take into account the time between exposure and disease, any observed differences in biomarkers of exposure might also be a consequence of the disease; therefore these studies could not contribute to a causal interpretation of the results of studies of nitrate intake and cancer risk.

Seven case–control studies on nitrate in drinking-water and/or food and cancers at various sites were reviewed. In the studies on nitrate in drinking-water, conflicting results were reported with regard to an association with non-Hodgkin lymphoma, and no association was found with brain tumours. In the studies on dietary nitrate, no association was found with oral, oesophageal, gastric or testicular cancer. No other cancer sites have been studied.

Three prospective cohort studies have been conducted on nitrate intake and cancer risk. A cohort study in the Netherlands, with 6 years of follow-up, found no significant association between the incidence of gastric cancer and

intake of nitrate from food or drinking-water, with relative risks for increasing quintiles of total nitrate intake of 1.0 (reference quintile), 1.2, 0.7, 0.9 and 0.9 for mean intakes of 60, 85, 100, 120 and 180 mg/day, respectively. Neither the relative risks nor the trend across relative risks was significant. A further analysis of the effect of nitrate within tertiles of vitamin C intake also did not reveal a positive association between nitrate intake and gastric cancer. A Finnish cohort study on dietary nitrate, with 24 years of follow-up, reported no association with the risks for tumours of the stomach, colorectum or head and neck. The average nitrate intake in this cohort was reported to be 77 mg/day. A cohort study in Iowa, USA, with 11 years of follow-up, revealed no consistent association between intake of nitrate from drinking-water and the risks for cancers at many sites, and an inverse association was reported with cancers of the uterus and rectum. Positive associations with nitrate intake were observed only for cancers of the ovary and urinary bladder, although it was not possible to determine whether other factors in drinking-water were responsible for these associations. In addition, no evidence of a dose–response relationship was found for any of the cancer sites addressed in the study in Iowa. The cohort studies included control for various potential confounders, such as intake of vegetables, age and smoking.

Overall, the epidemiological studies showed no consistently increased risk for cancer with increasing consumption of nitrate. These data, combined with the results of the epidemiological studies considered by the Committee at its forty-fourth meeting, did not provide evidence that nitrate is carcinogenic to humans.

A number of studies were performed to determine whether there are associations between nitrate intake in drinking-water and insulin-dependent diabetes mellitus, neural tube defects or sudden infant death syndrome. In none of these studies was a hypothesis proposed for the mechanism of an association. Two studies were conducted on the incidence of insulin-dependent diabetes mellitus and nitrate intake via drinking-water. One study in Yorkshire, United Kingdom, suggested a positive association, but the authors considered that the finding required confirmation. A study in the Netherlands with a larger number of subjects did not show a positive association. The two studies on nitrate intake and neural tube defects also showed no association. In a recent ecological study in Sweden, a correlation was reported between nitrate concentration in drinking-water and the occurrence of sudden infant death syndrome; however, no confounding factors were taken into account. The Committee concluded that it would be premature to include these observations in its safety assessment.

The Committee concluded that the pivotal observed toxic effects of nitrate are consequent on its conversion to nitrite in vivo. The Committee at its present meeting established an ADI of 0–0.07 mg/kg bw for nitrite (see earlier

part of this section). As the new data on nitrite would not provide a basis for a significant change in the previous ADI for nitrate, the Committee retained the ADI of 0–5 mg/kg bw expressed as sodium nitrate, or 0–3.7 mg/kg bw, expressed as nitrate ion, established at its forty-fourth meeting.

Intake

Ideally, all sources of nitrate should be included in an intake assessment; however, contributions from air were not included here. Nitrate intake from sources other than food additives, based on concentrations in food derived from European studies and the GEMS/Food regional diets and with an addition for water, was below the ADI (10–70% of the ADI for the various diets). Major contributors to intake were vegetables (30–65% of the estimated intake) and water (5–45% of the estimated intake). The nitrate content of both groundwater and surface water is highly variable, and wide variations are seen between countries.

The estimated intakes from use of nitrate as a food additive derived from national assessments were below the ADI, assuming the maximum levels in the Codex draft GSFA. The intake by consumers at the mean was about 10% of the ADI, while the intake of those at the 95th percentile was 30–35% of the ADI, on the basis of national data on food consumption. The intakes of nitrate from food additive use based on maximum permitted levels in national standards were also below the ADI (consumers at the mean, 10% of the ADI; consumers at the 95th percentile, 35% of the ADI). Major contributors from its use as a food additive were processed comminuted meats in national assessments (50–55% of estimated intake) and raw meats on the basis of GSFA maximum levels (50–55% of the estimated intake) from national food consumption data. These intakes were based on 24-h food consumption data, which tend to result in overestimates of the intake of consumers at high percentiles.

Assessments of intake of nitrate from all dietary sources, including drinking-water, showed that they were below the ADI. In total diet studies in the United Kingdom, the mean intakes were between 40% and 45% of the ADI and those by consumers at the 95th percentile were 60–75% of the ADI. Duplicate diet studies showed mean intakes representing 30–35% of the ADI and intakes by consumers at the 95th percentile representing 95–125% of the ADI. These studies included one of vegetarians, who are likely to have higher intakes of nitrate owing to their greater consumption of vegetables; however, their intakes were not considerably different from those of the general population. Major contributors to total dietary intake of nitrate were vegetables, which accounted for 70–75% of the total estimated intake. The Committee noted that the food additive use of nitate is not a major source of intake.

The Committee recommended that the Codex Committee on Food Additives and Contaminants reconsider the maximum levels of nitrate in the GSFA, as the estimated intakes of nitrate might exceed the ADI.

The Committee recommended that assessments of the intake of nitrate also include sources other than food additives, such as vegetables and drinking-water. Studies should be conducted in which more accurate methods of assessment are used, which provide estimates of intake based on analysed concentrations of chemicals in foods. Studies should be conducted in different seasons to account for natural variations in concentrations in foods such as vegetables.

An addendum to the toxicological monograph, including an assessment of intake, was prepared.

3.1.5 *Salatrim*

Explanation

Salatrim is the acronym for **s**hort- **a**nd **l**ong-chain **acyltri**glyceride **m**olecules. Salatrim preparations are tailored mixtures of triglycerides containing at least one long-chain fatty acid moiety (principally stearic acid) and one or two short-chain fatty acid moieties (acetic, propionic and/or butyric acid). Salatrim is synthesized by non-enzymatic inter-esterification of triacetin, tripropionin, tributyrin or their mixtures with hydrogenated canola, soya bean, cottonseed or sunflower oils. The physical properties of salatrim may be fitted to its food applications by selecting specific short-chain fatty acids and hydrogenated oils for synthesis. Salatrim is intended for use as a low-calorie fat in soft sweets, coatings (e.g., wafers and confectionery), dairy products (including spreads), margarines and bakery products.

Salatrim of various compositions was evaluated by the Committee at its forty-ninth meeting (Annex 1, reference *131*), when it concluded that the available studies did not provide an adequate basis for evaluating the safety and the nutritional effects of salatrim. At that meeting, the Committee recommended that additional, appropriately designed studies be performed to assess fully both the toxicological and nutritional consequences of ingestion of salatrim.

The Committee noted at its forty-ninth meeting that the specifications for salatrim permit compositions that include a triglyceride mixture with up to 0.87 g of stearate per gram of fat, but that the available biological data did not provide information on materials of such a composition. Since that time, the sponsor has proposed that the specifications for salatrim be limited to preparations with ≤ 70% by weight of total saturated long-chain fatty acids. Studies were available on the biological effects in humans of salatrim containing up to 0.61 g of stearate per gram of fat.

The Committee previously evaluated studies on the caloric value of salatrim, taking into account the fact that short-chain fatty acids supply fewer kilocalories per gram than long-chain fatty acids. Moreover, it concluded that the claim of reduced absorption of stearic acid has not been proven for humans. In addition, as there is no specific composition for salatrim, a single caloric value could not be assigned.

In evaluating the safety of salatrim at its forty-ninth meeting, the Committee considered studies in which salatrim of various compositions was administered to rats or minipigs at concentrations of up to 10% in the diet. These studies showed no toxicologically significant effects, but the study in minipigs was considered to have been of insufficient duration. The Committee also discussed one home-based trial and four clinic-based studies with volunteers who ingested up to 60 g salatrim per person per day. The studies indicated that the consumption of diets containing salatrim, particularly at 60 g per day, was associated with an increased incidence of mild gastrointestinal symptoms and significantly elevated serum enzyme activities.

Thus, the Committee concluded at its forty-ninth meeting that the available studies in experimental animals and humans did not provide an adequate basis for a toxicological evaluation. In addition, as the studies were not optimized to detect potential nutritional effects, the Committee concluded that they did not provide an adequate basis for a nutritional evaluation.

In response to the Committee's earlier request, four additional home-based trials in humans and one study of nutrition in rats were submitted for consideration at the present meeting.

Toxicological data

The Committee concluded that the newly submitted study of nutrition in rats did not resolve the issue of the extent to which salatrim might reduce energy intake since, as stated previously, the rat is not a good model for humans with respect to stearic acid absorption.

The aim of the home-based trials was to investigate plasma lipid profiles in small groups of adults ingesting salatrim at 30 g/day for up to 5 weeks. Diets containing salatrim did not affect the blood concentration of total high-density or low-density lipoprotein cholesterol. The post-prandial increase in serum triglyceride concentration was lower after ingestion of a meal containing 30 g of salatrim than after ingestion of a meal containing 30 g of oleate or cocoa butter. In one study, it was reported that some of the volunteers complained of gastric discomfort, nausea or feeling 'bloated' or 'satiated and averse to eating until the early evening' after a breakfast containing 30 g of salatrim. However, adequate controls were not included in this study, and it was not clear if these subjective symptoms were related to ingestion of

salatrim. The Committee was informed that, in one of these trials, serum liver enzyme activities were found to be within the normal range; however, these results were not included in the published manuscript.

Overall, the Committee concluded that the new studies did not respond to the questions raised at its forty-ninth meeting and the available information was inadequate for a toxicological evaluation. The Committee noted that, in general, toxicological studies in experimental animals should be conducted at doses that allow an adequate margin of safety in relation to anticipated human intake. Such safety margins cannot feasibly be attained with substances, such as salatrim, that are intended for use as major components of food. Additionally the rat is not a good model for humans with respect to stearic acid absorption, and further studies in experimental animals would not contribute to the safety evaluation of salatrim. The Committee therefore paid particular attention to the results of the studies in humans. These studies indicated that adverse effects (gastrointestinal and hepatic effects) might be experienced by adults consuming diets containing salatrim at 60 g/day (equivalent to 1 g/kg bw per day). The available information was not adequate to evaluate whether effects might occur at intakes of less than 60 g/day, nor if the effects differ with the composition of salatrim.

Intake

Data on the projected intake of salatrim were assessed by the Committee at its forty-ninth meeting. These data, with small revisions, and with projections of intake based on data on consumption in the United Kingdom, were submitted to the present meeting. Manufacturers' use levels for salatrim vary from 1–2 g/100 g in some dairy products and crackers to more than 80 g/100 g in margarine.

The mean intake of salatrim after hypothetical substitution of added fats by this substance in all food categories would be 45 g/day, but this value is unrealistic. The mean intake of salatrim based on hypothetical substitution of fats in specified food categories would vary from 11 to 13 g/day. Intake by adolescent consumers at the 90th percentile would reach 35 g/day. On a gram per kilogram body-weight basis, the highest intake would be that of children aged less than 2 years, as those at the 90th percentile of consumption would have an intake of 1.5 g/kg bw per day. Children aged 1–6 years who are consumers of the category 'chocolates and confectionery' at the 90th percentile would have an intake of salatrim from this food category alone of 1.1 g/kg bw per day, which is higher than the intake reported to have effects in adults in clinical studies.

The Committee concluded that the available data did not provide an adequate basis for evaluating the safety of salatrim and recommended that additional studies be performed in humans to assess fully the safety of salatrim covering

the range of compositions intended for use. The studies should be designed appropriately for safety evaluation and should include investigation of the gastrointestinal and hepatic effects observed in previous studies.

A monograph reproducing the previous monograph and incorporating the information that had become available since the previous evaluation was prepared. The updated monograph includes corrections to the information provided to the Committee at its forty-ninth meeting.

Specifications

The existing specifications for salatrim were revised. The assay was amended by introducing a maximum upper limit of 70% by weight of saturated long-chain fatty acids. Calculation of the weight per cent of saturated long-chain fatty acids in salatrim requires that the molar ratio of short-chain to long-chain fatty acids be determined with analysis for fatty acid butyl esters by gas chromatography (method I in the original specifications). Therefore, the alternative method II, with identification of fatty acid residues by proton nuclear magnetic resonance spectrometry, was considered to have no further value and was deleted.

3.2 Revision of specifications

3.2.1 *Amyloglucosidase from* Aspergillus niger, *var.*

Amyloglucosidase from *Aspergillus niger,* var. is a hydrolytic enzyme produced by controlled fermentation of this organism. The enzyme is isolated from the growth medium and is used to hydrolyse α-glucosidic linkages in starch.

The existing specifications for amyloglucosidase from *A. niger,* var. were revised, and a new procedure was incorporated for assaying enzyme activity in products, including those containing glucose. The tentative designation to the specifications was removed.

3.2.2 *Limits for heavy metals in colours and acidity regulators*

At its fifty-fifth meeting (Annex 1, reference *149*), the Committee began implementation of a systematic 5-year programme to replace the outdated test for heavy metals (as lead) in all existing food additive specifications with appropriate limits for individual metals of concern. At the present meeting, the heavy metals and arsenic limits of 52 colours and 44 acidity regulators were reviewed

Colours

In response to the call for data, some proposed limits and supporting data were received for a number of colours from biological sources ('natural colours'). No data were received for synthetic or inorganic colours.

The proposed changes to the current limits are:

For natural colours

- The limits for arsenic were maintained because information was received that the plant sources for certain natural colours grow in areas where the level of arsenic in groundwater is high. The Committee agreed to review these limits at a future meeting when arsenic is on the agenda for evaluation.
- The proposed limit for lead was set at 2 mg/kg, except in certain natural colours containing higher levels or levels set at meetings following the forty-ninth meeting of the Committee. The limit of 2 mg/kg is consistent with the previously agreed policy.
- No limits were proposed for cadmium.
- Limits for mercury were proposed for two natural colours.
- Limits for heavy metals (as lead) were deleted.

For synthetic colours in accordance with the Committee's policy:

- Limits for arsenic were deleted.
- The limit for lead was set at 2 mg/kg.
- No limits were proposed for cadmium.
- Limits for mercury were deleted.
- Limits for heavy metals (as lead) were deleted.

For inorganic colours

The Committee concluded that, because of the high levels of heavy metals in the present specifications for aluminium powder, iron oxides and titanium dioxide, the specifications should be reconsidered. Therefore the Committee maintained the existing limits and decided to call for data on the raw materials, manufacturing methods and analytical data on impurities for review at a future meeting.

Acidity regulators

No data were received. The Committee followed its past practice of including:

- a limit of 3 mg/kg of arsenic for phosphates and calcium compounds;
- a limit of 4 mg/kg of lead for phosphates, but 2 mg/kg for other substances.
- Levels of cadmium and mercury were not considered to be of concern and were not specified.
- Limits for heavy metals (as lead) were deleted.

The conclusions of the Committee on limits for heavy metals in colours and acidity regulators are summarized in Table 2.

Table 2
Limits for heavy metals in 52 colours and 44 acidity regulators

Category	Food additive	INS		As	Pb	Cd	Hg
Colour	Allura red AC	0129		-	2	-	-
Colour	Aluminum powder	0173		3	20	-	-
Colour	Amaranth	0123		-	2	-	-
Colour	Annatto extracts(oil & alkali extracted)	0160	b	3	2	-	1
Colour	Annatto extracts(solvent extracted)	0160	b	3	2	-	1
Colour	β-Apo-8'-carotenal	0160	e	-	2	-	-
Colour	β-Apo-8'-carotenic acid ethyl ester	0160	f	-	2	-	-
Colour	Azorubine	0122		-	2	-	-
Colour	Beet red	0162		3	2	-	-
Colour	Blackcurrant extract	0163	ii	-	2	-	-
Colour	Brillant Black BN	0151		-	2	-	-
Colour	Brillant Blue FCF	0133		-	2	-	-
Colour	Brown FK	0154		-	2	-	-
Colour	Brown HT	0155		-	2	-	-
Colour	Canthaxanthin	0161	g	-	2	-	-
Colour	Caramel colours	0150	a,b,c,d	1	2	-	-
Colour	Carmines	0120		-	5	-	-
Colour	β-Carotene, synthetic	0160	a(i)	-	2	-	-
Colour	β-Carotene from *Blakeslea trispora*	0160	a	-	2	-	-
Colour	Carotenes (algae)	0160	a(ii)	-	5	-	-
Colour	Carotenes (vegetable)	0160	a(ii)	-	5	-	-
Colour	Carthamus red	-		-	5	-	-
Colour	Carthamus yellow	-		-	5	-	-
Colour	Chlorophyllins, copper complexes	0141	ii	3	5	-	-
Colour	Chlorophylls	0140		3	5	-	-
Colour	Chlorophylls, copper complexes	0141	i	3	5	-	-
Colour	Cochineal extract	0120		-	5	-	-
Colour	Curcumin	0100		-	2	-	-
Colour	Erythrosine	0127		-	2	-	-
Colour	Fast Green FCF	0143		-	2	-	-
Colour	Fast Red E	-		-	2	-	-
Colour	Grape skin extract	0163	ii	3	2	-	-
Colour	Green S	0142		-	2	-	-
Colour	Indigotine	0132		-	2	-	-
Colour	Iron oxides	0172		3	10	10	1
Colour	Lithol rubine BK	0180		-	2	-	-
Colour	Mixed carotenoids			-	5	-	-
Colour	Paprika oleoresin	0160	c	3	2	-	-
Colour	Patent Blue V	0131		-	2	-	-
Colour	Ponceau 4R	0124		-	2	-	-
Colour	Quinoline Yellow	0104		-	2	-	-
Colour	Red 2G	0128		-	2	-	-
Colour	Riboflavin	0101	i	-	2	-	-
Colour	Riboflavin 5'-phosphate sodium	0101	ii	-	2	-	-
Colour	Riboflavin from *Bacillus subtilis*	0101	I	-	1	-	-
Colour	Saffron	-		3	2	-	-
Colour	Sunset Yellow FCF	0110		-	2	-	-
Colour	Tagetes extract	-		-	2	-	-
Colour	Tartrazine	0102		-	2	-	-
Colour	Titanium dioxide	0171		3	10	-	1
Colour	Turmeric oleoresin	0100	ii	3	2	-	-
Colour	Vegetable carbon	0153		3	2	-	-

Table 2 (continued)

Category	Food additive	INS		As	Pb	Cd	Hg
Acidity regulator	Acetic acid, glacial	0260		-	2	-	-
Acidity regulator	Ammonia solution	0527		-	2	-	-
Acidity regulator	Ammonium carbonate	0503	i	-	2	-	-
Acidity regulator	Ammonium dihydrogen phosphate	0342	i	3	4	-	-
Acidity regulator	Calcium citrates	0333		-	2	-	-
Acidity regulator	Calcium dihydrogen phosphate	0341	i	3	4	-	-
Acidity regulator	Calcium DL-malate	0352	ii	-	2	-	-
Acidity regulator	Calcium hydroxide	0526		-	2	-	-
Acidity regulator	Calcium lactate	0327		-	2	-	-
Acidity regulator	Calcium oxide	0529		-	2	-	-
Acidity regulator	Diammonium hydrogen phosphate	0342	ii	3	4	-	-
Acidity regulator	Dicalcium pyrophosphate	0450	vi	3	4	-	-
Acidity regulator	Dipotassium hydrogen phosphate	0340	ii	3	4	-	-
Acidity regulator	Disodium hydrogen phosphate	0339	ii	3	4	-	-
Acidity regulator	Disodium pyrophosphate	0450	i	3	4	-	-
Acidity regulator	Hydrochloric acid	0507		-	1	-	-
Acidity regulator	Magnesium hydroxide carbonate	0504	ii	-	2	-	-
Acidity regulator	Magnesium hydroxide	0528		-	2	-	-
Acidity regulator	Magnesium DL-lactate	0329		-	2	-	-
Acidity regulator	Phosphoric acid	0338		3	4	-	-
Acidity regulator	Potassium carbonate	0501	i	-	2	-	-
Acidity regulator	Potassium dihydrogen citrate	0332		-	2	-	-
Acidity regulator	Potassium hydrogen carbonate	0501	ii	-	2	-	-
Acidity regulator	Potassium hydroxide	0525		-	2	-	-
Acidity regulator	Sodium acetate	0262	I	-	2	-	-
Acidity regulator	Sodium carbonate	0500	I	-	2	-	-
Acidity regulator	Sodium dihydrogen citrate	0331	i	-	2	-	-
Acidity regulator	Sodium dihydrogen phosphate	0339	i	3	4	-	-
Acidity regulator	Sodium DL-malate	0350	ii	-	2	-	-
Acidity regulator	Sodium fumarate	0365		-	2	-	-
Acidity regulator	Sodium hydrogen carbonate	0500	ii	-	2	-	-
Acidity regulator	Sodium hydrogen DL-malate	0350	i	-	2	-	-
Acidity regulator	Sodium hydroxide	0524		-	2	-	-
Acidity regulator	Sodium sesquicarbonate	0500	iii	-	2	-	-
Acidity regulator	Sulfuric acid	0513		-	2	-	-
Acidity regulator	Triammonium citrate	0380		-	2	-	-
Acidity regulator	Tripotassium citrate	0332	ii	-	2	-	-
Acidity regulator	Tripotassium phosphate	0340	iii	3	4	-	-
Acidity regulator	Trisodium citrate	0331	iii	-	2	-	-
Acidity regulator	Trisodium phosphate	0339	iii	3	4	-	-

INS, International Numbering System

4. Flavouring agents

4.1 Flavouring agents evaluated by the Procedure for the Safety Evaluation of Flavouring Agents

Six groups of flavouring agents were evaluated using the Procedure for the Safety Evaluation of Flavouring Agents as outlined in Figure 1 (Annex 1, references *116, 122, 131, 137, 143, 149* and *154*). In applying the Procedure, the chemical is first assigned to a structural class as identified by the Committee at its forty-sixth meeting (Annex 1, reference *122*). The structural classes are as follows:

- Class I. Flavouring agents that have simple chemical structures and efficient modes of metabolism which would suggest a low order of toxicity by the oral route.
- Class II. Flavouring agents 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. Flavouring agents that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity.

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

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

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

Intake data

Estimates of the intake of flavouring agents by populations typically involve the acquisition of data on the amounts used in food. These data were derived from surveys in Europe and the USA. In Europe, a survey was conducted in 1995 by the International Organization of the Flavour 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.

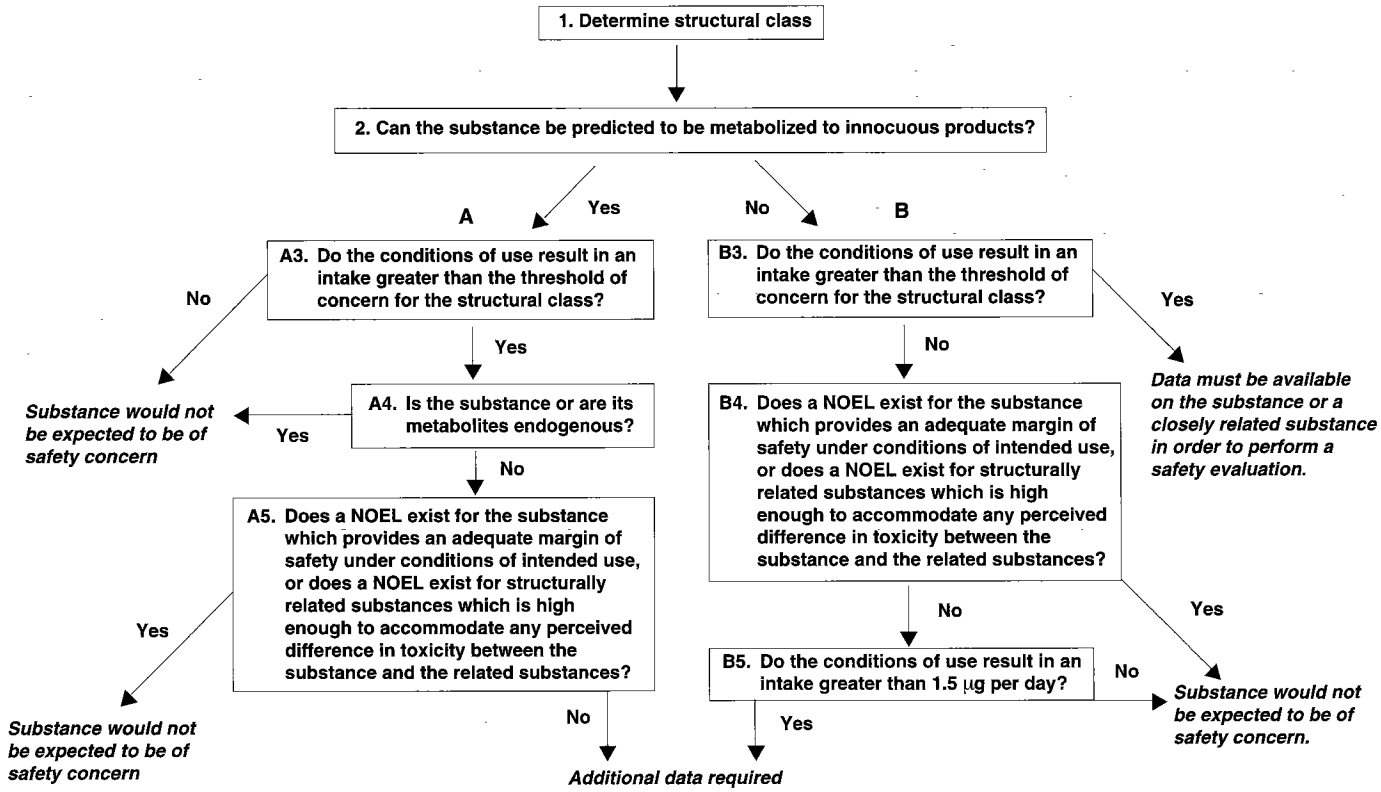


Figure 1
Procedure for the safety evaluation of flavouring agents

Manufacturers were requested to exclude use of flavouring agents in pharmaceutical, tobacco or cosmetic products.

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.

In using the data from these surveys to estimate intakes of flavouring agents, it was assumed that only 60% of the total amount used is reported in Europe and 80% of the amount used is reported in the USA and that the total amount used in food is consumed by only 10% of the population.

$$\text{Intake (}\mu\text{g per person per day)} = \frac{\text{annual volume of production (kg)} \times 10^9\ (\mu\text{g/kg})}{\text{population of consumers} \times 0.6 \text{ or } 0.8 \times 365 \text{ days}}$$

The population of consumers was assumed to be 32×10^6 in Europe and 26×10^6 in the USA.

Several of the flavouring agents that were evaluated at the present meeting were not included in the above surveys or were placed on the market after the surveys were conducted. Intakes of these flavouring agents were estimated on the basis of anticipated use by the manufacturer in the USA, and the standard formula was applied.

4.1.1 *Alicyclic primary alcohols, aldehydes, acids and related esters*

The Committee evaluated a group of 26 flavouring agents that included alicyclic primary alcohols, aldehydes, acids and related esters (see Table 3), using the Procedure for the Safety Evaluation of Flavouring Agents (see Figure 1). The Committee had not evaluated any of these agents previously.

Twenty of the 26 flavouring agents in this group are terpenoid alcohols, aldehydes or carboxylic acids or their related esters. Thirteen are common components of food and have been detected in vanilla, bourbon, rum, mango, rosemary, grapefruit juice, mandarin peel oil and blackberries.

Estimated daily per capita *intake*

The total annual volume of the 26 flavouring agents in this group that is produced is approximately 170 kg in Europe and 130 kg in the USA. None of the agents is produced in an annual volume greater than 55 kg. Most of the total annual volume in Europe is accounted for by (2,2,3-trimethylcyclopent-3-en-1-yl)acetaldehyde (No. 967; campholenic aldehyde), *p*-mentha-

Table 3

Summary of results of safety evaluation of alicyclic primary alcohols, aldehydes, acids and related esters used as flavouring agents

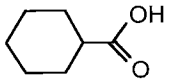
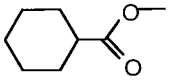
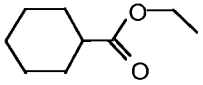
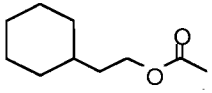
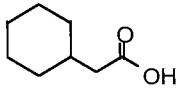
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
Structural class I						
Cyclohexanecarboxylic acid	961	98-89-5 	A3 – No Europe: 0.07 USA: 4	N/R	See note 1	No safety concern
Methyl cyclohexanecarboxylate	962	4630-82-4 	A3 – No Europe: 0.09 USA: 0.01	N/R	See notes 1,2	No safety concern
Ethyl cyclohexanecarboxylate	963	3289-28-9 	A3 – No Europe: ND USA: 0.1	N/R	See notes 1,2	No safety concern
Cyclohexaneethyl acetate	964	21722-83-8 	A3 – No Europe: 1 USA: ND	N/R	See notes 2,3	No safety concern
Cyclohexaneacetic acid	965	5292-21-7 	A3 – No Europe: 0.1 USA: 0.4	N/R	See note 3	No safety concern

Table 3 (continued)

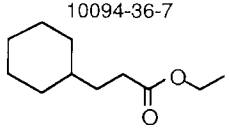
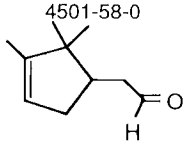
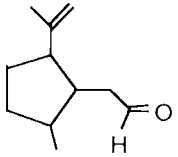
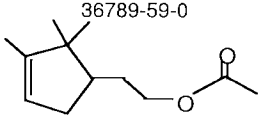
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
Ethyl cyclohexanepropionate	966	10094-36-7 	A3 – No Europe: ND USA: 0.1	N/R	See notes 1,2	No safety concern
2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	967	4501-58-0 	A3 – No Europe: 6 USA: ND	N/R	See note 4	No safety concern
cis-5-Isopropenyl-*cis*-2-methylcyclopentan-1-carboxaldehyde	968	55253-28-6 	A3 – No Europe: 0.01 USA: ND	N/R	See note 4	No safety concern
Campholene acetate	969	36789-59-0 	A3 – No Europe: 0.07 USA: ND	N/R	See notes 2,4	No safety concern

Table 3 (continued)

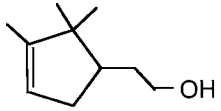
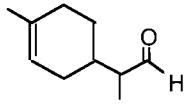
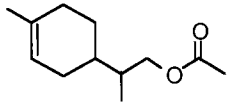
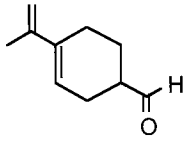
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
α-Campholenic alcohol	970	1901-38-8 	A3 – No Europe: 0.01 USA: ND	N/R	See note 4	No safety concern
p-Menth-1-ene-9-al	971	29548-14-9 	A3 – No Europe: 0.1 USA: ND	N/R	See note 4	No safety concern
1-*p*-Menthen-9-yl acetate	972	17916-91-5 	A3 – No Europe: 1 USA: ND	N/R	See notes 2,4	No safety concern
p-Mentha-1,8-dien-7-al	973	2111-75-3 	A3 – No Europe: 2 USA: 2	N/R	See note 4	No safety concern

Table 3 (continued)

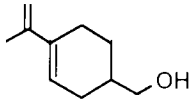
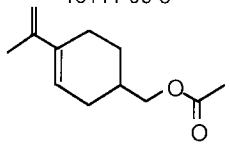
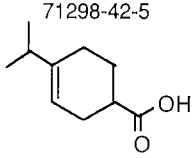
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
p-Mentha-1,8-dien-7-ol	974	536-59-4 	A3 – No Europe: 2 USA: 1	N/R	See note 4	No safety concern
p-Mentha-1,8-dien-7-yl acetate	975	15111-96-3 	A3 – No Europe: 0.4 USA: 0.07	N/R	See notes 2,4	No safety concern
1,2,5,6-Tetrahydrocuminic acid	976	71298-42-5 	A3 – No Europe: 0.01 USA: ND	N/R	See note 1	No safety concern

Table 3 (continued)

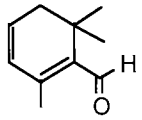
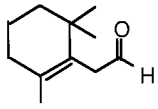
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
2,6,6-Trimethylcyclohexa-1,3-dienyl methanal	977	116-26-7 	B3 – No Europe: 4 USA: 0.07	Yes. The NOELs of 120 mg/kg bw per day for perillyl alcohol in 90-day studies in rats and dogs and NOELs of 10 mg/kg bw per day for α-ionone and β-ionone in a 90-day study in rats are > 2 million and > 200 000 times, respectively, the estimated intake of 2,6,6-trimethylcyclohexa-1,3-dienyl methanal when used as a flavouring agent.		No safety concern
2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde	978	472-66-2 	A3 – No Europe: 0.3 USA: 2	N/R	See note 3.	No safety concern

Table 3 (continued)

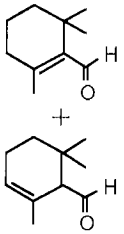
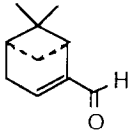
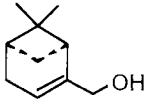
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
2,6,6-Trimethyl-1-cyclohexen-1-carboxaldehyde	979	432-25-7 	A3 – No Europe: 0.4 USA: ND	N/R	See note 1	No safety concern
2-Formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene	980	564-94-3 	A3 – No Europe: 4 USA: 7	N/R	See note 4	No safety concern
Myrtenol	981	515-00-4 	A3 – No Europe: 0.4 USA: 0.03	N/R	See note 4	No safety concern

Table 3 (continued)

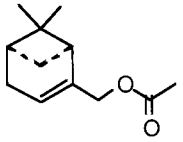
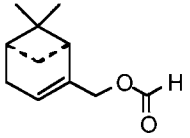
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
Myrtenyl acetate	982	1079-01-2 	A3 – No Europe: 0.3 USA: 0.04	N/R	See note 4	No safety concern
Myrtenyl formate	983	72928-52-0 	A3 – No Europe: 0.4 USA: ND	N/R	See note 4	No safety concern

Table 3 (continued)

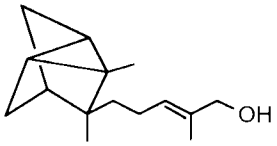
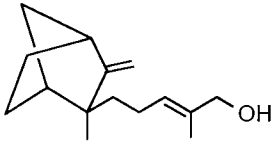
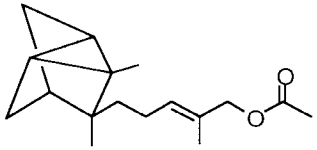
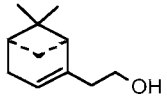
Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
Santalol (α and β)	984	115-71-9  α	A3 – No Europe: 0.04 USA: ND	N/R	See note 4	No safety concern
		77-42-9  β				
Santalyl acetate	985	1323-00-8 	A3 – No Europe: ND USA: 0.01	N/R	See note 4	No safety concern

Table 3 (continued)

Flavouring agent	No.	CAS No. and structure	Steps A3 and B3[a,b] Does intake exceed the threshold for human intake?	Step B4 Adequate margin of safety for the flavouring agent or related substance?	Comments	Conclusion based on current intake
10-Hydroxymethylene-2-pinene	986	128-50-7 	A3 – No Europe: ND USA: 0.01	N/R	See note 4	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported; N/R: not required for evaluation

[a] Step 2: Except for No. 977, all the flavouring agents in this group were predicted to be metabolized to innocuous products.

[b] The threshold for human intake for structural class I is 1800 µg/day. All intake values are expressed in µg/day. The combined intake of all flavouring agents in this group is 22 and 18 µg/person per day in Europe and the USA, respectively.

Notes:

1. Metabolized by β-oxidation, aromatization and conjugation with glycine and glucuronic acid
2. Metabolized by hydrolysis followed by oxidation and/or conjugation
3. Metabolized by β-oxidation and eliminated largely by metabolism via the citric acid cycle
4. Metabolized largely by oxidation of the side-chain to the corresponding carboxylic acid, which is excreted unchanged and as conjugates

1,8-dien-7-al (No. 973; perillaldehyde), *para*-mentha-1,8-dien-7-ol (No. 974; perillyl alcohol), 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal) and 2-formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (No. 980; myrtenal). In the USA, approximately 91% of the total annual volume is accounted for by cyclohexanecarboxylic acid (No. 961), *para*-mentha-1,8-dien-7-al (No. 973; perillaldehyde), 2,6,6-trimethyl-1-cyclohexen-1-acetaldehyde (No. 978; β-cyclocitral) and 2-formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (No. 980; myrtenal). The estimated daily *per capita* intake of 11 of the substances in this group is ≤ 10 μg.

Absorption, distribution, metabolism and elimination

The number of potential pathways of metabolism of alicyclic substances increases as the number and types of functional groups and ring substituents in the molecule increase. The cyclohexane derivatives (carboxylic acids and their related esters) in this group (Nos 961–966) can undergo β-oxidation and subsequent ring cleavage and/or aromatization of the cyclohexane ring and/or can be excreted in urine as cyclohexane carboxylic acid and its glycine and glucuronide conjugates. If there is an even number of carbons in the side-chain, β-oxidative cleavage leads to ring-opened oxygenated metabolites, primarily dicarboxylic acids, which are metabolized via the citric acid cycle. If there is an odd number of carbons in the side-chain, β-oxidative cleavage leads to a cyclohexane carboxylic acid derivative that may subsequently undergo dehydrogenation to yield unsaturated derivatives. The two non-terpenoid substances containing a cyclohexene ring (Nos 978 and 979) would be metabolized and eliminated by similar pathways. The substance with two endocyclic double bonds, 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal), is a structural analogue of dehydrodihydroionol (No. 397), which was evaluated by the Committee at its fifty-first meeting (Annex 1, reference *137*), and, like that agent, cannot be predicted to be metabolized to innocuous products.

The flavouring agents with a cyclopentane or cyclopentene ring (Nos 967–970) also have an oxygenated side-chain, and this is predicted to be the main site of oxidative metabolism prior to excretion of more polar acid metabolites. The processes of side-chain and alicyclic ring oxidation were considered by the Committee at its fifty-first meeting (Annex 1, reference *137*).

Monocyclic terpenoid primary alcohols (e.g., No. 974, perillyl alcohol) and aldehydes (e.g., Nos 971 and 973) would be oxidized to yield the corresponding carboxylic acid, while the esters (Nos 972 and 975) would undergo hydrolysis prior to oxidation. The acid metabolites of the above agents and 1,2,5,6-tetrahydrocuminic acid (No. 976) would be conjugated with glucuronic acid and excreted mainly in the urine. In a minor pathway,

the aldehyde can be reduced to the alcohol and excreted as the glucuronic acid conjugate. If an endocyclic double-bond is present, the flavouring agent or its metabolite could be reduced by the action of gut microflora. The acid metabolite may also undergo aromatization of the ring to yield a hippuric acid derivative. Bicyclic and tricyclic compounds (e.g., Nos 980–986) would undergo similar metabolism to the monocyclic terpenoids and, in addition, may undergo ring oxidation.

Four agents in this group contain an α,β-unsaturated carbonyl group (Nos 973, 977, 979 and 980), which is a structural alert for toxicity. The Committee, at previous meetings, devoted considerable attention to the safety of flavouring agents containing this reactive moiety. The Committee concluded at its fifty-seventh meeting (Annex 1, reference *154*) that the presence of protective processes in cells provides adequate detoxication capacity at the low doses associated with the use of compounds such as flavouring agents. These protective processes include conjugation with glutathione and reduction of the ketone to the corresponding alcohol (followed by conjugation of the alcohol with glucuronic acid).

Application of the Procedure for the Safety Evaluation of Flavouring Agents

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents, the Committee assigned all 26 agents to structural class I.

Step 2. The simple cyclohexane and cyclohexene derivatives (Nos 961–966, 978 and 979), the cyclopentane and cyclopentene compounds (Nos 967–970) and the simple mono-, bi- and tricyclic terpenoid derivatives (Nos 971–976 and 980–986) were predicted to be metabolized to innocuous products. The evaluation of these substances therefore proceeded *via* the A (left-hand) side of the decision tree (see Figure 1). The remaining substance, 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal), cannot be predicted to be metabolized to innocuous products and was therefore evaluated *via* the B (right-hand) side of the decision tree.

Step A3. The daily *per capita* intakes of each of the 25 flavouring agents evaluated at this step were below the daily human intake thresholds for structural class I (1800 μg per person), indicating that they present no safety concern when consumed as flavouring agents at current estimated levels.

Step B3. The daily *per capita* intake of the monocyclic substance with two endocyclic double-bonds evaluated at this step, 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal), was below the threshold for daily human intake of compounds of structural class I, and its evaluation therefore proceeded to step B4.

Step B4. As the agent evaluated at this step, 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal), is structurally related to perillyl alcohol

(No. 974), data on the toxicity of perillyl alcohol were used to evaluate its safety. Perillyl alcohol given by intragastric gavage changed the weights of several organs in female rats when given at 400 mg/kg bw per day, but not at 120 mg/kg bw per day, in a 90-day study; changes in organ weights were not reported in male rats. Doses of 40, 120 and 400 mg/kg bw per day produced hyperexcitability and salivation, which the authors considered may have been due to its irritating properties. A daily dose of 120 mg/kg bw was well tolerated by dogs in a 90-day study. The daily intake of 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal) is 0.052 μg/kg bw in Europe and 0.001 μg/kg bw in the USA. The margin of safety between these intakes and 120 mg/kg bw per day is > 2 000 000. The compound also shares structural similarities with α-ionone and β-ionone (Nos 388 and 389), which were evaluated by the Committee at its fifty-first meeting (Annex 1, reference *137*). The NOELs for these compounds were 10 mg/kg bw per day in a 90-day study in rats, providing a margin of safety of about 200 000. Therefore, 2,6,6-trimethylcyclohexa-1,3-dienyl methanal (No. 977; safranal) would not be a safety concern.

Consideration of combined intakes

In the unlikely event that all 26 flavouring agents were to be consumed concurrently on a daily basis, the estimated combined intake would not exceed the human intake threshold for structural class I. Therefore, the combined intake of the agents in this group would not represent a safety concern.

Conclusions

The Committee concluded that none of the 26 flavouring agents in this group of alicyclic primary alcohols, aldehydes, acids and related esters would present a safety concern at the current estimated levels of intake.

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

4.1.2 *Phenethyl alcohol, aldehyde, acid and related acetals and esters*

The Committee evaluated 43 flavouring agents that are derivatives of phenethyl alcohol (No. 987) and phenoxyethyl alcohol (see Table 4). The group includes 39 phenethyl derivatives, comprising phenylacetaldehyde (No. 1002), phenylacetic acid (No. 1007) and structurally related esters and acetals. The group also includes four phenoxyethyl alcohol derivatives: phenoxyacetic acid (No. 1026), the sodium salt of a structurally related phenoxyacetic acid (No. 1029), a phenoxyethyl ester (No. 1027) and a phenoxyacetic acid ester (No. 1028). The evaluations were conducted with the Procedure for the Safety Evaluation of Flavouring Agents (see Figure 1). None of these agents has previously been evaluated by the Committee.

Table 4

Summary of results of safety evaluations of phenethyl alcohol, aldehyde, acid, and related acetals and esters [a]

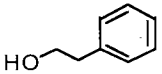
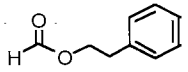
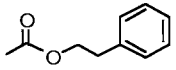
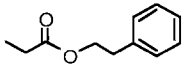
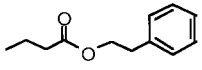
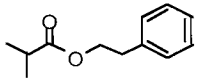
Flavouring agent	No.	CAS No. and structure	Step A3[b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Structural class I							
Phenethyl alcohol	987	60-12-8 	No Europe: 1400 USA: 330	N/R	N/R	See note 1.	No safety concern
Phenethyl formate	988	104-62-1 	No Europe: 2 USA: 30	N/R	N/R	See note 2.	No safety concern
Phenethyl acetate	989	103-45-7 	No Europe: 100 USA: 60	N/R	N/R	See note 2.	No safety concern
Phenethyl propionate	990	122-70-3 	No Europe: 1 USA: 3	N/R	N/R	See note 2.	No safety concern
Phenethyl butyrate	991	103-52-6 	No Europe: 30 USA: 30	N/R	N/R	See note 2.	No safety concern
Phenethyl isobutyrate	992	103-48-0 	No Europe: 20 USA: 60	N/R	N/R	See note 2.	No safety concern

Table 4 (contd)

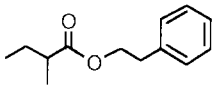
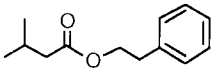
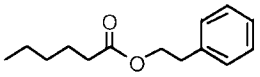
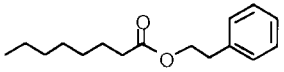
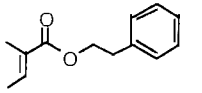
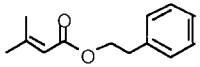
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Phenethyl 2-methylbutyrate	993	24817-51-4 	No Europe: 0.4 USA: ND	N/R	N/R	See note 2.	No safety concern
Phenethyl isovalerate	994	140-26-1 	No Europe: 100 USA: 30	N/R	N/R	See note 2.	No safety concern
Phenethyl hexanoate	995	6290-37-5 	No Europe: 10 USA: 2	N/R	N/R	See note 2.	No safety concern
Phenethyl octanoate	996	5457-70-5 	No Europe: 30 USA: 0.1	N/R	N/R	See note 2.	No safety concern
Phenethyl tiglate	997	55719-85-2 	No Europe: 0.3 USA: 1	N/R	N/R	See note 2.	No safety concern
Phenethyl senecioate	998	42078-65-9 	No Europe: 2 USA: ND	N/R	N/R	See note 2.	No safety concern

Table 4 (contd)

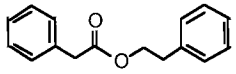
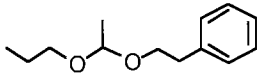
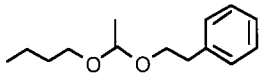
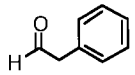
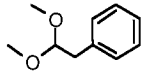
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Phenethyl phenylacetate	999	102-20-5 	No Europe: 40 USA: 80	N/R	N/R	See note 3.	No safety concern
Acetaldehyde phenethyl propyl acetal	1000	7493-57-4 	No Europe: 0.1 USA: 6	N/R	N/R	See note 4.	No safety concern
Acetaldehyde butyl phenethyl acetal	1001	64577-91-9 	No Europe: 0.01 USA: ND	N/R	N/R	See note 4.	No safety concern
Phenylacetaldehyde	1002	122-78-1 	No Europe: 40 USA: 60	N/R	N/R	See note 5.	No safety concern
Phenylacetaldehyde dimethyl acetal	1003	101-48-4 	No Europe: 20 USA: 40	N/R	N/R	See note 6.	No safety concern

Table 4 (contd)

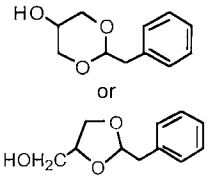
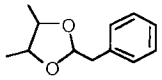
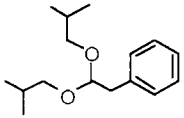
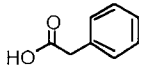
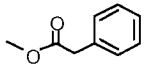
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Phenylacetaldehyde glyceryl acetal	1004	29895-73-6 	No Europe: 0.1 USA: 1	N/R	N/R	See note 6.	No safety concern
Phenylacetaldehyde 2,3-butylene glycol acetal	1005	5468-06-4 	No Europe: ND USA: 1	N/R	N/R	See note 6.	No safety concern
Phenylacetaldehyde diisobutylacetal	1006	68345-22-2 	No Europe: 30 USA: 0.4	N/R	N/R	See note 6.	No safety concern
Phenylacetic acid	1007	103-82-2 	No Europe: 290 USA: 60	N/R	N/R	See note 7.	No safety concern
Methyl phenylacetate	1008	101-41-7 	No Europe: ND USA: 20	N/R	N/R	See note 8.	No safety concern

Table 4 (contd)

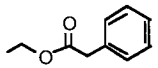
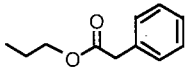
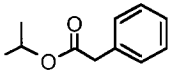
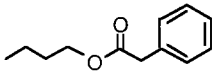
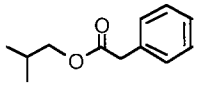
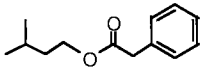
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Ethyl phenylacetate	1009	101-97-3 	No Europe: 130 USA: 20	N/R	N/R	See note 8.	No safety concern
Propyl phenylacetate	1010	4606-15-9 	No Europe: ND USA: 0.3	N/R	N/R	See note 8.	No safety concern
Isopropyl phenylacetate	1011	4861-85-2 	No Europe: 0.07 USA: ND	N/R	N/R	See note 8.	No safety concern
Butyl phenylacetate	1012	122-43-0 	No Europe: 3 USA: 3	N/R	N/R	See note 8.	No safety concern
Isobutyl phenylacetate	1013	102-13-6 	No Europe: 20 USA: 20	N/R	N/R	See note 8.	No safety concern
Isoamyl phenylacetate	1014	102-19-2 	No Europe: 30 USA: 30	N/R	N/R	See note 8.	No safety concern

Table 4 (contd)

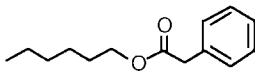
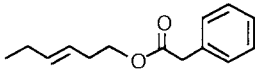
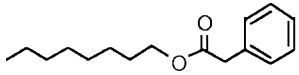
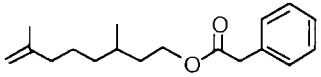
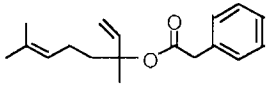
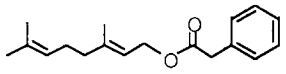
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Hexyl phenylacetate	1015	5421-17-0 	No Europe: 8 USA: ND	N/R	N/R	See note 8.	No safety concern
3-Hexenyl phenylacetate	1016	42436-07-7 	No Europe: 1 USA: 0.05	N/R	N/R	See note 8.	No safety concern
Octyl phenylacetate	1017	122-45-2 	No Europe: 0.004 USA: 0.006	N/R	N/R	See note 8.	No safety concern
Rhodinyl phenylacetate	1018	10486-14-3 	No Europe: 0.001 USA: ND	N/R	N/R	See note 9.	No safety concern
Linalyl phenylacetate	1019	7143-69-3 	No Europe: 0.09 USA: ND	N/R	N/R	See note 9.	No safety concern
Geranyl phenylacetate	1020	102-22-7 	No Europe: 2 USA: 2	N/R	N/R	See note 9.	No safety concern

Table 4 (contd)

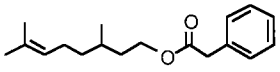
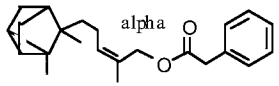
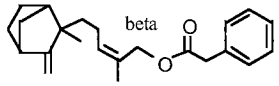
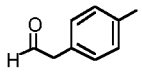
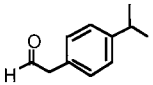
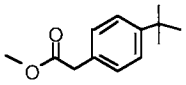
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Citronellyl phenylacetate	1021	139-70-8 	No Europe: 1 USA: 2	N/R	N/R	See note 9.	No safety concern
Santalyl phenylacetate	1022 α	1323-75-7 	No Europe: ND USA: 1	N/R	N/R	See note 9.	No safety concern
	β						
p-Tolyacetaldehyde	1023	104-09-6 	No Europe: 6 USA: 3	N/R	N/R	See note 5.	No safety concern
p-Isopropylphenyl-acetaldehyde	1024	4395-92-0 	No Europe: 0.1 USA: 0.01	N/R	N/R	See note 5.	No safety concern
Methyl *para-tert*-butylphenylacetate	1025	3549-23-3 	No Europe: 20 USA: 20	N/R	N/R	See note 8.	No safety concern

Table 4 (contd)

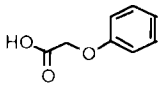
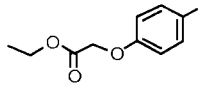
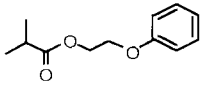
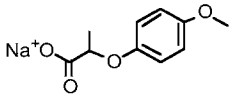
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Structural class III							
Phenoxyacetic acid	1026	122-59-8 	No Europe: 40 USA: 0.1	N/R	N/R	See note 10.	No safety concern
Ethyl (*p*-tolyl-oxy)acetate	1027	67028-40-4 	No Europe: 0.1 USA: ND	N/R	N/R	See note 11.	No safety concern
2-Phenoxyethyl isobutyrate	1028	103-60-6 	Yes Europe: 2 USA: 110	No	Yes. The NOEL of 15 mg/kg bw per day for the related chemical No. 1027 and the NOEL of 250 mg/kg bw per day for the related chemical No. 1029 are >1000 times the estimated intake of 2-phenoxyethyl isobutyrate when used as a flavouring agent.	See note 12.	No safety concern

Table 4 (contd)

Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Step A5 Adequate margin of safety for the flavouring agent or related chemical?	Comments	Conclusion based on current intake
Sodium 2-(4-methoxy-phenoxy)propanoate	1029	13794-15-5 	No Europe: ND USA: 6	N/R	N/R	See note 13.	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported; N/R: not required for evaluation.

[a] Step 2: All the flavouring agents in this group were predicted to be metabolized to innocuous products.

[b] The thresholds for human intake for classes I and III are 1800 µg/day and 90 µg/day, respectively. All intake values are expressed in µg/person per day. The combined intakes of flavouring agents in class I are 2300 and 920 µg/person per day in Europe and the USA, respectively. The combined intakes of flavouring agents in class III are 42 and 120 µg/person per day in Europe and the USA, respectively.

Notes:

1. Oxidized to phenylacetic acid and either completely oxidized or conjugated and excreted primarily in the urine
2. Hydrolysed to phenethyl alcohol (see note 1) and the corresponding acid, which is further oxidized to carbon dioxide and water
3. Hydrolysed to phenethyl alcohol (see note 1) and phenylacetic acid (see note 7)
4. Hydrolysed to phenethyl alcohol (see note 1) and the corresponding aldehyde, which is further oxidized to carbon dioxide and water
5. Phenylacetaldehyde derivative is oxidized to phenylacetic acid derivative (see note 7).
6. Hydrolysed to phenyacetaldehyde (see note 5) and the corresponding alcohol, which is further oxidized to carbon dioxide and water
7. Phenylacetic acid is excreted as the glutamine acid conjugate.
8. Hydrolysed to phenylacetic acid derivative (see note 7) and the corresponding alcohol, which is completely oxidized.
9. Hydrolysed to phenylacetic acid (see note 7) and terpene alcohol, which is further oxidized to a polar, excretable metabolite.
10. Excreted unchanged in the urine
11. Hydrolysed to *para*-tolyloxy acetic acid and ethanol; the acid is excreted unchanged.
12. Hydrolysed to isobutyric acid and 2-phenoxyethanol, which is oxidized to phenoxyacetic acid and excreted unchanged in the urine.
13. Excreted mainly unchanged and as the *O*-demethylated metabolite, (±)2-(4-hydroxyphenoxy) propionic acid.

Twenty of the 39 flavouring agents in this group are natural components of foods. Phenethyl alcohol has a mild rose aroma. The agents have been detected in a wide range of products; for example, the parent alcohol and its derivatives have been detected in beans, fruits, vegetables, cheeses, milk, oils and alcoholic and non-alcoholic beverages. Only one phenoxyacetic acid derivative is a natural component of food: sodium 2-(4-methoxyphenoxy)propanoate (No. 1029) has been detected in coffee.

Estimated daily per capita *intake*

The total annual volume of production of the 43 phenethyl alcohol and phenoxyethyl alcohol derivatives in this group is approximately 17 000 kg in Europe and 7800 kg in the USA. About 75% and 45% of the total annual volume in Europe and the USA, respectively, is accounted for by use of phenethyl alcohol (No. 987), its corresponding acetate ester (No. 989) and phenylacetic acid (No. 1007). The total annual volume of production of the four derivatives of phenoxyethyl alcohol (Nos 1026–1029) is approximately 260 kg in Europe and 870 kg in the USA, accounting for about 2% and 11% of the total annual volumes in Europe and the USA, respectively.

Five flavouring agents in the group account for the highest estimated intakes. These are 1400 mg/day for phenethyl alcohol (No. 987), 290 μg/day for phenylacetic acid (No. 1007), 130 μg/day for ethyl phenylacetate (No. 1009) and 100 μg/day for phenethyl acetate (No. 989) and for phenethyl isovalerate (No. 994) in Europe and 330 μg/day for phenethyl alcohol (No. 987) and 110 μg/day for phenoxyethyl isobutyrate (No. 1028) in the USA. The intakes of all the other flavouring agents in the group ranged from 0.001 to 80 μg/day, the intake of about 70% of them being less than 25 μg/day.

Absorption, distribution, metabolism and elimination

Phenethyl and phenylacetate esters and phenyacetaldehyde acetals are rapidly hydrolysed in vivo to yield phenethyl alcohol (No. 987), phenylacetic acid (No. 1007) and phenylacetaldehyde (No. 1002), respectively. Phenethyl alcohol and phenylacetaldehyde are both oxidized to phenylacetic acid, which is conjugated and excreted primarily in the urine. Similarly, the phenoxyethyl and phenoxyacetate esters, 2-phenoxyethyl isobutyrate (No. 1028) and ethyl (*para*-tolyloxy)acetate (No. 1027), respectively, are anticipated to be hydrolysed to their component acids and alcohols. Phenoxyethyl alcohol is rapidly oxidized to phenoxyacetic acid, which in turn is rapidly absorbed and excreted primarily unchanged in the urine. Sodium 2-(4-methoxyphenoxy)propanoate (No. 1029) is also rapidly absorbed and excreted primarily unchanged, with a small amount of the *O*-demethylated metabolite, (±)2-(4-hydroxyphenoxy) propionic acid. Therefore, all the flavouring agents in this group were predicted to hydrolyse and/or oxidize

to yield phenylacetic acid or a phenoxyacetic acid derivative that is excreted either free or in conjugated form.

Application of the Procedure for the Safety Evaluation of Flavouring Agents

Step 1. In applying the Procedure, the Committee assigned phenylacetic acid (No. 1007) to structural class I because it is a normal component of human urine. The other 38 phenethyl alcohol derivatives were also assigned to structural class I because they are simple aromatic compounds with a primary oxygenated functional group.

The Committee assigned all four phenoxyacetic acid derivatives in this group to structural class III. These are aromatic substances with an ether linkage between the benzene ring and an unsaturated side-chain with a primary oxygenated functional group.

Step 2. All the flavouring agents in this group were predicted to be metabolized to innocuous products. Their evaluation therefore proceeded via the A (left-hand) side of the decision tree.

Step A3. The estimated daily intakes of each of the 39 flavouring agents in structural class I are below the threshold for daily human intake for that class (1800 μg per person). According to the Procedure, the safety of these 39 flavouring agents raises no concern when they are consumed at currently estimated levels.

The estimated daily intakes of three of the four flavouring agents in structural class III are below the threshold for daily human intake for that class (90 μg per person). According to the Procedure, the safety of these three flavouring agents (Nos 1026, 1027 and 1029) raises no concern when they are consumed at their currently estimated levels. The daily intake of 2-phenoxyethyl isobutyrate (No. 1028) in the USA (110 mg /person) exceeds the threshold for daily human intake for compounds in structural class III (90 mg per person). Accordingly, the evaluation of this substance proceeded to step A4.

Step A4. 2-Phenoxyethyl isobutyrate (No. 1028) is not endogenous. Therefore, its evaluation proceeded to step A5.

Step A5. Although no NOEL was available for 2-phenoxyethyl isobutyrate (No. 1028), data were available on the toxicity of two structurally related flavouring agents in this group (Nos 1027 and 1029). The NOEL of 15 mg/kg bw per day for ethyl (*para*-tolyloxy)acetate (No. 1027) in a 90-day dietary study in rats and the NOEL of 250 mg/kg bw per day for sodium 2-(4-methoxyphenoxy)propanoate (No. 1029) in another 90-day dietary study in rats provide adequate margins of safety (> 1000 times) in relation to the estimated daily per capita intake of 2-phenoxyethyl isobutyrate (No. 1028) in Europe (0.03 μg/kg bw) and the USA (2 μg/kg bw). The Committee therefore concluded that the safety of this agent would not be a concern.

Consideration of combined intakes from use as flavouring agents

In the unlikely event that all 39 of the phenethyl alcohol derivatives (Nos 987–1025) were consumed concurrently on a daily basis, the estimated combined intake would exceed the threshold for daily human intake of compounds in structural class I (1800 mg per person). At the levels of intake associated with their use as flavouring agents, all 39 agents are expected to be metabolized efficiently, without saturating metabolic pathways. The same holds true for two of the four flavouring agents in structural class III: the estimated combined intakes of phenoxyacetic acid (No. 1026) and 2-phenoxyethyl isobutyrate (No. 1028) would exceed the threshold for daily human intake of compounds in structural class III (90 mg per person). At the levels of intake associated with their use as flavouring agents, both agents are expected to be metabolized efficiently, without saturating metabolic pathways. The other two agents, ethyl (*para*-tolyloxy)acetate (No. 1027) and sodium 2-(4-methoxyphenoxy)propanoate (No. 1029), are not converted to a common metabolite, and there is no need to consider their combined intake from use as flavouring agents. On the basis of the evaluation of all the data, combined intake would raise no safety concern.

Conclusions

The Committee concluded that none of the 43 flavouring agents in this group would present a safety concern at current estimated levels of intake. No data on toxicity were required for application of the Procedure to 42 of the 43 flavouring agents, as they were predicted to be metabolized to innocuous agents and the estimated intakes were below the human intake threshold associated with the relevant structural class. Data on the toxicity of related agents were used to evaluate 2-phenoxyethyl isobutyrate (No. 1028). Data on the toxicity and metabolism of phenethyl alcohol, phenylacetaldehyde, phenylacetic acid, phenoxyethanol and phenoxyacetic acid and related agents were consistent with the results of the safety evaluation.

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

4.1.3 *Sulfur-containing heterocyclic compounds*

The Committee evaluated a group of 30 flavouring agents comprising sulfur-containing heterocyclic compounds (see Table 5) using the Procedure for the Safety Evaluation of Flavouring Agents (see Figure 1). The group is composed of both five- and six-member S-containing aromatic and non-aromatic heterocyclic compounds, including thiazole itself and derivatives of thiazole, dithiazine, thiazoline and thiophene. Thiazole is a five-membered aromatic heterocyclic compound containing sulfur and nitrogen atoms in the 1- and 3-ring positions, respectively (Nos 1030–1044 and 1054–1057).

Table 5

Summary of the results of safety evaluations of sulfur-containing heterocyclic compounds[a]

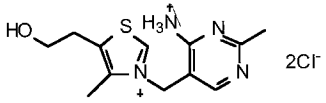
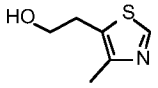
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
Structural class II							
Thiamine hydrochloride	1030	67-03-8 	Yes[c] A side	Yes Europe: 2900 USA: 1200	No	A5 Yes. The NOEL of 36 mg/kg bw per day is > 500 times the estimated intake of thiamine hydrochloride when used as a flavouring agent.	No safety concern
4-Methyl-5-thiazoleethanol	1031	137-00-8 	Yes[d] A side	No Europe: 170 USA: 380	N/R	N/R	No safety concern
Thiazole	1032	288-47-1 	No B side	No Europe: 0.01 USA: 0.07	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 900 000 times the estimated intake of thiazole when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

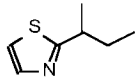
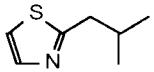
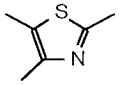
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-(1-Methylpropyl)-thiazole	1033	18277-27-5 	No B side	No Europe: 0.03 USA: 0.01	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 1 million times the estimated intake of 2-(1-methyl-propyl)-thiazole when used as a flavouring agent.	No safety concern
2-Isobutylthiazole	1034	18640-74-9 	No B side	No Europe: 3 USA: 0.4	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is 10 000 times the estimated intake of 2-isobutylthiazole when used as a flavouring agent.	No safety concern
4,5-Dimethyl-thiazole	1035	3581-91-7 	No B side	No Europe: 0.2 USA: 0.4	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 200 000 times the estimated intake of 4,5-dimethyl-thiazole when used as a flavouring agent.	No safety concern
2,4,5-Trimethyl-thiazole	1036	13623-11-5 	No B side	No Europe: 1 USA: 0.3	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 90 000 times the estimated intake of 2,4,5-trimethyl-thiazole when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

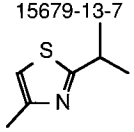
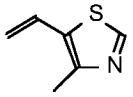
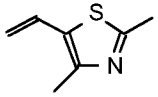
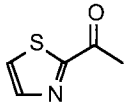
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Isopropyl-4-methylthiazole	1037	15679-13-7 	No B side	No Europe: 22 USA: 10	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 2000 times the estimated intake of 2-isopropyl-4-methylthiazole when used as a flavouring agent.	No safety concern
4-Methyl-5-vinylthiazole	1038	1759-28-0 	No B side	No Europe: 2 USA: 0.2	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 20 000 times the estimated intake of 4-methyl-5-vinylthiazole when used as a flavouring agent.	No safety concern
2,4-Dimethyl-5-vinylthiazole	1039	65505-18-2 	No B side	No Europe: ND USA: 0.007	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day is > 9 million times the estimated intake of 2,4-dimethyl-5-vinylthiazole when used as a flavouring agent.	No safety concern
2-Acetylthiazole	1041	24295-03-2 	No B side	No Europe: 11 USA: 10	N/R	B5 Yes. The NOEL of 50 mg/kg bw per day is > 200 000 times the estimated intake of 2-acetylthiazole when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

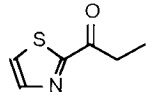
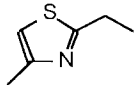
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Propionylthiazole	1042	43039-98-1 	No B side	No Europe: ND USA: 0.2	N/R	B5 Yes. The NOEL of 50 mg/kg bw per day for the related flavouring agent No. 1041 is > 10 million times the estimated intake of 2-propionylthiazole when used as a flavouring agent.	No safety concern
4-Methylthiazole	1043	693-95-8 	No B side	No Europe: 0.1 USA: 0.05	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 400 000 times the estimated intake of 4-methylthiazole when used as a flavouring agent.	No safety concern
2-Ethyl-4-methylthiazole	1044	15679-12-6 	No B side	No Europe: 4 USA: 1	N/R	B5 Yes. The NOEL of 0.92 mg/kg bw per day for the related flavouring agent No. 1039 is > 10 000 times the estimated intake of 2-ethyl-4-methylthiazole when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

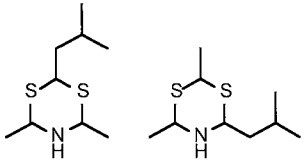
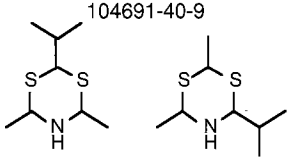
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Isobutyl-4,6-dimethyldihydro-1,3,5-dithiazine and 4-isobutyl-2,6-dimethyl-dihydro-1,3,5-dithiazine (mixture)	1046	101517-87-7 101517-86-6  18% 62%	No B side	No Europe: 0.1 USA: 0.05	N/R	B5 Yes. The NOEL of 11 mg/kg bw per day is > 5 million times the estimated intake of a mixture of 2-isobutyl-4,6-dimethyl and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine when used as a flavouring agent.	No safety concern
2-Isopropyl-4,6-dimethyl 2,6-dimethyldihydro-1,3,5-dithiazine and 4-isopropyl-2,6-dimethyl-dihydro-1,3,5-dithiazine (mixture)	1047	104691-41-0 104691-40-9  27% 44%	No B side	No Europe: ND USA: 0.07	N/R	B5 Yes. The NOEL of 11 mg/kg bw per day is > 10 million times the estimated intake of a mixture of 2-isopropyl-4,6-dimethyl and 4-isopropyl-2,6-dimethyldihydro-1,3,5-dithiazine when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

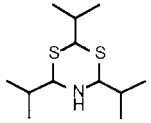
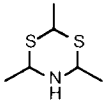
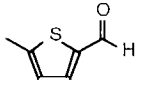
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2,4,6-Triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine	1048	74595-94-1 	No B side	No Europe: ND USA: 2.6	N/R	B5 Yes. The NOEL of 11 mg/kg bw per day for the related flavouring agent No. 1046 is > 200 000 times the estimated intake of 2,4,6-triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine when used as a flavouring agent.	No safety concern
2,4,6-Trimethyl-dihydro-4*H*-1,3,5-dithiazine	1049	638-17-5 	No B side	No Europe: ND USA: 3.3	N/R	B5 Yes. The NOEL of 11 mg/kg bw per day for the related flavouring agent No. 1046 is > 5 million times the estimated intake of 2,4,6-trimethyldihydro-4*H*-1,3,5-dithiazine when used as a flavouring agent.	No safety concern
5-Methyl-2-thio-phenecarboxy-aldehyde	1050	13679-70-4 	No B side	No Europe: 1 USA: 0.01	N/R	B5 Yes. The NOEL of 290 mg/kg bw per day for the related flavouring agent No. 1053 is > 20 million times the estimated intake of 5-methyl-2-thiophene-carboxyaldehyde when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

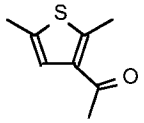
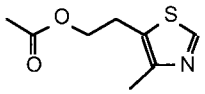
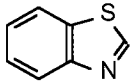
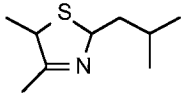
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
3-Acetyl-2,5-dimethylthiophene	1051	2530-10-1 	No B side	No Europe: 22 USA: 0.2	N/R	B5 Yes. The NOEL of 290 mg/kg bw per day for the related flavouring agent No. 1053 is > 700 000 times the estimated intake of 3-acetyl-2,5-dimethylthiophene when used as a flavouring agent.	No safety concern
4-Methyl-5-thiazoleethanol acetate	1054	656-53-1 	Yes[e] A side	No Europe: 10 USA: 3	N/R	N/R	No safety concern
Structural class III							
Benzothiazole	1040	95-16-9 	No B side	No Europe: 1 USA: 0.2	N/R	B5 Yes. The NOEL of 5.1 mg/kg bw per day is > 20 000 times the estimated intake of benzothiazole when used as a flavouring agent.	No safety concern
4,5-Dimethyl-2-isobutyl-3-thiazoline	1045	65894-83-9 	No B side	No Europe: 0.01 USA: 4	N/R	B5 Yes. The NOEL of 1.2 mg/kg bw per day for the related flavouring agent No. 1059 is > 10 000 times the estimated intake of 4,5-dimethyl-2-isobutyl-3-thiazoline when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

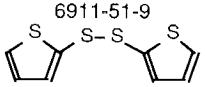
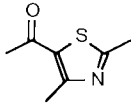
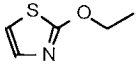
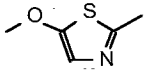
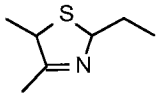
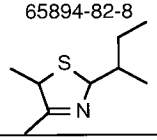
Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Thienyl mercaptan	1052	7774-74-5 	No B side	No Europe: 0.01 USA: 0.03	N/R	B5 Yes. The NOEL of 290 mg/kg bw per day for the related flavouring agent No. 1053 is > 700 million times the estimated intake of 2-thienyl mercaptan when used as a flavouring agent.	No safety concern
2-Thienyl disulfide	1053	6911-51-9 	No B side	No Europe: ND USA: 0.07	N/R	B5 Yes. The NOEL of 290 mg/kg bw per day is > 200 million times the estimated intake of 2-thienyl disulfide when used as a flavouring agent.	No safety concern
2,4-Dimethyl-5-acetylthiazole	1055	38205-60-6 	No B side	No Europe: 0.01 USA: 2	N/R	B5 Yes. The NOEL of 24 mg/kg bw per day is > 10 million times the estimated intake of 2,4-dimethyl-5-acetylthiazole when used as a flavouring agent.	No safety concern
2-Ethoxythiazole	1056	15679-19-3 	No B side	No Europe: 0.01 USA: 0.12	N/R	B5 Yes. The NOEL of 50 mg/kg bw per day for the related flavouring agent No. 1041 is > 20 million times the estimated intake of 2-ethoxythiazole when used as a flavouring agent.	No safety concern

Table 5 *(continued)*

Flavouring agent	No.	CAS No. and structure	*Step 2* Predicted to be metabolized to innocuous products?	*Step A3 /B3*[a,b] Does intake exceed threshold for structural class?	*Step A4* Is the flavouring agent or are its metabolites endogenous?	*Step A5 / B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Methyl-5-methoxythiazole	1057	38205-64-0 	No B side	No Europe: ND USA: 0.01	N/R	B5 Yes. The NOEL of 8.6 mg/kg bw per day is > 40 million times the estimated intake of 2-methyl-5-methoxythiazole when used as a flavouring agent.	No safety concern
4,5-Dimethyl-2-ethyl-3-thiazoline	1058	76788-46-0 	No B side	No Europe: ND USA: 0.01	N/R	B5 Yes. The NOEL of 1.2 mg/kg bw per day for the related flavouring agent No. 1059 is > 6 million times the estimated intake of 4,5-dimethyl-2-ethyl-3-thiazoline when used as a flavouring agent.	No safety concern
2-(2-Butyl)-4,5-dimethyl-3-thiazoline	1059	65894-82-8 	No B side	No Europe: ND USA: 5	N/R	B5 Yes. The NOEL of 1.2 mg/kg bw per day is > 10 000 times the estimated intake of 2-(2-butyl)-4,5-dimethyl-3-thiazoline when used as a flavouring agent.	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported; N/R: not required for evaluation

[a] Step 1. Twenty-one flavouring agents are in structural class II and nine flavouring agents are in structural class III.

[b] The thresholds for human intake for structural classes II and III are 540 µg/day and 90 µg/day, respectively. All intake values are expressed in µg/day. The combined per capita intake of flavouring agents in structural class II is 3100 µg/day in Europe and 1600 µg/day in the USA. The combined per capita intake of flavouring agents in structural class III is 1 µg/day in Europe and 11 µg/day in the USA.

[c] Enzymatically cleaved to yield 4-methyl-5-thiazoleethanol (No. 1031) and 2-methyl-4-amino-5-hydroxymethylpyrimidine. The thiazole and pyrimidine fragments are further oxidized to yield 4-methylthiazole-4-acetic acid and the 5-pyrimidine carboxylic acid derivative, respectively, which, together with thiamine, are excreted in the urine. Can also be converted to 2-methyl-4-amino-5-formylaminopyrimidine and thiamine acetic acid.

[d] Oxidized to yield 4-methylthiazole-4-acetic acid and excreted in the urine (See note c)

[e] Hydrolysed to yield 4-methylthiazole-4-acetic acid and excreted in urine (See note c)

Dithiazine is a six-membered non-aromatic heterocyclic compound containing two sulfur atoms and one nitrogen atom in the 1-, 3- and 5-positions, respectively (Nos 1046–1049). Thiazoline (partially reduced thiazole) is a five-membered non-aromatic heterocyclic compound containing sulfur and nitrogen atoms in the 1- and 3-positions, respectively (Nos 1045, 1058 and 1059). Thiophene is a five-membered aromatic heterocyclic compound containing a sulfur atom in the 1-position (Nos 1050–1053). Except for thiazole (No. 1032), all the flavouring agents in this group are ring-substituted with one or more of the following functional groups: alkyl, alkenyl, aryl, alcohol, keto, thiol and disulfide.

The Committee has not previously evaluated any of the members of this group.

Eighteen flavouring agents in the group have been detected as natural components of food, and quantitative data have been reported on the natural occurrence of eight agents (Nos 1032, 1034, 1036, 1040, 1041, 1043 and 1050). The foods in which one or more of these flavouring agents can be found include lean meat, beans, nuts, whole-grain cereals, fish, coffee, milk, beer, peanuts, popcorn, pork liver, shrimp, tomato, potato, grapes and apples.

Estimated daily per capita *intake*

The total annual volume of production of the 30 sulfur-containing heterocyclic compounds in this group was reported to be 22 000 kg in Europe and 12 000 kg in the USA. These values are equivalent to total daily *per capita* intakes of 3100 μg in Europe and 1600 μg in the USA.

In both Europe and the USA, thiamine hydrochloride (vitamin B1; No. 1030) and its principal metabolite, 4-methyl-5-thiazoleethanol (No. 1031), accounted for approximately 98% of the total *per capita* dietary intake of the flavouring agents in this group. In Europe, thiamine hydrochloride and 4-methyl-5-thiazoleethanol accounted for approximately 92% (2900 μg/day) and 6% (170 μg/day), respectively, of the total *per capita* intake. In the USA, thiamine hydrochloride and 4-methyl-5-thiazoleethanol accounted for approximately 75% (1200 μg/day) and 23% (380 μg/day), respectively, of the total *per capita* intake of the flavouring agents in this group.

The estimated intakes of the remaining flavouring agents are between 0.01 and 22 μg/day in both Europe and the USA, with most intakes below 4 μg/day.

Absorption, distribution, metabolism and elimination

Thiazole and its derivatives are metabolized primarily by side-chain oxidation or oxidation of the ring sulfur or nitrogen atoms; however, other routes of metabolism, involving ring cleavage, are possible. Derivatives of dithiazine, which are cyclic sulfides, are expected to be metabolized primarily by

S-oxidation to yield the corresponding sulfoxides and sulfones. Thiazoline is predicted to be similarly metabolized. Thiamine hydrochloride (No. 1030) at an intake of less than 5 mg/day is readily absorbed in the small intestine by an active transport system, followed by conversion to the coenzyme, thiamine pyrophosphate. Thiamine is metabolized primarily to a pyrimidine and a thiazole (4-methyl-5-thiazoleethanol, No. 1031) fragment. These fragments are further oxidized and excreted in the urine.

Thiophene derivatives are metabolized primarily by S-oxidation, followed by conjugation with glutathione; however, other routes of metabolism, involving ring cleavage, are also possible. The resulting mercapturic acid derivative is eliminated in the urine. The aromatic-fused thiazole, 2-acetylthiazole (benzothiazole; No. 1041), which lacks ring substituents, is metabolized by thiazole ring cleavage, yielding a series of free and conjugated *ortho*-aminophenyl sulfone and sulfoxide metabolites.

Application of the Procedure for the Safety Evaluation of Flavouring Agents

The stepwise evaluation of the 30 sulfur-containing heterocyclic compounds is described in detail below and summarized in Table 5.

Step 1. All the flavouring agents in this group are heterocyclic compounds, and five of these (Nos 1040, 1050, 1051, 1052 and 1053) are also aromatic[1]. One of the aromatic heterocyclic flavouring agents, benzothiazole (No. 1040) is unsubstituted and was therefore placed in structural class III. Of the other four substituted compounds, two (Nos 1050 and 1051) are common constituents of food and were therefore classified in structural class II, while the other two (Nos 1052 and 1053) are not common constituents of food and were therefore placed in structural class III.

Of the 25 non-aromatic heterocyclic flavouring agents, 19 (Nos 1030–1039, 1041–1044, 1046–1049 and 1054) are or are structurally closely related to common constituents of food and were therefore placed in structural class II. The remaining six flavouring agents (Nos 1045 and 1055–1059) were classified in structural class III.

Step 2. The data on most individual members of the group were, in most cases, insufficient to allow conclusions about their probable metabolic fate. The metabolism of thiamine hydrochloride (No. 1030) and its metabolite, 4-methyl-5-thiazoleethanol (No. 1031), is well characterized, and both are metabolized to innocuous products. 4-Methyl-5-thiazoleethanol acetate (No. 1054) is expected to be readily hydrolysed to 4-methyl-5-thiazole-

[1] According to the decision-tree process, an 'aromatic' compound has at least one benzene, furan, thiophene, pyridine or pyrole ring, however substituted and regardless of whether it is fused to another ring.

ethanol. The evaluation of all three flavouring agents therefore proceeded via the A (left-hand) side of the scheme. For all other flavouring agents in the group, the evaluation proceeded via the B (right-hand) side of the scheme.

Step A3. With respect to those flavouring agents evaluated via the A side of the scheme, the estimated daily *per capita* intakes of 4-methyl-5-thiazoleethanol (No. 1031) and 4-methyl-5-thiazoleethanol acetate (No. 1054) are below the threshold for human intake for structural class II (540 μg), and therefore these flavouring agents are not expected to raise any safety concern. The daily *per capita* intake of thiamine hydrochloride (No. 1030) is 2900 μg in Europe and 1200 μg in the USA. The intake of this flavouring agent therefore exceeds the threshold for human intake of compounds in structural class II, and its evaluation proceeded to step A4.

Step A4. Thiamine hydrochloride (No. 1030) is not endogenous; therefore, its evaluation proceeded to step A5.

Step A5. The NOEL of 36 mg/kg bw per day for thiamine hydrochloride (No. 1030) in a 90-day dietary study in rats is more than 500 times the estimated intake of this substance from its use as a flavouring agent in Europe (48 μg/kg bw per day) and more than 1000 times the estimated intake in the USA (22 μg/kg bw per day). Thiamine hydrochloride would therefore not be expected to be a safety concern.

Step B3 With regard to those flavouring agents evaluated via the B side of the scheme, the estimated daily *per capita* intakes of all 18 flavouring agents in structural class II (Nos 1032–1039, 1041–1044 and 1046–1051) are below the threshold for human intake for structural class II (540 μg per person per day). Similarly, the estimated daily *per capita* intakes of all nine flavouring agents in structural class III (Nos 1040, 1045, 1052, 1053 and 1055–1059) are below the threshold for human intake for compounds in this class (90 μg per person per day). The evaluation of all of these flavouring agents therefore proceeded to step B4.

Step B4 The NOEL for 2,4-dimethyl-5-vinylthiazole (No. 1039) in a 90-day dietary study in rats was 0.92 mg/kg bw per day, and this NOEL is appropriate for the structurally related flavouring agents, thiazole (No. 1032), 2-(1-methylpropyl)thiazole (No. 1033), 2-isobutylthiazole (No. 1034), 4,5-dimethylthiazole (No. 1035), 2,4,5-trimethylthiazole (No. 1036), 2-isopropyl-4-methylthiazole (No. 1037), 4-methyl-5-vinylthiazole (No. 1038), 4-methylthiazole (No. 1043) and 2-ethyl-4-methylthiazole (No. 1044).

The NOEL for 2-acetylthiazole (No. 1041) in a 90-day dietary study in rats was 50 mg/kg bw per day, and this NOEL is appropriate for the structurally related flavouring agent, 2-propionylthiazole (No. 1042).

The NOEL for 2-(2-butyl)-4,5-dimethyl-3-thiazoline (No. 1059) in a 90-day dietary study in rats was 1.2 mg/kg bw per day, and this NOEL is appropriate for the structurally related flavouring agents, 4,5-dimethyl-2-isobutyl-3-thiazoline (No. 1045) and 4,5-dimethyl-2-ethyl-3-thiazoline (No. 1058).

The NOEL for a mixture of 2-isobutyl-4,6-dimethyl and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine (No. 1046) and of a mixture of 2-isopropyl-4,6-dimethyl and 4-isopropyl-2,6-dimethyldihydro-1,3,5-dithiazine (No. 1047) in a 14-day dietary study in rats was 11 mg/kg bw per day, and this NOEL is appropriate for the structurally related agents, 2,4,6-triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine (No. 1048) and 2,4,6-trimethyldihydro-4*H*-1,3,5-dithiazine (No. 1049).

The NOEL for 2-thienyl disulfide (No. 1053) in a 90-day dietary study in rats was 290 mg/kg bw per day, and this NOEL is appropriate for the structurally related agents 5-methyl-2-thiophene carboxyaldehyde (No. 1050), 3-acetyl-2,5-dimethylthiophene (No. 1051) and 2-thienyl mercaptan (No. 1052).

The NOEL for benzothiazole (No. 1040) in a 90-day dietary study in rats was 5.1 mg/kg bw per day.

The NOEL for 2,4-dimethyl-5-acetylthiazole (No. 1055) in a dietary study in rats was 24 mg/kg bw per day.

The NOEL for 2-methyl-5-methoxythiazole (No. 1057) in a 90-day dietary study in rats was 8.6 mg/kg bw per day.

For all the above-mentioned flavouring agents (Nos 1032–1053, 1055–1059), therefore, a NOEL exists either for the substance itself, which provides an adequate margin of safety under the intended conditions of use, or for a structurally related substance, which is high enough to accommodate any perceived difference in toxicity between the substance itself and the related substance.

The NOEL used to evaluate each flavouring agent and the margins of safety they provide on the basis of current levels of intake are summarized in Table 6. On the basis of these data, these flavouring agents would not be expected to be a safety concern.

Consideration of combined intakes from use as flavouring agents

Although the 30 flavouring agents in this group are unlikely to produce common metabolites, consideration of their combined intake is appropriate since all are likely to be conjugated with glutathione before excretion.

Table 6

Margins of safety for thesulfur-containing heterocyclic compounds used as flavouring agents proceeding via the B side of the Procedure

Flavouring agent	No.	Related flavouring agent(s)	No.	NOEL (mg/kg bw per day)	Highest estimated intake (µg/kg bw per day)	Margin of safety
Structural class II						
Thiazole	1032	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.001	> 900 000
2-(1-Methylpropyl)thiazole	1033	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.0005	> 1 million
2-Isobutylthiazole	1034	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.05	> 10 000
4,5-Dimethylthiazole	1035	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.004	> 200 000
2,4,5-Trimethylthiazole	1036	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.01	> 90 000
2-Isopropyl-4-methylthiazole	1037	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.4	> 2000
4-Methyl-5-vinylthiazole	1038	2,4-dimethyl-5-vinylthiazole	1039	0.92[a]	0.04	> 20 000
2,4-Dimethyl-5-vinylthiazole	1039	NA	NA	0.92[a]	0.0001	> 9 million
2-Acetylthiazole	1041	NA	NA	50[a]	0.2	> 200 000
2-Propionylthiazole	1042	2-Acetylthiazole	1041	50[a]	0.003	> 10 million
4-Methylthiazole	1043	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.002	> 400 000
2-Ethyl-4-methylthiazole	1044	2,4-Dimethyl-5-vinylthiazole	1039	0.92[a]	0.06	> 10 000
2-Isobutyl-4,6-dimethyldihdro-1,3,5-dithiazine and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine (mixture)	1046	NA	NA	11[b]	0.002	> 5 million
2-Isopropyl-4,6-dimethyl 2,6-dimethyldihydro-1,3,5-dithiazine and 4-isopropyl-2,6-dimethyldihydro-1,3,5-dithiazine (mixture)	1047	NA	NA	11[b]	0.001	> 10 million
2,4,6-Triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine	1048	A mixture of 2-Isobutyl-4,6-dimethyl and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine	1046	11[b]	0.04	> 200 000
2,4,6-Trimethyldihydro-4*H*-1,3,5-dithiazine	1049	A mixture of 2-Isobutyl-4,6-dimethyl and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine	1046	11[b]	0.002	> 5 million
5-Methyl-2-thiophene-carboxyaldehyde	1050	2-Thienyl disulfide	1053	290[a]	0.01	> 20 million
3-Acetyl-2,5-dimethylthiophene	1051	2-Thienyl disulfide	1053	290[a]	0.4	> 700 000

Table 6 *(continued)*

Flavouring agent	No.	Related flavouring agent(s)	No.	NOEL (mg/kg bw per day)	Highest estimated intake (µg/kg bw per day)	Margin of safety
5-Methyl-2-thiophene-carboxyaldehyde	1050	2-Thienyl disulfide	1053	290[a]	0.01	> 20 million
3-Acetyl-2,5-dimethylthiophene	1051	2-Thienyl disulfide	1053	290[a]	0.4	> 700 000
Structural class III						
Benzothiazole	1040	NA	NA	5.1[a]	0.02	> 20 000
4,5-Dimethyl-2-isobutyl-3-thiazoline	1045	2-(2-Butyl)-4,5-dimethyl-3-thiazoline	1059	1.2[a]	0.07	> 10 000
2-Thienyl mercaptan	1052	2-Thienyl disulfide	1053	290[a]	0.0004	> 700 million
2-Thienyl disulfide	1053	NA	NA	290[a]	0.001	> 200 million
2,4-Dimethyl-5-acetylthiazole	1055	NA	NA	24[a]	0.03	> 10 million
2-Ethoxythiazole	1056	2-Acetylthiazole	1041	50[a]	0.002	> 20 million
2-Methyl-5-methoxythiazole	1057	NA	NA	8.6[a]	0.0002	> 40 million
4,5-Dimethyl-2-ethyl-3-thiazoline	1058	2-(2-Butyl)-4,5-dimethyl-3-thiazoline	1059	1.2[a]	0.0002	> 6 million
2-(2-Butyl)-4,5-dimethyl-3-thiazoline	1059	NA	NA	1.2[a]	0.09	> 10 000

NA, not applicable
[a]90-day study in rats
[b]14-day study in rats

In the unlikely event that all 21 flavouring agents in structural class II were to be consumed simultaneously on a daily basis, the estimated combined *per capita* intakes (3100 μg/day in Europe and 1600 μg/day in the USA) would exceed the threshold of human intake for their structural class (540 μg per person). Since, at these levels of intake, the conjugation capacity of the glutathione pool is unlikely to be depleted, this level of intake is not anticipated to be a safety concern.

In the unlikely event that the nine flavouring agents in structural class III were to be consumed simultaneously on a daily basis, the estimated combined per capita intakes (1 μg/day in Europe and 11 μg/day in the USA) would not exceed the threshold for human intake for their structural class (90 μg per person).

Conclusions

On the basis of the predicted metabolism and the NOELs for some members of the group, the Committee concluded that the 30 sulfur-containing heterocyclic compounds in this group would not raise safety concerns at current levels of intake.

The Committee noted that, for the three flavouring agents that were predicted to be metabolized to innocuous products, the available data on toxicity were consistent with the results of the safety evaluation.

A toxicological monograph was prepared.

4.1.4 *Sulfur-substituted furan derivatives*

The Committee evaluated a group of 33 flavouring agents that includes thiofuran and thiofurfuryl derivatives (see Table 7), using the Procedure for the Safety Evaluation of Flavouring Agents (See Figure 1). The Committee has not previously evaluated any member of the group.

Eighteen of the 33 flavouring agents in this group have been reported to occur naturally in foods. Thiofurfuryl and thiofuran derivatives have been detected mainly in coffee and cooked meats.

Estimated daily per capita *intake*

The total annual volume of production of the 33 sulfur-substituted furan derivatives is approximately 370 kg in Europe and 210 kg in the USA. Approximately 65% of the total annual volume in Europe and 40% of that in the USA arises from use of one substance, furfuryl mercaptan (No. 1072), with annual volumes of 240 kg in Europe and 82 kg in the USA. The estimated *per capita* intake of furfuryl mercaptan is 40 μg/day in Europe and 11 μg/day in the USA. The estimated daily intakes of each of the other 32 flavouring agents in this group are less than 5 μg per day in Europe and in the USA.

Table 7

Summary of results of safety evaluations of sulfur-substituted furan derivatives used as flavouring agents[a]

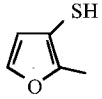
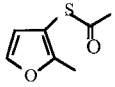
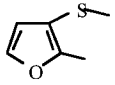
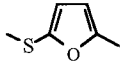
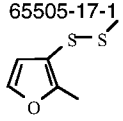
Flavouring agent	No.	CAS No. and structure	*Step B3*[b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
Structural class II					
2-Methyl-3-furanthiol	1060	28588-74-1 	No Europe: 0.6 USA: 0.9	Yes. The NOEL of 5 mg/kg bw per day is > 100 000 times the estimated intake of 2-methyl-3-furanthiol when used as a flavouring agent.	No safety concern
Ethanoic acid, S-(2-methyl-3-furanyl) ester	1069	55764-25-5 	No Europe: 0.01 USA: 0.07	Yes. The NOEL of 5 mg/kg bw per day for the related substance No. 1060 is > 1 million times the estimated intake of ethanoic acid, *S*-(2-methyl-3-furanyl) ester when used as a flavouring agent.	No safety concern
2-Methyl-3-(methylthio)furan	1061	63012-97-5 	No Europe: 1 USA: 0.1	Yes. The NOEL of 1.3 mg/kg bw per day for the related substance No. 1077 is > 10 000 times the estimated intake of 2-methyl-3-(methylthio)furan when used as a flavouring agent.	No safety concern
2-Methyl-5-(methylthio)furan	1062	13678-59-6 	No Europe: 1 USA: 0.02	Yes. The NOEL of 1.3 mg/kg bw per day for the related substance No. 1077 is > 10 000 times the estimated intake of 2-methyl-5-(methylthio)furan when used as a flavouring agent.	No safety concern
Methyl 2-methyl-3-furyl disulfide	1064	65505-17-1 	No Europe: 0.9 USA: 0.05	Yes. The NOEL of 1.2 mg/kg bw per day is > 10 000 times the estimated intake of methyl 2-methyl-3-furyl disulfide when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

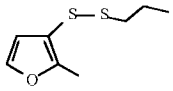
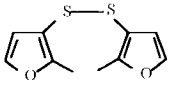
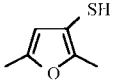
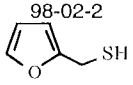
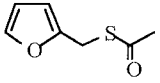
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
Propyl 2-methyl-3-furyl disulfide	1065	61197-09-9 	No Europe: ND USA: 0.7	Yes. The NOEL of 1.2 mg/kg bw per day for the related substance No. 1064 is > 100 000 times the estimated intake of propyl 2-methyl-3-furyl disulfide when used as a flavouring agent.	No safety concern
Bis(2-methyl-3-furyl) disulfide	1066	28588-75-2 	No Europe: 0.3 USA: 0.7	Yes. The NOEL of 0.45 mg/kg bw per day is > 10 000 times the estimated intake of bis(2-methyl-3-furyl) disulfide when used as a flavouring agent.	No safety concern
2,5-Dimethyl-3-furanthiol	1063	55764-23-3 	No Europe: 0.03 USA: 0.7	Yes. The NOEL of 5 mg/kg bw per day for the related substance No. 1060 is > 100 000 times the estimated intake of 2,5-dimethyl-3-furanthiol when used as a flavouring agent.	No safety concern
Furfuryl mercaptan	1072	98-02-2 	No Europe: 40 USA:11	Yes. The NOEL of 3 mg/kg bw per day is > 1000 times the estimated intake of furfuryl mercaptan when used as a flavouring agent.	No safety concern
Furfuryl thioacetate	1074	13678-68-7 	No Europe: 0.5 USA: 0.05	Yes. The NOEL of 0.83 mg/kg bw per day is > 100 000 times the estimated intake of furfuryl thioacetate when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

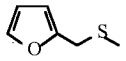
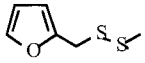
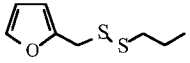
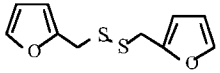
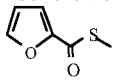
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
Furfuryl methyl sulfide	1076	1438-91-1 	No Europe: 1 USA: 0.1	Yes. The NOEL of 1.3 mg/kg bw per day for the related substance No. 1077 is > 10 000 times the estimated intake of furfuryl methyl sulfide when used as a flavouring agent.	No safety concern
Methyl furfuryl disulfide	1078	57500-00-2 	No Europe: 1 USA: 0.04	Yes. The NOEL of 1.2 mg/kg bw per day for the related substance No. 1064 is > 10 000 times the estimated intake of methyl furfuryl disulfide when used as a flavouring agent.	No safety concern
Furfuryl propyl disulfide	1079	2527366-36-0 	No Europe: ND USA: 3	Yes. The NOEL of 1.2 mg/kg bw per day for the related substance No. 1064 is > 10 000 times the estimated intake of furfuryl propyl disulfide when used as a flavouring agent.	No safety concern
2,2′-(Dithiodimethylene) difuran	1081	4437-20-1 	No Europe: 4 USA: 0.7	Yes. The NOEL of 3 mg/kg bw per day for the related substance No. 1072 is > 10 000 times the estimated intake of 2,2′-(dithiodimethylene) difuran when used as a flavouring agent.	No safety concern
Methyl thiofuroate	1083	13679-61-3 	No Europe: 0.4 USA: 0.1	Yes. The flavouring agent is expected to hydrolyse to methanethiol and furoic acid. The NOEL of 0.74 mg/kg bw per day for the related substance No. 1071, which also hydrolyses to furoic acid, is > 100 000 times the estimated intake of methyl thiofuroate when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

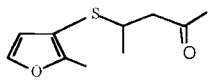
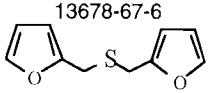
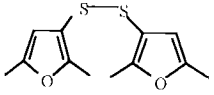
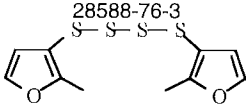
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
4-[(2-Methyl-3-furyl)thio]-2-pentanone	1084	180031-78-1 	No Europe: ND USA: 0.6	Yes. The NOEL of 3.8 mg/kg bw per day for the related substance No. 1085 is > 100 000 times the estimated intake of 4-[(2-methyl-3-furyl)thio]-2-pentanone when used as a flavouring agent.	No safety concern
2-Methyl-3-tetrahydrofuranthiol	1090	57124-87-5 	No Europe: 4 USA: 0.7	Yes. The NOEL of 8.3 mg/kg bw per day for the related substance No. 1089 is > 100 000 times the estimated intake of 2-methyl-3-tetrahydrofuranthiol when used as a flavouring agent.	No safety concern
2,2´-(Thiodimethylene) difuran	1080	13678-67-6 	No Europe: 0.9 USA: 0.005	Yes. The NOEL of 10 mg/kg bw per day is > 100 000 times the estimated intake of 2,2´-(thiodimethylene) when used as a flavouring agent.	No safety concern
Structural class III					
Bis(2,5-dimethyl-3-furyl)disulfide	1067	28588-73-0 	No Europe: 0.01 USA: 0.7	Yes. The NOEL of 0.45 mg/kg bw per day for the related substance No. 1066 is > 10 000 times the estimated intake of bis(2,5-dimethyl-3-furyl)disulfide when used as a flavouring agent.	No safety concern
Bis(2-methyl-3-furyl) tetrasulfide	1068	28588-76-3 	No Europe: ND USA: 0.7	Yes. The NOEL of 0.56 mg/kg bw per day is > 10 000 times the estimated intake of bis(2-methyl-3-furyl) tetrasulfide when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

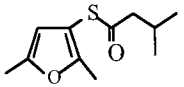
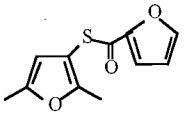
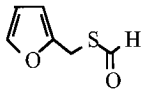
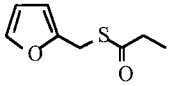
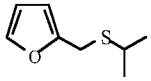
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2,5-Dimethyl-3-furan thioisovalerate	1070	55764-28-8 	No Europe: ND USA: 0.7	Yes. The NOEL of 0.73 mg/kg bw per day is > 10 000 times the estimated intake of 2,5-dimethyl-3-furan thioisovalerate when used as a flavouring agent.	No safety concern
S-2,5-Dimethyl-3-thiofuroyl furan	1071	65505-16-0 	No Europe: ND USA: 0.01	Yes. The NOEL of 0.74 mg/kg bw per day is > 1 million times the estimated intake of *S*-2,5-dimethyl-3-thiofuroyl furan when used as a flavouring agent.	No safety concern
Furfuryl thioformate	1073	59020-90-5 	No Europe: 2 USA: 0.02	Yes. The NOELs of 3 and 0.83 mg/kg bw per day for the related substances Nos 1072 and 1074 are > 1 million and > 10 000 times, respectively, the estimated intake of furfuryl thioformate when used as a flavouring agent.	No safety concern
Furfuryl thiopropionate	1075	59020-85-8 	No Europe: 0.01 USA: 0.005	Yes. The NOELs of 3 and 0.83 mg/kg bw per day for the related substances Nos 1072 and 1074 are > 1 million times the estimated intake of furfuryl thiopropionate when used as a flavouring agent.	No safety concern
Furfuryl isopropyl sulfide	1077	1883-78-9 	No Europe: 0.001 USA: 0.1	Yes. The NOEL of 1.3 mg/kg bw per day is > 100 000 times the estimated intake of furfuryl isopropyl sulfide when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

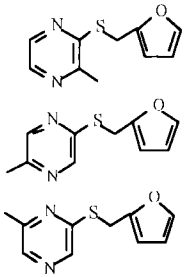
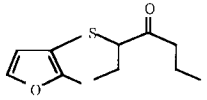
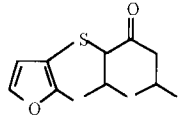
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
2-Methyl-3-, 5- or 6-(furfurylthio)pyrazine	1082	65530-53-2 	No Europe: 0.4 USA: 0.7	Yes. The NOEL of 1.7 mg/kg bw per day is > 100 000 times the estimated intake of 2-methyl-3-, 5- or 6-(furfurylthio)pyrazine when used as a flavouring agent.	No safety concern
3-[(2-Methyl-3-furyl)thio]-4-heptanone	1085	61295-41-8 	No Europe: ND USA: 0.7	Yes. The NOEL of 3.8 mg/kg bw per day is > 100 000 times the estimated intake of 3-[(2-methyl-3-furyl)thio]-4-heptanone when used as a flavouring agent.	No safety concern
2,6-Dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone	1086	61295-51-0 	No Europe: ND USA: 0.7	Yes. The NOEL of 3.8 mg/kg bw per day for the related substance No. 1085 is > 100 000 times the estimated intake of 2,6-dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

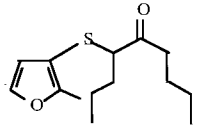
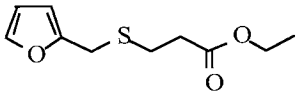
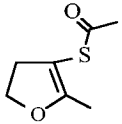
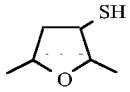
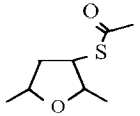
Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
4-[(2-Methyl-3-furyl)thio]-5-nonanone	1087	61295-50-9 	No Europe: ND USA: 0.7	Yes. The NOEL of 3.8 mg/kg bw per day for the related substance No. 1085 was > 100 000 times the estimqted intake of 4-[(2-methyl-3-furyl)thio]-5-nonanone when used as a flavouring agent.	No safety concern
Ethyl 3-(furfuryl-thio)propionate	1088	94278-27-0 	No Europe: 0.01 USA: 0.2	Yes. The NOEL of 17 mg/kg bw per day is > 1 million times the estimated intake of ethyl 3-(furfurylthio)propionate when used as a flavouring agent.	No safety concern
2-Methyl-3-thioacetoxy-4,5-dihydrofuran	1089	26486-14-6 	No Europe: ND USA: 0.7	Yes. The NOEL of 8.3 mg/kg bw per day is > 100 000 times the estimated intake of 2-methyl-3-thioacetoxy-4,5-dihydrofuran at when used as a flavouring agent.	No safety concern
cis- and *trans*-2,5-Dimethyl-3-tetrahydro-furanthiol	1091	26486-21-5 	No Europe: ND USA: 0.9	Yes. The NOEL of 8.3 mg/kg bw per day for the related substance No. 1089 is > 100 000 times the estimated intake of *cis*- and *trans*-2,5-dimethyl-3-tetrahydrofuranthiol when used as a flavouring agent.	No safety concern

Table 7 *(continued)*

Flavouring agent	No.	CAS No. and structure	*Step B3*[a,b] Does intake exceed threshold for human intake?	*Step B4* Adequate margin of safety for the flavouring agent or related chemical?	Conclusion based on current intake
cis- and *trans*-2,5-Dimethyltetrahydro-3-furyl thioacetate	1092	252736-39-3 	No Europe: ND USA: 2	Yes. The NOEL of 8.3 mg/kg bw per day for the related substance No. 1089 is > 100 000 times the estimated intake of *cis*- and *trans*-2,5-dimethyl-tetrahydro-3-furyl thioacetate when used as a flavouring agent.	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported

[a] Step 2: None of the flavouring agents in this group was predicted to be metabolized to innocuous products.

[b] The human intake threshold is 540 μg/person per day for class II and 90 μg/person per day for class III. All intake levels are expressed in μg/person per day. The combined intake of flavouring agents in class II is 56 and 20 μg/person per day in Europe and the USA, respectively. The combined intake of flavouring age in class III is 2.4 and 8.8 μg/person per day in Europe and the USA, respectively.

Absorption, distribution, metabolism and elimination

No data on the metabolism of these flavouring agents were available; however, all the members of the group contain a reactive divalent sulfur atom attached to the heteroaromatic or heterocyclic ring. Therefore, these flavouring agents are probably metabolized via reactions of the divalent sulfur, like other heteroaromatic ring systems containing sulfur as a side-chain substituent. However, in the absence of data on the disposition of these substances, the metabolic fate of this group of flavouring agents is unknown.

Application of the Procedure for the Safety Evaluation of Flavouring Agents

Step 1. Twenty-nine of the 33 flavouring agents in this group are aromatic heterocyclic compounds bearing ring substituents. Twenty-two of the 29 heteroaromatic *S*-substituted furan derivatives containing only one aromatic ring were assigned to structural class II if they were naturally occurring or to structural class III if they did not occur naturally in foods. The seven remaining heteroaromatic substances contain two aromatic rings. Of these, five agents (Nos 1066, 1067, 1068, 1071 and 1081) would be hydrolysed (thioester) or readily reduced (di- or tetra-sulfides) to mononuclear residues. They were assigned to structural class II or III depending on their natural occurrence. The two remaining substances (Nos 1080 and 1082), which are not readily converted to mononuclear residues, were placed in structural class III.

The remaining four flavouring agents are heterocyclic but not heteroaromatic (Nos 1089–1092). One agent, 2-methyl-3-tetrahydrofuranthiol (No. 1090), occurs naturally in foods and was placed in structural class II. The other three agents were placed in structural class III.

In summary, 18 of the 33 flavouring agents were assigned to structural class II because they are common components of food, while 15 that are not common components of food were assigned to structural class III.

Step 2. None of the flavouring agents in this group was predicted to be metabolized to innocuous products. The evaluation of these agents therefore proceeded down the B (right-hand) side of the decision tree.

Step B3. The current estimated daily *per capita* intakes of each of the 33 flavouring agents in this group are below the threshold for human intake for the respective structural classes (540 mg/day for structural class II and 90 mg/day for structural class III). Accordingly, the evaluation of all 33 substances in the group proceeded to step B4.

Step B4. The NOEL for 2-methyl-3-furanthiol (No. 1060) in a 90-day dietary study in rats was 5 mg/kg bw per day. This NOEL is appropriate for ethanoic acid, *S*-(2-methyl-3-furanyl) ester (No. 1069) because the acetate ester would

be hydrolysed to 2-methyl-3-furanthiol (No. 1060). This NOEL is also appropriate for the closely structurally related agent, 2,5-dimethyl-3-furanthiol (No. 1063).

The NOEL for furfuryl isopropyl sulfide (No. 1077) in a 90-day dietary study in rats was 1.3 mg/kg bw per day. This NOEL is also appropriate for three structurally related sulfides, 2-methyl-3-(methylthio)furan (No. 1061), 2-methyl-5-(methylthio)furan (No. 1062) and furfuryl methyl sulfide (No. 1076), which would be expected to participate in the same metabolic pathways as furfuryl isopropyl sulfide.

The NOEL for methyl 2-methyl-3-furyl disulfide (No. 1064) in a 90-day dietary study in rats was 1.2 mg/kg bw per day. This NOEL is also appropriate for three structurally related disulfides, propyl 2-methyl-3-furyl disulfide (No. 1065), methyl furfuryl disulfide (No. 1078) and furfuryl propyl disulfide (No. 1079).

The NOEL for bis(2-methyl-3-furyl) disulfide (No. 1066) in a 90-day dietary study in rats was 0.45 mg/kg bw per day. This NOEL is also appropriate for a structurally related bis-disulfide, bis(2,5-dimethyl-3-furyl) disulfide (No. 1067).

The NOEL for furfuryl mercaptan (No. 1072) in a multiple-dose, 13-week study in rats treated by gavage was 3 mg/kg bw per day; and the NOEL for furfuryl thioacetate (No. 1074) in a 90-day dietary study in rats was 0.83 mg/kg bw per day. These NOELs are also appropriate for the esters furfuryl thioformate (No. 1073) and furfuryl thiopropionate (No. 1075), because they are either close structural relatives of furfuryl thioacetate (No. 1074) or are expected to be hydrolysed to furfuryl mercaptan (No. 1072). The NOEL of 3 mg/kg bw per day for furfuryl mercaptan (No. 1072) is also appropriate for 2,2´-(dithiodimethylene) difuran (No. 1081), because this chemical is anticipated to be readily reduced to furfuryl mercaptan.

The NOEL for 2,5-dimethyl-3-thiofuroyl furan (No. 1071) in a 90-day dietary study in rats was 0.74 mg/kg bw per day. This NOEL is appropriate for methyl thiofuroate (No. 1083), because both 2,5-dimethyl-3-thiofuroyl furan and methyl thiofuroate would be hydrolysed to furoic acid.

The NOEL for 3-[(2-methyl-3-furyl)thio]-4-heptanone (No. 1085) in a 90-day dietary study in rats was 3.8 mg/kg bw per day. This NOEL is also appropriate for three structurally related thioketones, 4-[(2-methyl-3-furyl)thio]-2-pentanone (No. 1084), 2,6-dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone (No. 1086) and 4-[(2-methyl-3-furyl)thio]-5-nonanone (No. 1087).

The NOELs for 2,2´-(thiodimethylene) difuran (No. 1080), bis(2-methyl-3-furyl) tetrasulfide (No. 1068), 2,5-dimethyl-3-furan thioisovalerate (No.

1070), 2-methyl-3-, 5- or 6-(furfurylthio)pyrazine (No. 1082) and ethyl 3-(furfurylthio)propionate (No. 1088) in 14-day or 90-day dietary studies in rats were 10, 0.56, 0.73, 1.7 and 17 mg/kg bw per day, respectively.

The NOEL for 2-methylthioacetoxy-4,5-dihydrofuran (No. 1089) in a 1-year dietary study in rats was 8.3 mg/kg bw per day. This NOEL is also appropriate for three structurally related analogues, 2-methyl-3-tetrahydrofuranthiol (No. 1090), *cis*- and *trans*-2,5-dimethyl-3-tetrahydrofuranthiol (No. 1091) and *cis*- and *trans*-2,5-dimethyltetrahydro-3-furyl thioacetate (No. 1092), because these chemicals are expected to be hydrolysed to the corresponding dihydro- or tetrahydrofuranthiol.

The NOEL(s) used to evaluate each flavouring agent and the margins of safety they provide, on the basis of current intake levels, are summarized in Table 8.

Consideration of combined intakes from use as flavouring agents

The hydrolysis of furfuryl thioesters (Nos 1073, 1074 and 1075) or reduction of the disulfides (Nos 1078, 1079 and 1081) in this group would yield the common metabolite furfuryl mercaptan (No. 1072). In the unlikely event that these seven flavouring agents were to be consumed simultaneously on a daily basis, the estimated combined intakes (48 and 15 μg per person per day in Europe and the USA, respectively) would not exceed the threshold for daily human intake of compounds in structural class II (540 μg per person) or III (90 μg per person).

Likewise, hydrolysis of 2-methyl-3-furan thioester (No. 1069) or reduction of the corresponding disulfides (Nos 1064, 1065 and 1066) or tetrasulfide (No. 1068) would yield the common metabolite 2-methyl-3-furanthiol (No. 1060). In the unlikely event that these six flavouring agents were to be consumed simultaneously on a daily basis, the estimated combined daily intake would be less than 5 μg per person in Europe and the USA, which would not exceed the threshold for human daily intake of compounds in structural class II (540 μg per person) or III (90 μg per person).

On the basis of the evaluation of the collective data, the Committee identified no safety concern from combined intake.

Conclusions

The Committee concluded that use of flavouring agents in this group of 33 thiofurfuryl and thiofuran derivatives at current levels of intake would not present a safety concern. In the Procedure, data on toxicity were required for all the evaluations. The Committee noted the absence of data on the metabolic fate of these substances but considered that their potential

Table 8

NOELs and margins of safety for sulfur-substituted furan derivatives used as flavouring agents

Flavouring agent	No.	Related flavouring agent(s)	No.	NOEL (mg/kg bw per day)	Highest estimated intake (μg/kg bw per day)	Margin of safety
Structural class II						
2-Methyl-3-furanthiol	1060			5[a]	0.015	> 100 000
		Ethanoic acid, *S*-(2-methyl-3-furanyl) ester	1069		0.001	> 1 000 000
		2,5-Dimethyl-3-furanthiol	1063		0.01	> 100 000
Methyl 2-methyl-3-furyl disulfide	1064			1.2[a]	0.014	> 10 000
		Propyl 2-methyl-3-furyl disulfide	1065		0.01	> 100 000
		Methyl furfuryl disulfide	1078		0.017	> 10 000
		Furfuryl propyl disulfide	1079		0.04	> 10 000
Bis(2-methyl-3-furyl) disulfide	1066			0.45[a]	0.01	> 10 000
		Bis(2,5-dimethyl-3-furyl) disulfide	1067		0.01	> 10 000
Furfuryl mercaptan	1072			3[a]	0.58	> 1 000
		Furfuryl thioformate	1073		0.026	> 100 000
		Furfuryl thiopropionate	1075		0.0002	> 1 000 000
		2,2′-(Dithiodimethylene) difuran	1081		0.064	> 10 000
Furfuryl thioacetate	1074			0.83[a]	0.008	> 100 000
		Furfuryl thioformate	1073		0.026	> 10 000
		Furfuryl thiopropionate	1075		0.0002	> 1 000 000
4-[(2-Methyl-3-furyl)thio]-2-pentanone	1084			54[b,c]	0.01	> 1 000 000
		2-Methyl-3-tetrahydrofuranthiol	1090	12[b,c]	0.07	> 100 000
2,2′-(Thiodimethylene) difuran	1080			10[b]	0.014	> 100 000

Table 8 *(continued)*

Flavouring agent	No.	Related flavouring agent(s)	No.	NOEL (mg/kg bw per day)	Highest estimated intake (μg/kg bw per day)	Margin of safety
Structural class III						
Bis(2-methyl-3-furyl) tetrasulfide	1068			0.56[a]	0.01	> 10 000
2,5-Dimethyl-3-furan thioisovalerate	1070			0.73[a]	0.01	> 10 000
S-2,5-Dimethyl-3-thiofuroyl furan	1071			0.74[a]	0.0002	> 1 000 000
		Methyl thiofuroate	1083		0.002	> 100 000
Furfuryl isopropyl sulfide	1077			1.3[a]	0.002	> 100 000
		2-Methyl-3-(methylthio)furan	1061		0.024	> 10 000
		2-Methyl-5-(methylthio)furan	1062		0.021	> 10 000
		Furfuryl methyl sulfide	1076		0.02	> 10 000
2-Methyl-3-, 5- or 6-(furfurylthio)pyrazine	1082			1.7[a]	0.01	> 100 000
3-[(2-Methyl-3-furyl)thio]-4-heptanone	1085			3.8[a]	0.01	> 100 000
		4-[(2-Methyl-3-furyl)thiol]-2-pentanone	1084		0.01	> 100 000
		2,6-Dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone	1086		0.01	> 100 000
		4-[(2-Methyl-3-furyl)thio]-5-nonanone	1087		0.01	> 100 000
Ethyl 3-(furfurylthio)propionate	1088			17[a]	0.003	> 1 000 000
2-Methyl-3-thioacetoxy-4,5-dihydrofuran	1089			8.3[d]	0.01	> 100 000
		2-Methyl-3-tetrahydrofuranthiol	1090		0.07	> 100 000
		cis- and *trans*-2,5-Dimethyl-3-tetrahydrofuranthiol	1091		0.02	> 100 000
		cis- and *trans*-2,5-Dimethyltetrahydro-3-furyl thioacetate	1092		0.03	> 100 000

[a]90-day study
[b]14-day study
[c]This study was not used in the evaluation, as a 90-day study on a structurally related flavouring agent was available.
[d]1-year study

metabolism via the reactive divalent sulfur atom and their very low levels of use as flavouring agents were consistent with the outcome of the evaluations.

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

4.1.5 *Alicyclic ketones, secondary alcohols and related esters*

The Committee evaluated a group of 25 flavouring agents consisting of alicyclic ketones, secondary alcohols and related esters (see Table 9). The evaluations were conducted according to the Procedure for the Safety Evaluation of Flavouring Agents (See Figure 1). None of these agents has been evaluated previously by the Committee.

Twelve of the 25 substances (Nos 1093, 1098, 1100–1104, 1107, 1108, 1110, 1112 and 1114) have been reported to occur naturally in foods. They have been detected in fruits, vegetables, cheese, meats, seafood, grains, alcoholic beverages, coffee and tea.

Estimated daily per capita *intake*

The total annual volume of production of the 25 alicyclic ketones, secondary alcohols and related esters is approximately 520 kg in Europe and 310 kg in the USA. The reported annual production of only one agent, 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one (No. 1114), is greater than 100 kg (110 kg in Europe). The daily *per capita* intake of each of the agents in this group is $\leq$ 15 μg in Europe and in the USA.

Absorption, distribution, metabolism and elimination

Esters (Nos 1093–1098) in this group are hydrolysed to their corresponding alcohols and carboxylic acids by carboxylesterases, which are found abundantly in hepatocytes. The resulting alicyclic secondary alcohols are conjugated with glucuronic acid and excreted mainly in the urine. Side-chain oxidation of methyl groups may also occur.

Alicyclic ketones (Nos 1100–1117) are reduced to the corresponding secondary alcohol and excreted primarily as glucuronic acid conjugates. If a double bond is present, the chemical may be reduced to the corresponding dihydro derivative. Reduction of the double bond in metabolites excreted in the bile is probably associated with the action of gut microflora. Endocyclic double bonds (Nos 1105, 1107 and 1110–1115) are more prone to reduction than exocyclic double bonds (Nos 1098 and 1106). Alicyclic ketones containing an alkyl side-chain (Nos 1098, 1099 and 1102–1117) can not only follow reductive pathways but can undergo oxidation of the side-chain to form poly-oxygenated metabolites, which are excreted as the glucuronic acid or sulfate conjugates in the urine and, to a lesser extent, in the faeces.

Table 9
Summary of results of the safety evaluation of alicyclic ketones, secondary alcohols and related esters used as flavouring agents[a]

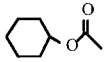
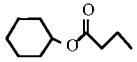
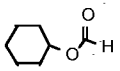
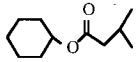
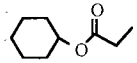
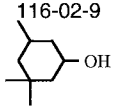
Flavouring agent	No.	CAS No. and structure	*Step A3*[b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
Structural class I					
Cyclohexyl acetate	1093	622-45-7 	No Europe: 14 USA: 10	See note 1.	No safety concern
Cyclohexyl butyrate	1094	1551-44-6 	No Europe: ND USA: 0.1	See note 1.	No safety concern
Cyclohexyl formate	1095	4351-54-6 	No Europe: 0.01 USA: 0.2	See note 1.	No safety concern
Cyclohexyl isovalerate	1096	7774-44-9 	No Europe: 0.3 USA: 0.05	See note 1.	No safety concern
Cyclohexyl propionate	1097	6222-35-1 	No Europe: 0.01 USA: 0.05	See note 1.	No safety concern
3,3,5-Trimethyl cyclohexanol	1099	116-02-9 	No Europe: 0.1 USA: 0.1	See note 2.	No safety concern

Table 9 *(continued)*

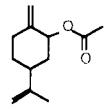
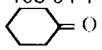
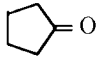
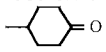
Flavouring agent	No.	CAS No. and structure	*Step A3*[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
Structural class II					
cis- and *trans-para*-1(7),8-Menthadien-2-yl acetate	1098	71660-03-2 	No Europe: ND USA: 0.6	See note 1.	No safety concern
Cyclohexanone	1100	108-94-1 	No Europe: 0.1 USA: 0.1	See note 2.	No safety concern
Cyclopentanone	1101	120-92-3 	No Europe: 0.02 USA: 0.02	See note 2.	No safety concern
2-Methylcyclohexanone	1102	583-60-8 	No Europe: 0.1 USA: 0.1	See note 2.	No safety concern
3-Methylcyclohexanone	1103	591-24-2 	No Europe: 0.1 USA: 0.1	See note 2.	No safety concern
4-Methyl cyclohexanone	1104	589-92-4 	No Europe: 0.1 USA: 0.1	See note 2.	No safety concern

Table 9 *(continued)*

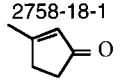
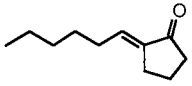
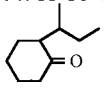
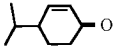
Flavouring agent	No.	CAS No. and structure	*Step A3*[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
1-Methyl-1-cyclopenten-3-one	1105	2758-18-1 	No Europe: 0.07 USA: ND	See note 3.	No safety concern
Structural class II					
2-Hexylidene cyclopentanone	1106	17373-89-6 	No Europe: 0.3 USA: 0.01	See notes 3 and 4.	No safety concern
3-Methyl-2-cyclohexen-1-one	1107	1193-18-6 	No Europe: 0.01 USA: 0.1	See note 3.	No safety concern
2,2,6-Trimethylcyclo-hexanone	1108	2408-37-9 	No Europe: 2.4 USA: 0.04	See note 2.	No safety concern
2-*sec*-Butylcyclohexanone	1109	14765-30-1 	No Europe: 6 USA: ND	See note 4.	No safety concern
4-Isopropyl-2-cyclo-hexenone	1110	500-02-7 	No Europe: 0.001 USA: 0.001	See note 3.	No safety concern

Table 9 *(continued)*

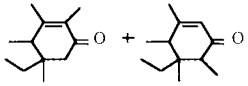
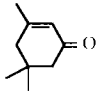
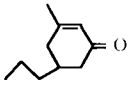
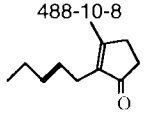
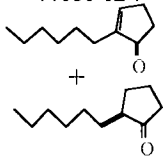
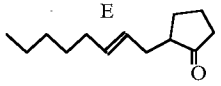
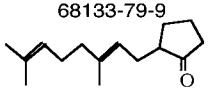
Flavouring agent	No.	CAS No. and structure	*Step A3*[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
Tetramethyl ethyl cyclohexenone (mixture of isomers)	1111	17369-60-7 	No Europe: 9 USA: 0.2	See note 3.	No safety concern
Isophorone	1112	78-59-1 	No Europe: 5.4 USA: 0.1	See note 3.	No safety concern
3-Methyl-5-propyl-2-cyclohexen-1-one	1113	3720-16-9 	No Europe: 0.1 USA: 4.1	See note 3.	No safety concern
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one	1114	488-10-8 	No Europe: 16 USA: 7.2	See notes 3 and 4.	No safety concern
Isojasmone	1115	11050-62-7 	No Europe: 0.4 USA: 0.01	See notes 3 and 4.	No safety concern

Table 9 *(continued)*

Flavouring agent	No.	CAS No. and structure	*Step A3*[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
(E)-2-(2-Octenyl) cyclopentanone	1116	65737-52-2 	No Europe: 7 USA: 6.6	See note 4.	No safety concern
2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone	1117	68133-79-9 	No Europe: 7.1 USA: 6.6	See note 4.	No safety concern

CAS: Chemical Abstracts Service; ND: No intake data reported

[a] Step 2: All of the flavouring agents in this group were predicted to be metabolized to innocuous products.

[b] The threshold for human intake is 1800 μg/person per day for class I and 540 μg/person per day for class II. All intake levels are expressed in μg/person per day. The combined intake of flavouring agents in class I is 14 and 10 μg per person per day in Europe and the USA, respectively. The combined intake of flavouring agents in class II is 54 and 26 μg per person per day in Europe and the USA, respectively.

Notes:

1. Detoxicated by hydrolysis of ester and glucuronic acid conjugation of the resulting alicyclic alcohol and complete oxidation of the carboxylic acid
2. Detoxicated by reduction of the ketone followed by glucuronic acid conjugation of the corresponding alcohol
3. Detoxicated by reduction of the ketone functional group followed by glucuronic acid conjugation of the resulting alcohol and glutathione conjugation of the parent ketone
4. Detoxicated by reduction of the ketone and alkyl side-chain oxidation and excretion

The nine chemicals that are α,β-unsaturated ketones (Nos 1105–1107 and 1110–1116) are subject to glutathione conjugation, with subsequent elimination in the urine as mercapturic acids.

As the α,β-unsaturated carbonyl group is a structural alert for toxicity, the Committee, at previous meetings, has devoted considerable attention to the safety of flavouring agents containing this reactive moiety. The Committee concluded at its fifty-seventh meeting (Annex 1, reference *154*) that the presence of protective processes in cells provides adequate detoxication capacity at the low doses associated with use of such compounds as flavouring agents. With respect to α,β-unsaturated ketones, these protective processes include reduction of the ketone to the corresponding alcohol (followed by conjugation of the alcohol with glucuronic acid) and conjugation with glutathione. These processes operate for the aliphatic ketones used as flavouring agents.

Application of the Procedure for the Safety Evaluation of Flavouring Agents

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents to the above-mentioned flavouring agents, the Committee assigned six (Nos 1093–1097 and 1099) of the 25 substances to structural class I. These agents are either alicyclic secondary alcohols or are readily hydrolysed to secondary alcohols and simple short-chain carboxylic acids. They are simple aliphatic substances containing secondary hydroxyl groups, which have low toxicity. The remaining 19 compounds, which are monocyclic alkanones (Nos 1100–1117) or have a secondary alcohol attached to a vinyl group (No. 1098), were assigned to structural class II.

Step 2. All the flavouring agents in this group were predicted to be metabolized to innocuous products. The evaluation of these agents therefore proceeded *via* the A (left-hand) side of the decision tree.

Step A3. The estimated daily *per capita* intake of each of the six flavouring agents in structural class I and each of the 19 agents in structural class II is below the threshold for daily human intake of compounds in the respective structural class (i.e., 1800 μg per person for class I and 540 μg per person for class II). According to the Procedure, the safety of these 25 flavouring agents raises no concern when consumed at currently estimated levels.

Table 9 summarizes the evaluations of acyclic ketones, secondary alcohols and related esters used as flavouring agents.

Consideration of combined intakes from use as flavouring agents

In the unlikely event that all the flavouring agents in structural class I or II were to be consumed concurrently on a daily basis, the estimated combined intake would not exceed the threshold for human intake of either class.

Conclusions

The Committee concluded that none of the flavouring agents in this group of alicyclic ketones, secondary alcohols and related esters would raise a safety concern at current estimated levels of intake. Other data on the toxicity of alicyclic ketones, secondary alcohols and related esters were consistent with the results of the safety evaluation.

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

4.1.6 *Aliphatic secondary alcohols, ketones and related esters*

The Committee evaluated a group of 39 flavouring agents that includes aliphatic acyclic secondary alcohols and ketones and esters derived from aliphatic secondary alcohols (see Table 10), using the Procedure for the Safety Evaluation of Flavouring Agents (See Figure 1). The Committee had not previously evaluated any of these agents.

Twenty-six of the 39 substances in this group of flavouring agents (Nos 1118, 1120, 1122–1132, 1134–1136, 1139, 1142, 1144, 1147, 1148, 1150–1152, 1154 and 1156) have been reported to occur naturally in foods. They have been found in fruits, juices, spices, vegetables, cocoa, coffee and tea.

Estimated daily per capita *intake*

The total annual volume of production of the 39 aliphatic secondary alcohols and ketones in this group is approximately 3900 kg in Europe and 1100 kg in the USA. Approximately 73% and 47% of the total annual production volume in Europe and the USA, respectively, is accounted for by 6-methyl-5-hepten-2-one (No. 1120) and 1-octen-3-ol (No. 1152). The daily *per capita* intake of 6-methyl-5-hepten-2-one (No. 1120) and 1-octen-3-ol (No. 1152) was 120 μg and 290 μg in Europe and 44 μg and 23 μg, respectively, in the USA, respectively.

Absorption, distribution, metabolism and elimination

In general, the aliphatic esters in this group hydrolyse to the corresponding secondary alcohols. The secondary alcohols and their corresponding ketones are interconvertible under physiological conditions. In the principal excretion pathway, the ketones are reduced to the corresponding secondary alcohols, which are subsequently conjugated with glucuronic acid and excreted.

When the ketone carbonyl function is located at the 2-position (i.e. a methyl ketone), the methyl group may undergo α-hydroxylation and subsequent oxidation, to yield a corresponding ketocarboxylic acid. The ketoacids are intermediary metabolites (e.g. α-ketoacids), which can undergo oxidative decarboxylation to yield carbon dioxide and simple aliphatic carboxylic acids.

Table 10

Summary of the results of safety evaluations of aliphatic secondary alcohols, ketones and related esters used as flavouring agents[a]

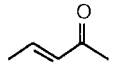
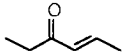
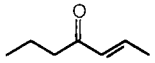
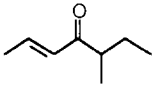
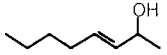
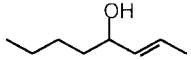
Flavouring agent	No.	CAS No. and structure	Step A3[b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
Structural class I					
3-Penten-2-one	1124	625-33-2 	No Europe: 0.3 USA: ND	See notes 1, 3 and 4.	No safety concern
4-Hexen-3-one	1125	2497-21-4 	No Europe: 15 USA: 1	See notes 1 and 3.	No safety concern
2-Hepten-4-one	1126	4643-25-8 	No Europe: 0.01 USA: ND	See notes 1 and 3.	No safety concern
5-Methyl-2-hepten-4-one	1133	81925-81-7 	No Europe: 7 USA: 1	See notes 1 and 3.	No safety concern
3-Octen-2-ol	1140	76649-14-4 	No Europe: 1 USA: ND	See note 1.	No safety concern
(E)-2-Octen-4-ol	1141	20125-81-9 	No Europe: ND USA: 1	See note 1.	No safety concern

Table 10 *(continued)*

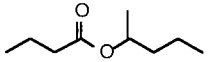
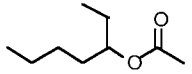
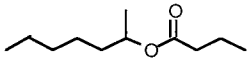
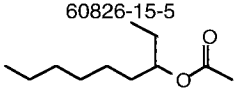
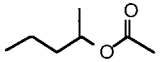
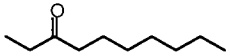
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
2-Pentyl butyrate	1142	60415-61-4 	No Europe: ND USA: 1	See note 2.	No safety concern
(±) Heptan-3-yl acetate	1143	5921-83-5 	No Europe: 4 USA: 3	See note 2.	No safety concern
(±) Heptan-2-yl butyrate	1144	39026-94-3 	No Europe: 4 USA: 3	See note 2.	No safety concern
(±) Nonan-3-yl acetate	1145	60826-15-5 	No Europe: 4 USA: 3	See note 2.	No safety concern
2-Pentyl acetate	1146	626-38-0 	No Europe: 3 USA: 3	See note 2.	No safety concern
Structural class II					
3-Decanone	1118	928-80-3 	No Europe: 4 USA: 3	See notes 1 and 3.	No safety concern

Table 10 *(continued)*

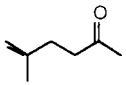
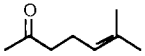
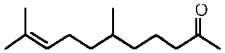
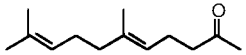
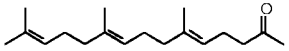
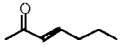
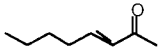
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
5-Methyl-5-hexen-2-one	1119	3240-09-3 	No Europe: ND USA: 0.3	See notes 1, 3 and 4.	No safety concern
6-Methyl-5-hepten-2-one	1120	110-93-0 	No Europe: 120 USA: 44	See notes 1 and 4.	No safety concern
3,4,5,6-Tetrahydro-pseudoionone	1121	4433-36-7 	No Europe: ND USA: 0.01	See notes 1 and 4.	No safety concern
6,10-Dimethyl-5,9-undecadien-2-one	1122	3796-70-1 	No Europe: 49 USA: 2	See notes 1 and 4.	No safety concern
2,6,10-Trimethyl-2,6,10-pentadecatrien-14-one	1123	762-29-8 	No Europe: 0.1 USA: ND	See notes 1 and 4.	No safety concern
3-Hepten-2-one	1127	1119-44-4 	No Europe: 0.2 USA: 0.07	See notes 1, 3 and 4.	No safety concern
3-Octen-2-one	1128	1669-44-9 	No Europe: 1 USA: 1	See notes 1, 3 and 4.	No safety concern

Table 10 *(continued)*

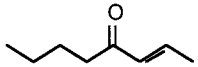
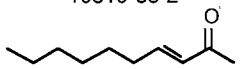
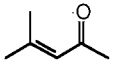
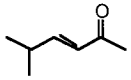
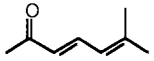
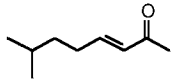
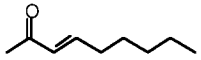
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
2-Octen-4-one	1129	4643-27-0 	No Europe: 1 USA: 3	See notes 1 and 3.	No safety concern
3-Decen-2-one	1130	10519-33-2 	No Europe: 0.01 USA: ND	See notes 1, 3 and 4.	No safety concern
4-Methyl-3-penten-2-one	1131	141-79-7 	No Europe: 0.4 USA: ND	See notes 1 and 4.	No safety concern
5-Methyl-3-hexen-2-one	1132	5166-53-0 	No Europe: ND USA: 0.1	See notes 1, 3 and 4.	No safety concern
6-Methyl-3,5-heptadien-2-one	1134	1604-28-0 	No Europe: 15 USA: 5	See notes 1, 3 and 4.	No safety concern
(E)-7-Methyl-3-octen-2-one	1135	33046-81-0 	No Europe: ND USA: 2	See notes 1, 3 and 4.	No safety concern
3-Nonen-2-one	1136	14309-57-0 	No Europe: 14 USA: 13	See notes 1, 3 and 4.	No safety concern

Table 10 *(continued)*

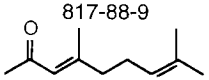
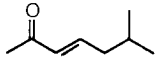
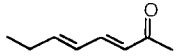
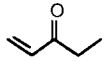
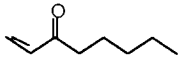
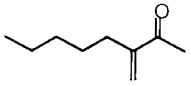
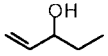
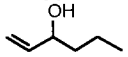
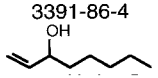
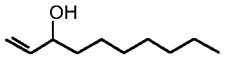
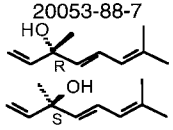
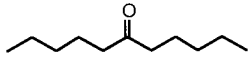
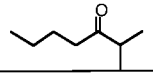
Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
(E) & (Z)-4,8-Dimethyl-3,7-nonadien-2-one	1137	817-88-9 	No Europe: 7 USA: 7	See notes 1, 3 and 4.	No safety concern
(E)-6-Methyl-3-hepten-2-one	1138	20859-10-3 	No Europe: 4 USA: 3	See notes 1, 3 and 4.	No safety concern
(E,E)-3,5-Octadien-2-one	1139	30086-02-3 	No Europe: 4 USA: 3	See notes 1, 3 and 4.	No safety concern
1-Penten-3-one	1147	1629-58-9 	No Europe: 0.3 USA: 0.1	See notes 1 and 3.	No safety concern
1-Octen-3-one	1148	4312-99-6 	No Europe: 1 USA: 0.1	See notes 1 and 3.	No safety concern
2-Pentyl-1-buten-3-one	1149	63759-55-7 	No Europe: 0.2 USA: ND	See notes 1, 3 and 4.	No safety concern
1-Penten-3-ol	1150	616-25-1 	No Europe: 2 USA: 1	See note 1.	No safety concern

Table 10 *(continued)*

Flavouring agent	No.	CAS No. and structure	Step A3[a,b] Does intake exceed the threshold for human intake?	Comments	Conclusion based on current intake
1-Hexen-3-ol	1151	4798-44-1 	No Europe: 1 USA: 2	See note 1.	No safety concern
1-Octen-3-ol	1152	3391-86-4 	No Europe: 290 USA: 23	See note 1.	No safety concern
1-Decen-3-ol	1153	51100-54-0 	No Europe: ND USA: 0.1	See note 1.	No safety concern
(E,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol	1154	20053-88-7 	No Europe: ND USA: 6	See note 1.	No safety concern
6-Undecanone	1155	927-49-1 	No Europe: 4 USA: 3	See note 1.	No safety concern
2-Methylheptan-3-one	1156	13019-20-0 	No Europe: 4 USA: 3	See note 1.	No safety concern

CAS: Chemical Abstracts Service; ND: No intake data reported

[a] Step 2: All the flavouring agents in this group were predicted to be metabolized to innocuous products.

[b] The human intake threshold is 1800 μg per person per day for class I and 540 μg per person per day for class II. All intake levels are expressed in μg per person per day. The combined intake of flavouring agents in class I is 58 and 16 μg per person per day in Europe and the USA, respectively. The combined intake of flavouring agents in class II is 520 and 120 μg per person per day in Europe and the USA, respectively.

Notes:

1. Detoxicated by reduction of the ketone followed by glucuronic acid conjugation of the corresponding alcohol or direct glucuronic acid conjugation of the secondary alcohol
2. Detoxicated by hydrolysis of the ester and glucuronic acid conjugation of the resulting alicyclic alcohol and complete oxidation of the carboxylic acid
3. Detoxicated by reduction of the ketone functional group followed by glucuronic acid conjugation of the resulting alcohol and glutathione conjugation of the parent ketone
4. Detoxicated by reduction of the ketone and alkyl side-chain oxidation and excretion

The acid may be completely metabolized in the fatty acid pathway and citric acid cycle. When the substance is an α,β-unsaturated ketone (Nos 1124–1139 and 1147–1149) or secondary alcohol (Nos 1140–1141 and 1150–1154) which is oxidized to an α,β-unsaturated ketone, it can conjugate with glutathione. The glutathione conjugates are converted to the corresponding mercapturic acid derivatives (*N*-acetylcysteine derivative) and excreted.

As the α,β-unsaturated carbonyl group is a structural alert for toxicity, the Committee, at previous meetings, has devoted considerable attention to the safety of flavouring agents containing this reactive moiety. The Committee concluded at its fifty-seventh meeting (Annex 1, reference *154*) that the presence of protective processes in cells provides adequate detoxication capacity at the low doses associated with use of such compounds as flavouring agents. With respect to α,β-unsaturated ketones, these protective processes include reduction of the ketone to the corresponding alcohol (followed by conjugation of the alcohol with glucuronic acid) and conjugation with glutathione. These processes operate for the aliphatic ketones used as flavouring agents.

Application of Procedure for the Safety Evaluation of Flavouring Substances

Step 1. In applying the Procedure for the Safety Evaluation of Flavouring Agents to these chemicals, the Committee assigned 11 of the 39 agents to structural class I on the basis that they are acyclic saturated and unsaturated aliphatic ketones with no other functional groups and three or fewer carbons on either side of the keto group (Nos 1124–1126 and 1133) and secondary alcohols (Nos 1140–1141) or esters of secondary alcohols (Nos 1142–1146). The remaining 28 flavouring agents, which are acyclic aliphatic ketones with four or more carbons on either side of the keto group (Nos 1118–1123, 1127–1132, 1134–1139, 1148, 1155 and 1156) and either a ketone (Nos 1147 and 1149) or a secondary alcohol (Nos 1150–1154) attached to a terminal vinyl group, were assigned to structural class II.

Step 2. All the flavouring agents in this group were predicted to be metabolized to innocuous products. The evaluation of these substances therefore proceeded *via* the A (left-hand) side of the decision tree.

Step A3. The estimated daily *per capita* intakes of the 11 flavouring agents in structural class I and the 28 flavouring agents in structural class II are below the threshold for human intake for each class (i.e., 1800 μg per person for structural class I and 540 μg per person for structural class II). According to the Procedure, the safety of these 39 flavouring agents raises no concern when they are used at their current estimated levels of intake.

Table 10 summarizes the evaluation of aliphatic secondary alcohols, ketones and related esters used as flavouring agents.

Consideration of combined intakes from use as flavouring agents

In the unlikely event that all the flavouring agents in this group were to be consumed concurrently on a daily basis, the estimated combined intake would not exceed the human intake threshold for structural class I or II.

Conclusions

The Committee concluded that none of the flavouring agents in this group of 39 aliphatic secondary alcohols, ketones and related esters would raise a safety concern at the current estimated levels of intake. Other data on the toxicity of aliphatic secondary alcohols, ketones and related esters are consistent with the results of the safety evaluation.

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

4.2 Evaluation of secondary components of flavouring agents

The Committee had previously considered the procedure for evaluating flavouring agents for which the minimum assay figures were below 95%. It has followed the general principle that specifications should be designated as tentative if less than 95% of the material in the commercial product consists of the named compound, and known secondary components should be taken into account in the safety evaluation.

At its present meeting, the Committee considered information on the presence of known secondary components in all 51 flavouring agents evaluated at its forty-sixth through fifty-fifth meetings, for which the minimum assay was less than 95%, in order to assess whether these were covered by the existing safety evaluations of the named compounds.

In most cases, the secondary components of known chemical identity were found to be normal metabolites of the named compound, or to have chemical structures that are sufficiently similar that they fit within the same group evaluations. In two cases, the secondary components were not closely related to the named compound: the safety of 6-hydroxy-3,7-dimethyloctanoic acid (No. 237) was evaluated by reference to the NOEL for a similar compound, while that of the secondary component in 2,3-pentadione (No. 410) was assessed by reference to its likely metabolism .

In the light of all the available data on secondary components present in materials of commerce containing less than 95% of the named compound, the Committee concluded that the secondary components do not raise safety concerns and confirmed its conclusion that the flavouring agents listed in Annex 4 do not present any safety concern at the current estimated levels of intake.

The specifications for the 51 flavouring agents listed in Annex 4 that were originally evaluated at the forty-sixth to the fifty-fifth meetings will be reviewed at a future meeting.

4.3 Chemicals requiring confirmation of flavour use

The Committee received information from the flavour industry (*4*) concerning 18 flavouring agents for which the evaluations could not be finalized at the fifty-seventh meeting (Annex 1, reference *154*), pending information on whether they were in current use as flavouring agents.

Glycerol (No. 909) and *propylene glycol (No. 925)* have a long history of use as solvents and humectants (inter alia). With respect to their use as flavouring agents, the Committee was informed only that these substances provide 'a sweet taste', although propylene glycol was also reported to produce 'a warm burning sensation in the mouth' in certain aqueous applications. With the exception of the category 'meats', the reported flavouring uses of these compounds require high levels of addition, in many cases greater than 10 000 mg/kg (1%), and any 'flavouring' effect might either be a corollary of a more significant technical effect as a carrier or humectant or be related to the acknowledged sweetening properties. On the basis of the information provided, the Committee was not convinced that the reported uses of glycerol and propylene glycol are those of a flavouring agent. The Committee did not finalize the evaluations pending development of a definition of 'flavouring agent'.

Benzoic acid (No 860) and benzoate salts have known uses as preservatives, particularly in certain beverages. The flavouring properties of benzoic acid appear to be well established, and the Committee accepted that this chemical can be added to some foods primarily for its flavouring effect. The Committee noted that the levels used as a flavouring agent are lower than those generally associated with the preservative uses of benzoates, although the possibility of a secondary preservative effect in some flavouring applications cannot be excluded. The group ADI of 0–5 mg/kg bw for benzoic acid and related compounds was maintained at the forty-sixth meeting (Annex 1, reference *122*). The contribution of the intake of benzoic acid arising from its use as a flavouring agent to the total intake of benzoic acid and benzoates does not represent a safety concern.

The remaining 15 chemicals were reported to be added to foods as flavouring agents with the expectation that they will be hydrolysed to release flavour molecules, either under storage or during processing of the food. In some cases, hydrolysis is followed by further chemical changes (decarboxylation or oxidation) to generate the ultimate flavouring species. Because the end-products which are ingested by the consumer have been defined (see section

2.2.1), the Committee concluded that it is appropriate to evaluate these 15 chemicals by the Procedure for the Safety Evaluation of Flavouring Agents.

At its fifty-seventh meeting (Annex 1, reference *154*), the Committee predicted that all 15 chemicals would be metabolized to innocuous products, and they were therefore evaluated via the left-hand side of the decison tree.

Glyceryl tribenzoate (No. 861) and *propylene glycol dibenzoate (No. 862)* were considered by the Committee at its fifty-seventh meeting in the group of benzyl derivatives (Annex 1, reference *154*). The estimated intakes were below the threshold for human intake of their structural class (Step A3). They are partially hydrolysed in food under acidic conditions, giving rise to benzoic acid and glycerol and benzoic acid and propylene glycol. The group ADI of 0–5 mg/kg bw for benzoic acid and related compounds was maintained at the forty-sixth meeting (Annex 1, reference *122*). An ADI 'not specified'[1] was established for glycerol by the Committee at its twentieth meeting (Annex 1, reference *41*), and an ADI of 0–25 mg/kg bw was established for propylene glycol at the seventeenth meeting (Annex 1, reference *32*). The intakes of the hydrolysis products resulting from the flavouring uses of these agents are included in the relevant ADI. There are no safety concerns in relation to use of these chemicals as flavouring agents.

Butyl para-*hydroxybenzoate (No. 870)* was considered at the fifty-seventh meeting in the group of hydroxy- and alkoxy-substituted benzyl derivatives (Annex 1, reference *154*). The estimated intake was below the threshold for human intake of the structural class (step A3). When baked goods containing this chemical are heated, it is partially hydrolysed to butyl alcohol and *para*-hydroxybenzoic acid. Butyl alcohol (No. 85) was evaluated as a flavouring agent at the forty-ninth meeting and was considered not to be a safety concern (Annex 1, reference *131*). The intake of butyl alcohol from the flavouring use of butyl *para*-hydroxybenzoate would not significantly increase the total intake of this alcohol. *para*-Hydroxybenzoic acid was evaluated as a flavouring agent at the fifty-seventh meeting and was considered not to be a safety concern. The formation of *para*-hydroxybenzoic acid from the hydrolysis of butyl *para*-hydroxybenzoate would not significantly increase the total intake of this acid. There is no safety concern in relation to use of this chemical as a flavouring agent.

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

3-Oxodecanoic acid glyceride (No. 914), 3-oxododecanoic acid glyceride (No. 915), 3-oxotetradecanoic acid glyceride (No. 916) and *3-oxohexadecanoic acid glyceride (No. 917)* were considered at the fifty-seventh meeting in the group of aliphatic acyclic diols, triols and related substances (Annex 1, reference *154*). The estimated intake of No. 914 was above the threshold for human intake of its structural class, class III, while the intakes of the others were below the thresholds for their corresponding structural classes (I and III) (step A3). After absorption, the glycerides would be hydrolysed to glycerol and the corresponding β-keto acid, which are endogenous. All these agents are hydrolysed in food, and flavour arises from the corresponding keto acid and glycerol. The keto acids are unstable and would undergo decarboxylation to the corresponding ketones (2-nonanone, 2-undecanone, 2-tridecanone and 2-pentadecanone, respectively). After absorption, the ketones would be metabolized by reduction to the corresponding aliphatic secondary alcohol, followed by conjugation with glucuronic acid. The ketones (Nos 292, 296, 298 and 299) were assigned to structural class II when they were evaluated at the fifty-first meeting (Annex 1, reference *137*) and considered not to be of safety concern at their estimated intakes as flavouring agents. The additional intake arising from intake of agents Nos 914–917 would not result in intakes of the ketones above the threshold for structural class II. There are no safety concerns in relation to use of these chemicals as flavouring agents.

Glyceryl monostearate (No. 918), glyceryl monooleate (No. 919) and *propylene glycol monostearate (No. 926)* were considered at the fifty-seventh meeting in the group of aliphatic acyclic diols, triols and related substances (Annex 1, reference *154*). The estimated intake of propylene glycol monostearate (No. 926) was above the threshold for human intake of structural class I, while the intakes of the others were below the intake threshold (Step A3). After absorption, the glyceryl esters would be hydrolysed to glycerol and the corresponding saturated or unsaturated fatty acid, which are endogenous. Mono- and diglycerides (including glycerol monostearate and glyceryl monooleate) were allocated an ADI 'not limited' at the seventeenth meeting of the Committee (Annex 1, reference *32*). Propylene glycol monostearate (No. 926) would be hydrolysed to stearic acid and propylene glycol, for which an ADI of 0–25 mg/kg bw was established at the seventeenth meeting. All these agents are hydrolysed in food to the corresponding fatty acid and glycerol and, under certain ageing conditions, may be partially oxidized, imparting a rancid note to certain food flavours. The intake of the hydrolysis products resulting from the flavouring uses of these agents are included in the relevant ADI. There is no safety concern in relation to use of these chemicals as flavouring agents.

Triacetin (No. 920) was considered at the fifty-seventh meeting in the group of aliphatic acyclic diols, triols and related substances (Annex 1, reference *154*). The estimated intake exceeded the threshold for human intake of its structural class (Step A3), and triacetin was evaluated under Step A4. When used in foods that are heated or otherwise processed, triacetin would be hydrolysed to glycerol and acetic acid, both of which are endogenous. An ADI 'not specified' was established for glyceryl acetates by the Committee at its twentieth meeting (Annex 1, reference *41*), and the flavouring use of triacetin is included in this ADI. There is no safety concern in relation to the intake of triacetin or its hydrolysis products arising from its use as a flavouring agent.

Glyceryl tripropionate (No. 921) and *tributyrin (No. 922)* were considered at the fifty-seventh meeting in the group of aliphatic acyclic diols, triols and related substances (Annex 1, reference *154*). The estimated intakes were below the threshold for human intake of their structural class (Step A3). With heating, the substances are partially or completely hydrolysed to glycerol and the corresponding carboxylic acid. Propionic and butyric acids were evaluated at the forty-ninth meeting (Annex 1, reference *131*), and their use as flavouring agents (Nos 84 and 87, respectively) was considered not to represent a safety concern. Glycerol and both acids are endogenous, and the intakes arising from flavouring use of substances Nos 921 and 922 would not significantly alter the total intake of either acid. There is no safety concern in relation to use of these chemicals as flavouring agents.

Glycerol 5-hydroxydecanoate (No. 923) and *glycerol 5-hydroxydodecanoate (No. 924)* were considered at the fifty-seventh meeting in the group of aliphatic acyclic diols, triols and related substances (Annex 1, reference *154*). The estimated intakes were below the threshold for human intake of their structural class (step A3). With heating, the substances are partially or completely hydrolysed to glycerol and the corresponding carboxylic acid. The acids are unstable and would rapidly cyclize to δ-decalactone and δ-dodecalactone, respectively. These lactones were evaluated at the forty-ninth meeting (Annex 1, reference *131*), and their uses as flavouring agents (Nos 232 and 236, respectively) were considered not to represent a safety concern, on the basis of the availability of a NOEL for a structural analogue. The intakes of δ-decalactone and δ-dodecalactone arising from flavouring use of Nos 923 and 924 would not significantly alter the total intakes of either lactone. There is no safety concern in relation to use of these chemicals as flavouring agents.

The conclusions of the present meeting relating to the flavouring properties of these chemicals are summarized in Table 11.

Table 11
Information on flavouring properties of chemicals evaluated by the Procedure for the Safety Evaluation of Flavouring Agents

No.	Chemical	Level of use as a flavouring agent (mg/kg)	Reported flavouring properties	Evaluation based on current intake as a flavouring agent
850	Benzoic acid[a]	≤ 100	Aromatic acid with a sweet–sour, acrid note or a balsamic note at concentrations up to 100 mg/kg	No safety concern[b]
861	Glyceryl tribenzoate	≤ 100 (beverages only)	Flavour depends on hydrolysis to *benzoic acid* and *glycerol/propylene glycol*	No safety concern[b]
862	Propylene glycol dibenzoate	≤ 100 (beverages only)	Flavour depends on hydrolysis to *benzoic acid* and *glycerol/propylene glycol*	No safety concern[b]
870	Butyl-*para*-hydroxybenzoate	20 (baked goods) 1000 (beverages)	Flavour depends on hydrolysis to *butyl alcohol* and *para-hydroxybenzoic acid*	No safety concern[b]
909	Glycerol[c]	40 (meats) 500–23 000 (other foods)	Provides a sweet taste (0.6 times as sweet as cane sugar)	Evaluation not finalized, pending definition of 'flavouring agent'
914	3-Oxodecanoic acid glyceride	75 (baked goods and imitation dairy products)	Flavour depends on hydrolysis on heating or during storage. The resulting 3-oxo acid is unstable and decarboxylates to form *2-nonanone* (up to 50 mg/kg).	No safety concern[b]
915	3-Oxododecanoic acid glyceride	75 (baked goods and imitation dairy products)	Flavour depends on hydrolysis on heating or during storage. The resulting 3-oxo acid is unstable and decarboxylates to form *2-undecanone* (up to 50 mg/kg).	No safety concern[b]
916	3-Oxotetradecanoic acid glyceride	75 (baked goods and imitation dairy products)	Flavour depends on hydrolysis on heating or during storage. The resulting 3-oxo acid is unstable and decarboxylates to form *2-tridecanone* (up to 50 mg/kg).	No safety concern[b]
917	3-Oxohexadecanoic acid glyceride	75 (baked goods and imitation dairy products)	Flavour depends on hydrolysis on heating or during storage. The resulting 3-oxo acid is unstable and decarboxylates to form *2-pentadecanone* (up to 50 mg/kg).	No safety concern[b]
918	Glyceryl monostearate[d]	500–3900	Flavour depends on hydrolysis on heating or during storage. The resulting *stearic acid* has flavouring properties. It may be further oxidized to produce 'rancid' flavour notes.	No safety concern[b]

Table 11 *(continued)*

No.	Chemical	Level of use as a flavouring agent (mg/kg)	Reported flavouring properties	Evaluation based on current intake as a flavouring agent
919	Glyceryl monooleate[d]	≤ 100	Flavour depends on hydrolysis on heating or during storage. The resulting *oleic acid* has flavouring properties. It may be further oxidized to produce 'rancid' flavour notes.	No safety concern[b]
920	Triacetin[e]	350 (jams and jellies) ≤ 100 (other foods)	Flavour depends on hydrolysis in heated or otherwise processed foods to *glycerol* and *acetic acid*	No safety concern[b]
921	Glyceryl tripropionate (Tripropionin)	≤ 50	Flavour depends on hydrolysis in heated or otherwise processed foods to *glycerol* and *propionic acid*	No safety concern[b]
922	Tributyrin	≤ 100	Flavour depends on hydrolysis in heated or otherwise processed foods to *glycerol* and *butyric acid*	No safety concern[b]
923	Glycerol 5-hydroxy-decanoate	25	Flavour depends on hydrolysis in heated foods and spontaneous cyclization of the 5-hydroxy acid to δ-*decalactone* (up to 20 mg/kg)	No safety concern[b]
924	Glycerol 5-hydroxy-dodecanoate	25	Flavour depends on hydrolysis in heated foods and spontaneous cyclization of the 5-hydroxy acid to δ-*dodecalactone* (up to 20 mg/kg)	No safety concern[b]
925	Propylene glycol[f]	10 (meats) 690–100 000 (other foods)	Provides a mildly sweet taste. In an aqueous environment, may leave a warm burning sensation in the mouth	Evaluation not finalized, pending definition of 'flavouring agent'
926	Propylene glycol stearate[g]	3000–7000	Flavour depends on hydrolysis on heating or during maturation. The resulting *stearic acid* has flavouring properties. It may be further oxidized to produce a 'rancid' flavour note.	No safety concern[b]

[a] Previously evaluated for use as a preservative
[b] The flavouring uses of this agent are included in the relevant ADI of the agent and/or its hydrolysis products.
[c] Previously evaluated for use as a carrier and humectant and for other uses
[d] Previously evaluated (as mono- and di-glycerides) for use as an emulsifier
[e] Previously evaluated for use as a carrier
[f] Previously evaluated for use as a carrier and humectant and for other uses
[g] Previously evaluated for use as an emulsifier

At its fifty-seventh meeting, the Committee mistakenly included *isoamyl pyruvate (No. 939)* in its evaluation of the aliphatic acyclic diols, triols and related substances, even though there was no information on its current use as a flavouring agent (Annex 1, reference *154*). Since the fifty-seventh meeting, the flavour industry has provided information that the reported annual volume is approximately 1 kg per year in the USA (*5*). On the basis of the equation in section 4.1, this corresponds to a daily *per capita* intake of 0.1 μg, which is below the threshold of concern for its structural class (class I, 1800 μg). Therefore, the present Committee confirmed that there is no safety concern in relation to the use of isoamyl pyruvate as a flavouring agent.

4.4 Specifications of purity for flavouring agents

4.4.1 *Specifications for flavouring agents evaluated for the first time*

Specifications were prepared for 196 flavouring agents being evaluated for the first time and for six flavouring agents that were evaluated for safety at the fifty-seventh meeting but for which specifications were not prepared (Annex 1, reference *154*). At the present meeting, none of the 202 specifications was designated 'tentative'. This is the first time since the review of flavouring agents began that no tentative designations were made for new submissions for specifications for flavouring agents and reflects the high quality of the information received.

4.4.2 *Reconsideration of existing specifications for flavouring agents*

Since 1996, a number of specifications for flavouring agents have been classified as 'tentative' either because of missing physical data or of uncertainty about their use as flavouring agents. In addition the Codex Committee on Food Additives and Contaminants referred 29 specifications of flavouring agents evaluated at the fifty-fifth meeting (Annex 1, reference *151*) to the Committee for reconsideration of certain parameters.

The call for data for the present meeting did not include all these substances, but they had been included in previous calls for data and in the reports of previous meetings. As data had been received before the present meeting, the Committee added them to the agenda.

Chemicals used as flavouring agents

At its fifty-seventh meeting, the Committee questioned whether a number of chemicals were used as flavouring agents (Annex 1, reference *154*). At its present meeting, it agreed that some of these substances have a flavouring function (see section 4.3), and therefore the tentative designation was deleted. Additionally, data missing on some of the substances had subsequently been supplied. Nevertheless, the specifications for glycerol monostearate (No.

918) and glycerol monooleate (No. 919) were maintained as tentative because of missing or inconsistent data. The specifications for glycerol-5-hydroxydecanoate (No. 923) and glycerol 5-hydroxydodecanoate (No. 924) were also maintained as tentative because the assay method was called into question.

The Committee did not finalize its evaluations of glycerol (No. 909) and propylene glycol (No. 925), pending development of a definition of 'flavouring agent'. The Committee agreed that benzoic acid (No. 850) was used as a flavouring agent but that in this use it should comply with the specifications established for benzoic acid used as a preservative. The Committee recommended that the existing specifications for glycerol, propylene glycol, triacetin (No. 920) and benzoic acid be reviewed at a future meeting, especially in relation to the functional uses of these food additives.

The status of the specifications of these chemicals is listed in Table 12.

Missing physical data

In the request for data for the present meeting, 12 flavouring agents with 'tentative' specifications were listed, with a request for the missing data. These data were provided, and the specifications of these flavouring agents were revised and the tentative status deleted. The Committee also considered the specifications of 10 flavouring agents that were designated 'tentative' at the fifty-seventh meeting and for which data were supplied. The specifications were revised and the tentative designation removed, except in the case of

Table 12
Specifications of chemicals for which functional use as flavouring agents was considered at the present meeting

No.	Chemical	Specifications[a]
861	Glyceryl tribenzoate	S
862	Propylene glycol dibenzoate	S
870	Butyl *para*-hydroxybenzoate	S
914	3-Oxodecanoic acid glyceride	R
915	3-Oxododecanoic acid glyceride	R
916	3-Oxotetradecanoic acid glyceride	R
917	3-Oxohexadecanoic acid glyceride	R
918	Glyceryl monostearate	R,T
919	Glyceryl monooleate	R,T
921	Glyceryl tripropanoate	S
922	Tributyrin	S
923	Glycerol 5-hydroxydecanoate	S,T
924	Glycerol 5-hydroxydodecanoate	S,T
926	Propylene glycol stearate	R

[a] R, existing specifications revised: S, specifications exist, revision not considered or required; T, the existing or revised specifications are tentative and comments are invited.

pyruvaldehyde (No. 937), which was maintained as tentative. The status of the specifications of these flavouring agents is provided in Table 13.

Specifications referred to the Committee

Table 14 summarizes the specifications of flavouring agents that were referred to the Committee by the Codex Committee on Food Additives and Contaminants for reconsideration.

5. Future work

1. The Committee concluded that it is not desirable to develop dual specifications, as has been done, for example, for chemicals that were evaluated both by the Procedure for the Safety Evaluation of Flavouring Agents and also as food additives. The Committee recommended that the existing specifications for such chemicals be reviewed at a future meeting, with a view to consolidating and revising them to incorporate all functional uses and new information.

Table 13
Specifications of flavouring agents previously designated as 'tentative'

No.	Chemical	Specifications[a]
111	Lauric acid	R
113	Myristic acid	R
115	Palmitic acid	R
116	Stearic acid	R
390	γ-Ionone	R
490	Allyl thiopropionate	R
814	α-Methylphenethylbutyrate	R
817	4-(*para*-Tolyl)-2-butanone	R
847	Benzyl 2,3-dimethylcrotonate	R
866	Tolualdehydes (mixed *ortho*, *meta* and *para*)	R
872	Anisyl formate	R
609	1,4-Nonanediol diacetate	R
627	Aconitic acid	R
642	3-Phenylpropyl hexanoate	R
678	α-Amylcinnamyl isovalerate	R
729	Dihydroxyacetophenone	R
752	2-Phenyl3-carboethoxyfuran	R
910	3-Oxohexanoic acid glyceride	R
911	3-Oxooctanoic acid glyceride	R
937	Pyruvaldehyde	S,T
943	Acetaldehyde ethyl *cis*-3-hexenyl acetal	R
954	Ethyl vanillin propylene glycol acetal	R

[a]R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing specifications are tentative and comments are invited.

Table 14
Specifications of flavouring agents referred to the Committee

No.	Chemical	Specifications[a]
182	Isoamyl laurate	R
230	Hydroxynonanoic acid δ-lactone	S
238	δ-Tetradecalactone	S
250	γ-Methyldecalactone	S
310	Isopropyl isovalerate	R
455	Butyl sulfide	R
476	Ethyl 3-methylthiopropionate	R
483	Ethyl thioacetate	R
492	Methylthio 2-(acetyloxy)propionate	R
493	Methylthio 2-(propionyloxy)propionate	R
540	1,6-Hexanedithiol	R
542	1,9-Nonanedithiol	R
551	2-Mercaptopropionic acid	R
553	Ethyl 3-mercaptopropionate	R
566	Propyl disulfide	R
601	Ethyl 3-hydroxyhexanoate	R
602	Ethyl 3-oxohexanoate	R
606	Laevulinic acid	R
608	Butyl laevulinate	R
614	Diethyl malonate	R
616	Dimethyl succinate	R
617	Diethyl succinate	R
622	Diethyl tartrate	R
624	Diethyl sebacate	R
625	Dibutyl sebacate	R
626	Ethylene brassylate	R
743	Furfuryl 3-methylbutanoate	S
745	5-Methylfurfural	R

[a]R, existing specifications revised; S, specifications exist, revision not considered or required.

2. The Committee recommended that the acute toxicity of nitrite be evaluated at a future meeting.

3. The Committee agreed to continue its activity to update the heavy metals specifications in food additives and concluded that specifications for antioxidants and other functional uses should be reviewed at the next meeting on food additives.

4. The Committee recognized the need for a working definition of the term 'flavouring agent' and recommended that such a definition be agreed at a future meeting of the Committee.

5. As noted in section 2.7, the present Committee considered several guidelines that had been prepared by the Joint Secretariat and made comments and suggestions for improvement, including the following:

   — The Technical Data Sheets prepared by Committee experts, which summarize the available technological information, should

provide authors of working papers on intake with information on the levels of use of the additive in current practice.

— Data for intake assessments of food additives should preferably be submitted in a standard format. The Joint Secretariat should publish a *Format for submission of intake data* as a separate document and encourage its use when calling for data.

— The Secretariat should publish amended versions of guidelines for working papers on both the FAO and the WHO Internet sites for further comments and suggestions.

— The Committee recommended that the *Guidelines for the preparation of working papers (monographs) on flavouring agents* be updated to include consideration of the evaluation of flavouring agents that are members of groups that have been evaluated previously.

6. Recommendations

In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, the important role of the recommendations of the Committee in the development of international food standards and of regulations in many countries and the need to maintain 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.

Acknowledgements

This report of the Committee is dedicated to Dr John L. Herrman, who joined WHO as Joint Secretary of the Joint FAO/WHO Joint Committee on Food Additives in 1988. From his first meeting, the thirty-third, he demonstrated the unique management skills required of his position. He has served as Joint Secretary at 27 meetings, culminating in the present one, his last before retirement.

Over the course of his career, he has steadfastly supported the work of the Committee and is largely responsible for the emergence of JECFA as the leading international body on food safety.

As WHO Joint Secretary he has displayed immense dedication and leadership, resulting in his international recognition as a leading scientist in food safety. His timely introduction to the Committee of new concepts in safety evaluation has kept the Committee at the forefront of science, has contributed to its continued success and ensures that its advice is based on the best possible science.

The Committee wishes John Herrman a happy and successful retirement.

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Annex 1
Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

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37. *Specifications for the identity and purity of some food colours, enhancers, thickening agents, and certain food additives.* FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.
38. *Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances.* (Nineteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.
39. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.
40. *Specifications for the identity and purity of certain food additives.* FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.
41. *Evaluation of certain food additives* (Twentieth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Food and Nutrition Meetings Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.
42. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 10, 1976.
43. *Specifications for the identity and purity of some food additives.* FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additives Series, No. 11, 1977.
44. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.

45. *Summary of toxicological data of certain food additives.* WHO Food Additives Series, No. 12, 1977.
46. *Specifications for identity and purity of some food additives, including antioxidant, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.
47. *Evaluation of certain food additives and contaminants* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.
48. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series, No. 13, 1978.
49. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 7, 1978.
50. *Evaluation of certain food additives* (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980, and corrigenda.
51. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1980.
52. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.
53. *Evaluation of certain food additives* (Twenty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 653, 1980.
54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.
55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.
56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.
57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1981.
58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.
59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.
60. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 17, 1982.
61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.
62. *Evaluation of certain food additives and contaminants* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.
63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.
64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.
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71. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 34, 1986.
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76. *Principles for the safety assessment of food additives and contaminants in food.* WHO Environmental Health Criteria, No. 70. Geneva, World Health Organization, 1987 (out of print). The full text is available electronically at www.who.int/pcs.
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81. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 23. Cambridge University Press, 1988.
82. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41, 1988.
83. *Evaluation of certain food additives and contaminants* (Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 776, 1989.
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87. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/2, 1990.
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89. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 26, 1990.
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91. *Evaluation of certain veterinary drug residues in food* (Thirty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 799, 1990.
92. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 27, 1991.
93. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/3, 1991.
94. *Evaluation of certain food additives and contaminants* (Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 806, 1991, and corrigenda.
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99. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/4, 1991.
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111. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 33, 1994.
112. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/6, 1994.
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117. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 35, 1996.
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121. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/8, 1996.
122. *Evaluation of certain food additives and contaminants* (Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 868, 1997.
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124. *Compendium of food additive specifications, addendum 4.* FAO Food and Nutrition Paper, No. 52, Add. 4, 1996.
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132. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 40, 1998.
133. *Compendium of food additive specifications: addendum 5.* FAO Food and Nutrition Paper, No. 52, Add. 5, 1997.
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135. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 41, 1998.
136. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/11, 1999.
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139. *Compendium of food additive specifications, addendum 6.* FAO Food and Nutrition Paper, No. 52, Add. 6, 1998.
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142. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/12, 2000.
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144. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 44, 2000.
145. *Compendium of food additive specifications, addendum 7.* FAO Food and Nutrition Paper, No. 52, Add. 7, 1999.
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148. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/13, 2000.
149. *Evaluation of certain food additives and contaminants* (Fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 901, 2001.
150. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 46, 2001.
151. *Compendium of food additive specifications: addendum 8.* FAO Food and Nutrition Paper, No. 52, Add. 8, 2000.
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153. *Safety evaluation of certain mycotoxins in food.* WHO Food Additives Series, No. 47/ FAO Food and Nutrition Paper 74, 2001.
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155. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 48, 2002.

156. *Compendium of food additive specifications: addendum 9.* FAO Food and Nutrition Paper, No. 52, Add. 9, 2001.
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Annex 2

Acceptable daily intakes, other recommendations and information on specifications

Food additives evaluated toxicologically

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Alitame	R	0–1 mg/kg bw[b]
Cross-linked sodium carboxymethyl cellulose	N	Included in the group ADI 'not specified'[c] with other modified celluloses
Mineral oils (low- and medium-viscosity)		
Class I[d]	R	0–10 mg/kg bw
Class II[e] and Class III[f]	R	0–0.01 mg/kg bw (group ADI) (temporary)[g]
Nitrite	S	0–0.07 mg/kg bw (expressed as nitrite ion)
Nitrate	S	0–3.7 mg/kg bw (expressed as nitrate ion)
Salatrim (short- and long-chain acyltriglyceride molecules)	R	Adequate information was not available to evaluate safety and nutritional effects.

[a] N, new specifications prepared; R, existing specifications revised; S, existing specifications were not considered.

[b] ADI was established at the forty-sixth meeting (WHO Technical Report Series No, 868, 1997). Evaluation of a 90-day study of teolerance in patients with diabetes was postponed.

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

[d] Including P70(H) oil.

[e] Including N70(H) and N70(A) oils.

[f] Including P15(H), N15(H), and N10(A) oils

[g] See Annex3.

Food additive considered for specifications only

Food additive	Specifications[a]
Amyloglucosidase from *Aspergillus niger*, var.	R

[a] R, existing specifications revised

Flavouring agents evaluated by the Procedure for the Safety Evaluation of Flavouring Agents

A. Alicyclic primary alcohols, aldehydes, acids and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Cyclohexanecarboxylic acid	961	N	No safety concern
Methyl cyclohexanecarboxylate	962	N	No safety concern
Ethyl cyclohexanecarboxylate	963	N	No safety concern
Cyclohexaneethyl acetate	964	N	No safety concern
Cyclohexaneacetic acid	965	N	No safety concern
Ethyl cyclohexanepropionate	966	N	No safety concern
2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	967	N	No safety concern
cis-5-Isopropenyl-*cis*-2-methylcyclopentan-1-carboxaldehyde	968	N	No safety concern
Campholene acetate	969	N	No safety concern
α-Campholenic alcohol	970	N	No safety concern
para-Menth-1-en-9-al	971	N	No safety concern
1-*para*-Menthen-9-yl acetate	972	N	No safety concern
para-Mentha-1,8-dien-7-al	973	N	No safety concern
para-Mentha-1,8-dien-7-ol	974	N	No safety concern
para-Mentha-1,8-dien-7-yl acetate	975	N	No safety concern
1,2,5,6-Tetrahydrocuminic acid	976	N	No safety concern
2,6,6-Trimethylcyclohexa-1,3-dienyl methanal	977	N	No safety concern
2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde	978	N	No safety concern
2,6,6-Trimethyl-1&2-cyclohexen-1-carboxaldehyde	979	N	No safety concern
2-Formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (Myrtenal)	980	N	No safety concern
Myrtenol	981	N	No safety concern
Myrtenyl acetate	982	N	No safety concern
6,6-Myrtenyl formate	983	N	No safety concern
Santalol (α and β)	984	N	No safety concern
Santalyl acetate (α and β)	985	N	No safety concern
10-Hydroxymethylene-2-pinene	986	N	No safety concern

[a]N, new specifications prepared

B. Phenethyl alcohol, aldehyde, acid and related acetals and esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Phenethyl alcohol	987	N	No safety concern
Phenethyl formate	988	N	No safety concern
Phenethyl acetate	989	N	No safety concern
Phenethyl propionate	990	N	No safety concern
Phenethyl butyrate	991	N	No safety concern
Phenethyl isobutyrate	992	N	No safety concern
Phenethyl 2-methylbutyrate	993	N	No safety concern
Phenethyl isovalerate	994	N	No safety concern
Phenethyl hexanoate	995	N	No safety concern
Phenethyl octanoate	996	N	No safety concern
Phenethyl tiglate	997	N	No safety concern
Phenethyl senecioate	998	N	No safety concern
Phenethyl phenylacetate	999	N	No safety concern
Acetaldehyde phenethyl propyl acetal	1000	N	No safety concern
Acetaldehyde butyl phenethyl acetal	1001	N	No safety concern
Phenylacetaldehyde	1002	N	No safety concern
Phenylacetaldehyde dimethyl acetal	1003	N	No safety concern
Phenylacetaldehyde glyceryl acetal	1004	N	No safety concern
Phenylacetaldehyde 2,3-butylene glycol acetal	1005	N	No safety concern
Phenylacetaldehyde diisobutyl acetal	1006	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Phenylacetic acid	1007	N	No safety concern
Methyl phenylacetate	1008	N	No safety concern
Ethyl phenylacetate	1009	N	No safety concern
Propyl phenylacetate	1010	N	No safety concern
Isopropyl phenylacetate	1011	N	No safety concern
Butyl phenylacetate	1012	N	No safety concern
Isobutyl phenylacetate	1013	N	No safety concern
Isoamyl phenylacetate	1014	N	No safety concern
Hexyl phenylacetate	1015	N	No safety concern
3-Hexenyl phenylacetate	1016	N	No safety concern
Octyl phenylacetate	1017	N	No safety concern
Rhodinyl phenylacetate	1018	N	No safety concern
Linalyl phenylacetate	1019	N	No safety concern
Geranyl phenylacetate	1020	N	No safety concern
Citronellyl phenylacetate	1021	N	No safety concern
Santalyl phenylacetate (α and β)	1022	N	No safety concern
para-Tolylacetaldehyde	1023	N	No safety concern
para-Isopropylphenylacetaldehyde	1024	N	No safety concern
Methyl *para-tert*-butylphenylacetate	1025	N	No safety concern
Phenoxyacetic acid	1026	N	No safety concern
Ethyl (*para*-tolyloxy)acetate	1027	N	No safety concern
2-Phenoxyethyl isobutyrate	1028	N	No safety concern
Sodium 2-(4-methoxyphenoxy)propanoate	1029	N	No safety concern

[a]N, new specifications prepared

C. Sulfur-containing heterocyclic compounds

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Thiamine hydrochloride	1030	N	No safety concern
4-Methyl-5-thiazoleethanol	1031	N	No safety concern
Thiazole	1032	N	No safety concern
2-(1-Methylpropyl)thiazole	1033	N	No safety concern
2-Isobutylthiazole	1034	N	No safety concern
4,5-Dimethylthiazole	1035	N	No safety concern
2,4,5-Trimethylthiazole	1036	N	No safety concern
2-Isopropyl-4-methylthiazole	1037	N	No safety concern
4-Methyl-5-vinylthiazole	1038	N	No safety concern
2,4-Dimethyl-5-vinylthiazole	1039	N	No safety concern
Benzothiazole	1040	N	No safety concern
2-Acetylthiazole	1041	N	No safety concern
2-Propionylthiazole	1042	N	No safety concern
4-Methylthiazole	1043	N	No safety concern
2-Ethyl-4-methylthiazole	1044	N	No safety concern
4,5-Dimethyl-2-isobutyl-3-thiazoline	1045	N	No safety concern
2-Isobutyl-4,6-dimethyldihydro-1,3,5-dithiazine and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine (mixture)	1046	N	No safety concern
2-Isopropyl-4,6-dimethyl and 4-isopropyl-2,6-dimethyldihydro-1,3,5-dithiazine (mixture)	1047	N	No safety concern
2,4,6-Triisobutyl-5,6-dihydro-4*H*-1,3,5-dithiazine	1048	N	No safety concern
2,4,6-Trimethyldihydro-4*H*-1,3,5-dithiazine	1049	N	No safety concern
5-Methyl-2-thiophenecarboxaldehyde	1050	N	No safety concern
3-Acetyl-2,5-dimethylthiophene	1051	N	No safety concern
2-Thienylmercaptan	1052	N	No safety concern
2-Thienyl disulfide	1053	N	No safety concern
4-Methyl-5-thiazoleethanol acetate	1054	N	No safety concern
2,4-Dimethyl-5-acetylthiazole	1055	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
2-Ethoxythiazole	1056	N	No safety concern
2-Methyl-5-methoxythiazole	1057	N	No safety concern
4,5-Dimethyl-2-ethyl-3-thiazoline	1058	N	No safety concern
2-(2-Butyl)-4,5-dimethyl-3-thiazoline	1059	N	No safety concern

[a]N, new specifications prepared

D. Sulfur-substituted furan derivatives

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
2-Methyl-3-furanthiol	1060	N	No safety concern
2-Methyl-3-(methylthio)furan	1061	N	No safety concern
2-Methyl-5-(methylthio)furan	1062	N	No safety concern
2,5-Dimethyl-3-furanthiol	1063	N	No safety concern
Methyl 2-methyl-3-furyl disulfide	1064	N	No safety concern
Propyl 2-methyl-3-furyl disulfide	1065	N	No safety concern
Bis(2-methyl-3-furyl) disulfide	1066	N	No safety concern
Bis(2,5-dimethyl-3-furyl) disulfide	1067	N	No safety concern
Bis(2-methyl-3-furyl) tetrasulfide	1068	N	No safety concern
2-Ethanethoic acid, *S*-(2-methyl-3-furanyl) ester	1069	N	No safety concern
2,5-Dimethyl-3-furan thioisovalerate	1070	N	No safety concern
2,5-Dimethyl-3-thiofuroylfuran	1071	N	No safety concern
Furfuryl mercaptan	1072	N	No safety concern
S-Furfuryl thioformate	1073	N	No safety concern
S-Furfuryl thioacetate	1074	N	No safety concern
S-Furfuryl thiopropionate	1075	N	No safety concern
Furfuryl methyl sulfide	1076	N	No safety concern
Furfuryl isopropyl sulfide	1077	N	No safety concern
Methyl furfuryl disulfide	1078	N	No safety concern
Propyl furfuryl disulfide	1079	N	No safety concern
2,2'-(Thiodimethylene)difuran	1080	N	No safety concern
2,2'-(Dithiodimethylene)difuran	1081	N	No safety concern
2-Methyl-3-, 5- or 6-(furfurylthio)pyrazine	1082	N	No safety concern
S-Methyl thiofuroate	1083	N	No safety concern
4-[(2-Furanmethyl)thio]-2-pentanone	1084	N	No safety concern
3-[(2-Methyl-3-furyl)thio]-4-heptanone	1085	N	No safety concern
2,6-Dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone	1086	N	No safety concern
4-[(2-Methyl-3-furyl)thio]-5-nonanone	1087	N	No safety concern
Ethyl 3-(furfurylthio)propionate	1088	N	No safety concern
2-Methyl-3-thioacetoxy-4,5-dihydrofuran	1089	N	No safety concern
2-Methyl-3-tetrahydrofuranthiol	1090	N	No safety concern
2,5-Dimethyl-3-tetrahydrofuranthiol, *cis* and *trans* isomers	1091	N	No safety concern
2,5-Dimethyl-3-thioacetoxy-tetrahydrofuran, *cis* and *trans* isomers	1092	N	No safety concern

[a]N, new specifications prepared

E. Alicyclic ketones, secondary alcohols and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Cyclohexyl acetate	1093	N	No safety concern
Cyclohexyl butyrate	1094	N	No safety concern
Cyclohexyl formate	1095	N	No safety concern
Cyclohexyl isovalerate	1096	N	No safety concern
Cyclohexyl propionate	1097	N	No safety concern
cis and *trans*-*para*-1(7)8-Menthadien-2-yl acetate	1098	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
3,3,5-Trimethyl cyclohexanol	1099	N	No safety concern
Cyclohexanone	1100	N	No safety concern
Cyclopentanone	1101	N	No safety concern
2-Methylcyclohexanone	1102	N	No safety concern
3-Methylcyclohexanone	1103	N	No safety concern
4-Methylcyclohexanone	1104	N	No safety concern
1-Methyl-1-cyclopenten-3-one	1105	N	No safety concern
2-Hexylidene cyclopentanone	1106	N	No safety concern
3-Methyl-2-cyclohexen-1-one	1107	N	No safety concern
2,2,6-Trimethylcyclohexanone	1108	N	No safety concern
2-*sec*-Butylcyclohexanone	1109	N	No safety concern
4-Isopropyl-2-cyclohexenone	1110	N	No safety concern
Tetramethylethylcyclohexenone (mixture of isomers)	1111	N	No safety concern
Isophorone	1112	N	No safety concern
3-Methyl-5-propyl-2-cyclohexen-1-one	1113	N	No safety concern
3-Methyl-2-(2-pentenyl)-2-cyclopenten-1-one	1114	N	No safety concern
Isojasmone	1115	N	No safety concern
(*E*)-2-(2-Octenyl)cyclopentanone	1116	N	No safety concern
2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone	1117	N	No safety concern

[a]N, new specifications prepared

F. Aliphatic secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
3-Decanone	1118	N	No safety concern
5-Methyl-5-hexen-2-one	1119	N	No safety concern
6-Methyl-5-hepten-2-one	1120	N	No safety concern
3,4,5,6-Tetrahydropseudoionone	1121	N	No safety concern
6,10-Dimethyl-5,9-undecadien-2-one	1122	N	No safety concern
2,6,10-Trimethyl-2,6,10-pentadecatrien-14-one	1123	N	No safety concern
3-Penten-2-one	1124	N	No safety concern
4-Hexen-3-one	1125	N	No safety concern
2-Hepten-4-one	1126	N	No safety concern
3-Hepten-2-one	1127	N	No safety concern
3-Octen-2-one	1128	N	No safety concern
2-Octen-4-one	1129	N	No safety concern
3-Decen-2-one	1130	N	No safety concern
4-Methyl-3-penten-2-one	1131	N	No safety concern
5-Methyl-3-hexen-2-one	1132	N	No safety concern
5-Methyl-2-hepten-4-one	1133	N	No safety concern
6-Methyl-3,5-heptadien-2-one	1134	N	No safety concern
(*E*)-7-Methyl-3-octen-2-one	1135	N	No safety concern
3-Nonen-2-one	1136	N	No safety concern
(*E*) and (Z)-4,8-Dimethyl-3,7-nonadien-2-one	1137	N	No safety concern
(*E*)-6-Methyl-3-hepten-2-one	1138	N	No safety concern
(*E*,*E*)-3,5-Octadien-2-one	1139	N	No safety concern
3-Octen-2-ol	1140	N	No safety concern
(*E*)-2-Octen-4-ol	1141	N	No safety concern
2-Pentyl butyrate	1142	N	No safety concern
(+/–)Heptan-3-yl acetate	1143	N	No safety concern
(+/–)Heptan-2-yl butyrate	1144	N	No safety concern
(+/–)Nonan-3-yl acetate	1145	N	No safety concern
2-Pentyl acetate	1146	N	No safety concern
1-Penten-3-one	1147	N	No safety concern
1-Octen-3-one	1148	N	No safety concern
2-Pentyl-1-buten-3-one	1149	N	No safety concern

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
1-Penten-3-ol	1150	N	No safety concern
1-Hexen-3-ol	1151	N	No safety concern
1-Octen-3-ol	1152	N	No safety concern
1-Decen-3-ol	1153	N	No safety concern
(*E*,R)-3,7-Dimethyl-1,5,7-octatrien-3-ol	1154	N	No safety concern
6-Undecanone	1155	N	No safety concern
2-Methylheptan-3-one	1156	N	No safety concern

[a]N, new specifications prepared

Flavouring agents considered for specifications only

No.	Flavouring agent	Specifications[a]
111	Lauric acid	R
113	Myristic acid	R
115	Palmitic acid	R
116	Stearic acid	R
182	Isoamyl laurate	R
310	Isopropyl isovalerate	R
390	γ-Ionone	R
455	Butyl sulfide	R
476	Ethyl 3-methylthiopropionate	R
483	Ethyl thioacetate	R
490	Allyl thiopropionate	R
492	Methylthio 2-(acetyloxy)propionate	R
493	Methylthio 2-(propionyloxy) propionate	R
540	1,6-Hexanedithiol	R
542	1,9-Nonanedithiol	R
551	2-Mercaptopropionic acid	R
553	Ethyl 3-mercaptopropionate	R
564	Dimethyl disulfide	R
566	Propyl disulfide	R
601	Ethyl 3-hydroxyhexanoate	R
602	Ethyl 3-oxohexanoate	R
606	Laevulinic acid	R
608	Butyl levulinate	R
609	1 4-Nonanediol diacetate	R
614	Diethyl malonate	R
616	Dimethyl succinate	R
617	Diethyl succinate	R
622	Diethyl tartrate	R
624	Diethyl sebacate	R
625	Dibutyl sebacate	R
626	Ethylene brassylate	R
627	Aconitic acid	R
642	3-Phenylpropyl hexanoate	R
678	α-Amylcinnamyl isovalerate	R
729	Dihydroxyacetophenone	R
745	5-Methylfurfural	R
752	2-Phenyl-3-carbethoxyfuran	R
814	α-Methylphenethyl butyrate	R
817	4-(*para*-Tolyl)-2-butanone	R
847	Benzyl 2 3-dimethylcrotonate	R
861	Glyceryl tribenzoate	R
862	Propylene glycol dibenzoate	S
866	Tolualdehydes (mixed *ortho meta* and *para*)	R
870	Butyl *para*-hydroxybenzoate	S
872	Anisyl formate	R

No.	Flavouring agent	Specifications[a]
910	3-Oxohexanoic acid diglyceride	R
911	3-Oxooctanoic acid glyceride	R
914	3-Oxodecanoic acid glyceride	R
915	3-Oxododecanoic acid glyceride	R
916	3-Oxotetradecanoic acid glyceride	R
917	3-Oxohexadecanoic acid glyceride	R
918	Glyceryl monostearate	R,T
919	Glyceryl monooleate	R,T
921	Glyceryl tripropanoate	S
922	Tributyrin	S
923	Glycerol 5-hydroxydecanoate	S,T
924	Glycerol 5-hydroxydodecanoate	S T
926	Propylene glycol stearate	R
937	Pyruvaldehyde	S,T
943	Acetaldehyde ethyl cis-3-hexenyl acetal	R
954	Ethyl vanillin propylene glycol acetal	R
955	4-Hydroxybenzyl alcohol	N
956	4-Hydroxybenzaldehyde	N
957	4-Hydroxybenzoic acid	N
958	2-Hydroxybenzoic acid	N
959	4-Hydroxy-3-methoxy benzoic acid	N
960	Vanillin erythro- and threo-butan-2 3-diol acetal	N

[a]N, new specifications prepared; R, existing specifications revised; S, existing specifications were maintained; T, the existing, new, or revised specifications are tentative and new information is required.

Flavouring agents for which confirmation of flavour use was required

The Committee could not complete its evaluation of 18 substances at its fifty-seventh meeting, pending confirmation that they were in current use as flavouring agents. The Committee received information from the flavour industry on these substances, and concluded that flavour uses have been established for 16 of them. The conclusions of the Committee are summarized in the following table.

No.	Flavouring agent	Evaluation based on current intake as a flavouring agent
850	Benzoic acid[a]	No safety concern
861	Glyceryl tribenzoate	No safety concern
862	Propylene glycol dibenzoate	No safety concern
870	Butyl-*para*-hydroxybenzoate	No safety concern
909	Glycerol[b]	Evaluation not finalized, pending definition of 'flavouring agent'
914	3-Oxodecanoic acid glyceride	No safety concern
915	3-Oxododecanoic acid glyceride	No safety concern
916	3-Oxotetradecanoic acid glyceride	No safety concern
917	3-Oxohexadecanoic acid glyceride	No safety concern
918	Glyceryl monostearate[c]	No safety concern
919	Glyceryl monooleate[c]	No safety concern
920	Triacetin[d]	No safety concern
921	Glyceryl tripropionate (Tripropionin)	No safety concern
922	Tributyrin	No safety concern
923	Glycerol 5-hydroxydecanoate	No safety concern
924	Glycerol 5-hydroxydodecanoate	No safety concern
925	Propylene glycol[e]	Evaluation not finalized, pending definition of 'flavouring agent'
926	Propylene glycol stearate[f]	No safety concern

Annex 3
Further information required or desired

Mineral oils (low- and medium-viscosity), class II and class III

Information on the relevance to humans of the response of Fischer 344 and Sprague-Dawley rats to these materials is required for evaluation in 2006. In order that the data be applicable to as wide a range of mineral oils as possible, the Committee suggested that commercial mineral oils of the lowest viscosity be used in such studies. Additional studies might be required, depending on the outcome of these studies.

Aluminium powder, iron oxides and titanium dioxide

The high levels of heavy metals set in the present specifications for these inorganic colours should be reconsidered. The Committee maintained the existing limits but decided to call for data on the raw materials and manufacturing methods and analytical data on impurities for review at a future meeting.

Annex 4

Summary of conclusions on flavouring agents with minimum assay values of 95% or less

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
42	Isoamyl formate	92	4–8% isoamyl alcohol	Isoamyl alcohol (No. 52) has been evaluated by JECFA.	Secondary components do not raise safety concern.
53	Citronellyl formate	86	5–10% citronellol	NOEL for citronellol is > 50 mg/kg bw per day in rats (Trubek Laboratories, Inc., 1958); oral LD_{50} in rats: 3400 mg/kg bw (Moreno, 1973)	Secondary components do not raise safety concern.
54	Geranyl formate	85 (total esters)	8–10% geraniol; 2–4% nerol	Data for geraniol in rats: 28-week NOEL: 50 mg/kg bw per day (Hagan et al., 1967) 13-week NOEL: 500 mg/kg bw per day (Hagan et al., 1967) 16-week NOEL: 50 mg/kg bw per day (Food and Drug Administration, 1954) Oral LD_{50}: 3600 mg/kg bw (Jenner et al., 1964) Geranyl and citronellyl acetate had no effect at 2000 mg/kg bw per day for 2 years in F344 rats or $B6C3F_1$ mice (National Toxicology Program, 1987). Nerol is metabolized by oxidation of the primary alcohol and ω-oxidation to yield polar, excretable metabolites. Oral LD_{50} in rats: 4500 mg/kg bw (Moreno, 1972)	Secondary components do not raise safety concern.
55	Neryl formate	85	4–6% geraniol; 1–3% nerol	For data on geraniol and nerol, see No. 54 above.	Secondary components do not raise safety concern.
56	Rhodinyl formate	85 (total esters)	10–13% rhodinol	Rhodinol is metabolized by oxidation of the primary alcohol and ω-oxidation to yield polar, excretable metabolites. Acute toxicity in rats treated orally: 3/10 deaths at 5000 mg/kg bw (Moreno, 1973)	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
57	Citronellyl acetate	92 (total esters)	4–6% citronellol	For data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.
60	Rhodinyl acetate	87 (total esters)	9–12% rhodinol	For data on rhodinol, see No. 56 above.	Secondary components do not raise safety concern.
61	Citronellyl propionate	90 (total esters)	5–8% citronellol	For data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.
62	Geranyl propionate	92 (total esters)	3–4% geraniol; 1–2% nerol	For data on geraniol and nerol, see No. 54 above.	Secondary components do not raise safety concern.
65	Citronellyl butyrate	90 (total esters)	6–8% citronellol	For data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.
66	Geranyl butyrate	92 (total esters)	3–5% geraniol; 1% nerol	For data on geraniol, and nerol, see No. 54 above.	Secondary components do not raise safety concern.
68	Rhodinyl butyrate	90	3–5% rhodinol	For data on rhodinol, see No. 56 above.	Secondary components do not raise safety concern.
71	Citronellyl isobutyrate	92 (total esters)	3–5% citronellol	For data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
73	Neryl isobutyrate	92	2–5% nerol; 1–2% geraniol	For data on geraniol and nerol, see No. 54 above.	Secondary components do not raise safety concern.
95	Heptanal	92	4–7% 2-methylhexanal	2-Methylhexanal is oxidized to 2-methylhexanoic acid, which is oxidized in the fatty acid pathway similarly to 2-methyldecanoic acid (see No. 107)	Secondary components do not raise safety concern.
98	Octanal	92	4–7% 2-methylheptanal	2-Methylheptanal is oxidized to 2-methylheptanoic acid, which is oxidized in the fatty acid pathway and citric acid cycle.	Secondary components do not raise safety concern.
101	Nonanal	92	4–8% 2-methyloctanal	2-Methyloctanal (No. 270) has been evaluated by JECFA.	Secondary components do not raise safety concern.
104	Decanal	92	4–7% 2-methylnonanal	2-Methylnonanal is oxidized to 2-methylnonanoic acid, which is oxidized in the fatty acid pathway and citric acid cycle.	Secondary components do not raise safety concern.
107	Undecanal	92	4–8% 2-methyldecanal	2-Methyldecanal is oxidized to the corresponding acid, which undergoes β-oxidation to yield a propionic acid fragment and octanoyl coenzyme A, which is metabolized to carbon dioxide and water. Acute toxicity Rats: 0/10 deaths at 5000 mg/kg bw (Moreno, 1975) Rabbits: 1/10 deaths at 5000 mg/kg bw (Moreno, 1975)	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
110	Lauric aldehyde	90	3–6% tetradecanal; 2–5% decanal; 1–2% hexadecanal	Tetradecanal (No. 112) has been evaluated by JECFA. Decanal (No. 104) has been evaluated by JECFA. Hexadecanal is oxidized to palmitic acid and enters the fatty acid pathway, where it is completely metabolized.	Secondary components do not raise safety concern.
112	Myristaldehyde	85	10–12% dodecanal, hexadecanal and octadecanal	Dodecanal (No. 110) has been evaluated by JECFA. Hexadecanal and octadecanal are oxidized to palmitic and stearic acid, respectively, and metabolized in the fatty acid pathway and citric acid cycle.	Secondary components do not raise safety concern.
117	Propyl formate	94	4–6% propyl alcohol	Propyl alcohol (No. 82) has been evaluated by JECFA.	Secondary components do not raise safety concern.
119	n-Amyl formate	92	4–8% *n*-amyl alcohol	Amyl alcohol (No. 88) has been evaluated by JECFA.	Secondary components do not raise safety concern.
124	Isobutyl formate	94	4–6% isobutyl alcohol	Isobutyl alcohol (No. 251) has been evaluated by JECFA.	Secondary components do not raise safety concern.
170	n-Amyl heptanoate	93	4–7% *n*-amyl 2-methylhexanoate	*n*-Amyl-2-methylhexanoate is hydrolysed to amyl alcohol (No. 88) and 2-methylhexanoic acid (No. 265), which have been evaluated by JECFA.	Secondary components do not raise safety concern.
180	Methyl laurate	90	3–6% methyl tetradecanoate; 2–5% methyl decanoate; 1–2% methyl hexadecanoate	Methyl tetradecanoate (No. 183) has been evaluated by JECFA. A 90-day study of a mixture of methyl tetradecanoate, methyl decanoate and methyl hexadecanoate in rats showed no effects with any of the materials at 1% of the diet, equivalent to 500 mg/kg bw per day (Alfin-Slater et al., 1965).	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
205	Methyl 2-methylbutyrate	92	5–7% methyl isovalerate	Methyl isovalerate (No. 195) has been evaluated by JECFA.	Secondary components do not raise safety concern.
212	2-Methylbutyl 2-methylbutyrate	90	5–7% 2-methylbutyl 3-methylbutyrate	2-Methylbutyl 3-methylbutyrate (No. 204) has been evaluated by JECFA.	Secondary components do not raise safety concern.
237	6-Hydroxy-3,7-dimethyloctanoic acid lactone	90	5–6% 6-hydroxy-3,7-dimethyl-2-octenoic acid lactone	The secondary component differs from the primary component only in the presence of a double bond at the 2-position of the secondary component. The NOEL for a similar 2-alkenoic acid lactone (5-hydroxy-2,4-decadienoic acid-$^{\delta}$-lactone) in a 90-day study in rats was 12 mg/kg bw per day (Cox et al., 1974a).	Secondary components do not raise safety concern.
272	3,7-Dimethyl-1-octanol	90	5–7% geraniol and citronellol	For data on geraniol, see No. 54 above; for data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.
302	2,6-Dimethyl-4-heptanone	80	15–17% 4,6-dimethyl-2-heptanone	4,6-Dimethyl-2-heptanone is reduced in vivo, and the resulting alcohol is conjugated with glucuronic acid and excreted in the urine. Oral LD_{50} in rats: 5800 mg/kg bw (Bar & Griepentrog, 1967)	Secondary components do not raise safety concern.
303	2,6-Dimethyl-4-heptanol	90	8–9% 2-heptanol	2-Heptanol (No. 284) has been evaluated by JECFA.	Secondary components do not raise safety concern.
322	*cis*-5-Octen-1-ol	90	7–9% *trans*-5-octen-1-ol	*trans*-5-Octen-1-ol is oxidized to *trans*-5-octenoic acid, which is oxidized in the fatty acid pathway and the citric acid cycle.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
323	*cis*-5-Octenal	85	10–15% *trans*-5-octenal	*trans*-5-Octenal is oxidized to the corresponding carboxylic acid, which is oxidized in the fatty acid pathway and citric acid cycle.	Secondary components do not raise safety concern.
325	*cis*-6-Nonenal	90	6–9% *trans*-6-nonenal	*trans*-6-Nonenal is oxidized to 6-nonenoic acid, which is completely metabolized in the fatty acid pathway.	Secondary components do not raise safety concern.
332	Linoleic acid	62	44–46% linolenic acid; 18–20% linoleic acid; 22–25% stearic and oleic acid; 7–8% palmitic acid	Stearic acid (No. 116), oleic acid (No. 333) and palmitic acid (No. 115) have all been evaluated by JECFA.	Secondary components do not raise safety concern.
346	Methyl linoleate and methyl linolenate	60	44–46% methyl linolenate; 18–20% methyl linoleate; 22–25% methyl stearate and methyl oleate; 7–8% methyl palmitate	The NOELs for methyl stearate, methyl oleate and methyl palmitate fed to rats for 90 days at 1% of the diet was 500 mg/kg bw per day (Alfin-Slater et al., 1965).	Secondary components do not raise safety concern.
348	2,6-Dimethyl-6-hepten-1-ol	90	5–10% 6-methyl-5-hepten-2-one	6-Methyl-5-hepten-2-one (No. 1120) was evaluated at the present meeting.	Secondary components do not raise safety concern.
349	2,6-Dimethyl-5-heptenal	85	9–10% 6-methyl-5-hepten-2-one; 1–2% 2,6-dimethyl-6-heptenal	For data on 6-methyl-5-hepten-2-one, see No. 348 above. 2,6-Dimethyl-6-heptenal is oxidized to the corresponding acid, which undergoes β-oxidation.	Secondary components do not raise safety concern.
358	Linalyl formate	90	6–8% linalool	Linalool (No. 356) has been evaluated by JECFA.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
360	Linalyl propionate	92	2–5% linalool	For data on linalool, see No. 358 above.	Secondary components do not raise safety concern.
384	β-Damascone	90 (sum of *cis* and *trans* isomers)	5–8% α- and δ-damascone	α-Damascone (No. 385) and δ-damascone (No. 386) have been evaluated by JECFA.	Secondary components do not raise safety concern.
385	α-Damascone	98 (sum of *cis* and *trans* isomers)	92–96% *trans*, 4–8% *cis* isomers	The NOEL in a 90-day study with α-damascone containing a *trans*- and *cis*-isomer mixture listed in specifications was 2 mg/kg bw per day (Posternak & Vodoz, 1975). The position of the double bond and the presence of *cis* and *trans* isomers is not expected to alter metabolic detoxication pathways. α-Damascone is metabolized by reduction of the side-chain ketone group to yield the corresponding alcohol, which is excreted as the glucuronic acid conjugate.	Secondary components do not raise safety concern.
399	Methyl-β-ionone	88 (sum of *cis* and *trans* isomers of α-, β- and γ-methylionone)	7–10% α- and β-isomethylionone	α- and β-Isomethylionone and α- and β-methylionone are prepared by methylation of ionone. Metabolic detoxication proceeds by reduction of the ketone followed by conjugation of the resulting alcohol with glucuronic acid; the presence of a methyl group is not anticipated to alter the metabolism significantly.	Secondary components do not raise safety concern.
410	2,3-Pentadione	93	2–3% 2,5-diethylcyclohexadien-1,4-dione	2,3-Pentadione dimerizes to 2,5-diethylcyclohexadien-1,4-dione, which is expected to be reduced to the corresponding alcohol and excreted or conjugated with glutathione.	Secondary components do not raise safety concern.
419	Ethyl cyclopentenolone	90	5–10% 3-ethylcyclopentan-1,2-dione (enolic form)	The secondary component is the enol form of the principal substance, ethyl cyclopentenolone (keto form), which is a diketone in equilibrium with the corresponding enol.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
435	*para*-Menth-1-en-3-one	94	2–3% menthol and menthone	Menthol (No. 427) and menthone (No. 429) have been evaluated by JECFA.	Secondary components do not raise safety concern.
592	Citronellyloxy-acetaldehyde	75	20–21% geranyloxyacetaldehyde; 1–2% citronellol	The structures of geranyloxyacetaldehyde and citronellyloxyaldehyde differ only in the presence of a second double-bond at the 2-position of geranyloxyaldehyde. The safety evaluation of the named flavouring agent also applies to the secondary component. Acute toxicity of oral citronellyloxyaldehyde in rats: no deaths at 5000 mg/kg bw (Moreno, 1976). For data on citronellol, see No. 53 above.	Secondary components do not raise safety concern.
604	3-(Hydroxymethyl)-2-heptanone	90	5–8% 1-hydroxy-3-ocatanone	The secondary component, 1-hydroxy-3-octanone, is oxidized to 3-oxooctanoic acid, which is predicted to be metabolized in the fatty acid pathway.	Secondary components do not raise safety concern.
625	Dibutyl sebacate	93	2–4% butyl esters of C14, C16 and C18 fatty acids	As the acid is prepared by oxidative cleavage of unsaturated fatty acids, small amounts of fatty acids are secondary components of sebacate esters. The butyl esters of C14, C16 and C18 fatty acids are hydrolysed and metabolized as endogenous fatty acids.	Secondary components do not raise safety concern.
668	Linalyl cinnamate	94	3–5% linalool	For data on linalool, see No. 358 above.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
978	2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde	92	2.6% β-cyclocitral; 0.5% β-ionone; 3% methyl β-homocyclogeranate; 0.6% ethyl β-homocyclogeranate	β-Cyclocitral is a mixture of predominantly 2,6,6-trimethyl-1-cyclohexene-1-aldehyde (No. 979) and 2,6,6-trimethyl-2-cyclohexene-1-aldehyde. The NOEL for the structurally related 2,2,3-trimethylcyclopent-3-ene-1-aldehyde (No. 967) in a 90-day study in rats was 12 mg/kg bw per day (BIBRA, 1976). β-Ionone (No. 392) has been evaluated by JECFA. Methyl β-homocyclogeranate and ethyl β-homocyclogeranate are esters of (2,6,6-trimethyl-2-cyclohexen-1-yl)acetic acid (CAS No. 24739-72-8), a simple cyclohexylacetic acid derivative. The esters are expected to be hydroysed to the corresponding acid in vivo. The acid may be excreted directly as a glucuronic acid conjugate or undergo β-oxidation of the side-chain.	Secondary components do not raise safety concern.
1005	Phenylacetaldehyde 2,3-butylene glycol acetal	93	2–3% butane-2,3-diol	Butanediol is the diol formed by hydrolysis of phenylacetaldehyde 2,3-butanediol acetal. The diol is excreted as the glucuronide conjugate.	Secondary components do not raise safety concern.
1046	A mixture of 2-isobutyl-4,6-dimethyl and 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine	64% 2-isobutyl-4,6-dimethyldihydro-1,3,5-dithiazine; 18% 4-isobutyl-2,6-dimethyldihydro-1,3,5-dithiazine	12% 2,4,6-trimethyldihydro-1,3,5-dithiazine; 4% 2,4-diisobutyl-6-methyl-1,3,5-dithiazine; 2% 2,6-dimethyl-4-butyldihydro-1,3,5-dithiazine; < 1% substituted 1,3,5-thiadiazine	The cyclic compound 2-methyl-1,3-dithiolane has a similar structure to these heterocyclic compounds, and the NOEL in a 90-day study in rats was 7 mg/kg bw per day (Griffiths et al., 1979). The NOELs in dietary 14-day studies on the structural analogues 2-isobutyl-4,6-dimethyldihydrothiazine (Rush, 1989a) and 2-isopropy-4,6-dimethyldihydro-1,3,5-dithiazine (Rush, 1989b) were 11 mg/kg bw per day and 10 mg/kg bw per day, respectively. The secondary components are all structural isomers or homologues of the principal components and were present in the 14-day studies on the flavouring agent. Metabolic pathways for these substances include *S*-oxidation to polar sulfoxides and sulfones.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
1047	Mixture of 2-isopropyl-4,6-dimethyl and 4-isopropyl-2,6-dimethyldihydro-1,3,5-dithiazine	44% 2-isopropyl-4,6-dimethyldi-hydro-1,3,5-dithiazine; 27% 4-isopropyl-2,6-dimethyldi-hydro-1,3,5-dithiazine	13% 2,4,6-trimethyldihydro-1,3,5-dithiazine; 8% 6-methyl-2,4-diisopropyl-1,3,5-dithiazine; 4% 4-methyl-2,6-diisopropyl-1,3,5-dithiazine; 2% 2,4,6-triisopropyl-dihydro-1,3,5-dithiazine	See No. 1046 above.	Secondary components do not raise safety concern.
1069	2-Ethanoic acid, *S*-(2-methyl-3-furanyl) ester	92	< 7% *cis*- and *trans*-2-methyl-3-tetrahydrofuranthiol acetate	This secondary component is an ester that is hydrolysed to 2-methyl-3-tetrahydrofuranthiol (No. 1090), which has been evaluated by JECFA.	Secondary components do not raise safety concern.
1086	2,6-Dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone	94	5.5% 2-[(2-methyl-3-furyl)thio]-4-heptanone isomer	The NOEL for the structural analogue 3-[(2-methyl-3-furyl)thio]-4-heptanone in a 90-day study in rats was 3.8 mg/kg bw per day (Gallo et al., 1976).	Secondary components do not raise safety concern.
1092	2,5-Dimethyl-3-thioacetoxy-tetrahydrofuran, *cis* and *trans* isomers	90% as mixture of 4 stereoisomers (2 pairs of diastereomers)	< 4% 2,5-dimethyltetrahydrofuran-3-thiol; < 2% dimethyltetrahydro-3-furyl dithioacetate	The structural analogue 2-methyl-3-tetrahydrofuranthiol (No. 1090) has been evaluated by JECFA.	Secondary components do not raise safety concern.

No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components	Evaluation
1109	2-*sec*-Butylcyclohexanone	94	2–2.5% 2-isobutylcyclohexanone	In a 90-day study in rats, the gas chromatography data for the *2-sec*-butylcyclohexanone tested showed the presence of 2-isobutylcyclohexanone as a secondary component. As the secondary component was present in the test material, this would not be a safety concern (Hummler, 1969). The NOEL in a 90-day study on a structurally related 2-alkyl-substituted cyclopentanone, 2-hexylidenecyclopentanone, was 2.9 mg/kg bw per day (Posternak et al., 1969).	Secondary components do not raise safety concern.
1128	3-Octen-2-one	94	4–6% 4-octen-2-one	The NOEL for 2-octen-4-one (No. 1129) and 1-octene-3-one in a 90-day oral study in rats was 7.5 mg/kg bw per day (Cox, 1974a,b).	Secondary components do not raise safety concern.
1135	(*E*)-7-Methyl-3-octen-2-one	94	2–4% 7-methyl-4-octen-2-one; 5,6-dimethyl-3-hepten-2-one; 3-nonen-2-one	The secondary components are all aliphatic α,β-unsaturated ketones and are metabolized by reaction with glutathione to a mercapturic acid derivative and reduction to the corresponding alcohol. The NOELs in 90-day studies in rats with three structurally related α,β-unsaturated ketones were 6 mg/kg bw per day with 4-hexene-3-one (Shellenberger, 1970), 7.5 mg/kg bw per day with 2-octen-4-one (Cox et al., 1974a) and 7.5 mg/kg bw per day with 1-octen-3-one (Cox et al., 1974b). 3-Nonen-2-one is a straight-chain analogue of these unsaturated ketones.	Secondary components do not raise safety concern.
1137	(*E*) & (*Z*)-4,8-Dimethyl-3,7-nonadien-2-one	94	3–4% 4,8-dimethyl-3,7-nonadien-2-ol	As the secondary component is an alcohol which is interconvertible in vivo with the ketone, the safety evaluation appplies to both.	Secondary components do not raise safety concern.
1154	(*E,R*)-3,7-Dimethyl-1,5,7-octatrien-3-ol	93	3–5% linalool and lesser quantities of linalool oxide and nerol oxide	For data on linalool, see No. 358 above.	Secondary components do not raise safety concern.

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